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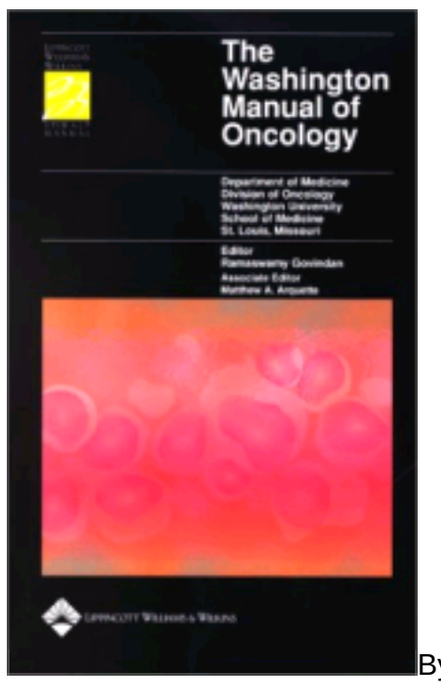

By OkDoKeY

The Washington Manual of Oncology

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Edited by
Ramaswamy Govindan, M.D.
Attending Physician
Barnes-Jewish Hospital;
Assistant Professor
Department of Medicine
Division of Oncology
Washington University School of Medicine
St. Louis, Missouri

Associate Editor
Matthew A. Arquette, M.D.
Assistant Professor
Department of Medicine
Division of Oncology
Washington University School of Medicine
St. Louis, Missouri

THIS BOOK IS DEDICATED TO MY PARENTS

Kollengode A. Ramaswamy
Pankajam Ramaswamy

for their selfless sacrifice

PREFACE

These are exciting times in oncology. The novel imaging techniques, improved supportive care, and the availability of several new agents that have novel mechanisms of action hold considerable promise in improving the outcomes of cancer patients. In this era of information overload, it is critically important to have a practical manual that is helpful to physicians taking care of patients with cancer.

The chapters are arranged in a logical order beginning with evaluation of symptoms and proceeding in an orderly fashion through the work-up, staging, and stage-directed therapy, and finally ending with discussion on epidemiology and current focus of research. We have embarked on this first edition of *The Washington Manual of Oncology* to provide a very practical manual that is helpful to medical residents, fellows in training, nurse practitioners, and other practitioners of clinical oncology. Our plan is to publish this book in a timely fashion every two years to keep the information current and up-to-date.

Ramaswamy Govindan, M.D.

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CHAPTER 1. PRINCIPLES OF CLINICAL TRIALS

Kathryn M. Trinkaus and J. Philip Miller

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I. **What is a clinical trial?**

Broadly speaking, a clinical trial is the process of testing the effect of any drug, medical or surgical procedure, medical device, or other intervention (collectively referred to here as “treatments”) in human beings to determine its efficacy and safety in preventing, alleviating, or curing illness or injury. This requires that there be genuine doubt concerning the benefit of the treatment relative to the best, current treatment (**standard of care**), sometimes referred to as a state of, “**equipoise.**”

II. **Principles of good clinical practice**
   A. Current definitions of good clinical practice can be found in the **Declaration of Helsinki** (World Medical Association, revised October 2000), the **Belmont Report** (OPRR Report, April 18, 1979), and **Good Clinical Practice: Consolidated Guideline** (International Conference on Harmonisation *Fed Reg* 1997;May 9). In brief, these sources state that the rights, welfare, and ability to make decisions of individual study participants take precedence over possible benefits to collective entities such as science or society. Individual consent is essential and must be fully informed and freely given. The informed consent safeguards the participants' welfare by describing in detail and in nontechnical (e.g., eighth-grade reading level) language the protocol to be followed. It fully informs participants of any known or anticipated risks, benefits, or other aspects of the trial that may affect their willingness to participate.
   B. **Autonomy.** Informed consent also affirms the participants' autonomy by stating their right to withdraw without penalty at any time. The participant gives consent by signing and dating the form. The clinical staff member presenting the consent form answers any questions posed by the participant. The staff member also signs and dates the form. Consent must be voluntary, without restraint, coercion, or fear that future medical care will be compromised. Reconsent is obtained if the trial is amended or new scientific information becomes available that may alter the participants' willingness to be included in the trial.
   C. **Beneficence and justice.** Known or anticipated risks and benefits must be weighed and the trial conducted only if benefits outweigh risks. Investigators are obligated to minimize risks. Participants who bear the risks and inconveniences of participation in the trial must have a fair share in the benefits of improved treatment.
   D. **Scientific merit.** The research questions under investigation must be supported by the best available scientific information, and the trial must be conducted in such a way as to produce sound, scientifically valid results. Study personnel must have skills, education, training, and experience appropriate to their roles. All aspects of the trial must be adequately documented and available for monitoring or auditing as needed.

III. **Initiating a cancer clinical trial**
   A. **What is the question being asked?** The first steps are identification of the scientific question(s) to be addressed, formulation of **research hypotheses,** and definition of **study objectives. Prevention trials** are concerned with health promotion or prevention of cancer in those not previously diagnosed with cancer and with the prevention of new primary tumors in persons previously diagnosed with cancer. **Diagnostic trials** focus on means of better identifying cancer, especially on early detection. **Therapeutic trials** are concerned with alleviation or cure of preexisting cancer.
   B. **How will the question be answered?** Clinical trials may be organized in several ways. A **retrospective trial** collects data on events or responses that have occurred before its initiation, whereas a **prospective trial** follows up participants and measures end points at fixed times or as relevant events occur. Trials may include both retrospective and prospective components or a combination of preventive, diagnostic, and therapeutic aims. The ultimate goal may be to determine whether there is a **difference** in effectiveness of treatments. Alternatively, the trial may attempt to determine whether the effects of two treatments differ by less than a clinically relevant, maximal allowable amount, or are **equivalent.** A **cross-sectional trial** gathers data from each participant during a brief interval, whereas a **longitudinal trial** measures the same quantities repeatedly from each participant over an extended time. Participants in a **parallel trial** study group may receive a single treatment before their results are compared, or participants in each group may **cross over** and receive the other's treatment before comparison within and between study groups. If participants cross over to receive a second treatment, a **washout** or rest period is often included to ensure that the effect of the first treatment has ceased before the second begins.
   C. **How many institutions will be involved?** Small trials are often carried out at a single institution. If large numbers of participants are needed or if the cancer of interest is rare, then several institutions may collaborate in a multicenter trial. The **National Cancer Institute Cooperative Group** program currently supports about a dozen cooperative oncology groups, each with an organizational framework for the conduct of multicenter clinical trials. At this time, cooperative group trials involve 8,000 researchers at 1,500 institutions and enroll more than 20,000 participants each year in clinical trials.
   D. **What are the end points being studied?** Once the objectives are clearly stated, the next step is to choose measurements of the effects of interest, or **end points.** If these cannot be measured directly, then careful consideration is needed to find the best available surrogates. Informative study end points are clearly related to the study hypotheses and objectives, unambiguously measurable with minimal error, and available within a reasonable period. Information-rich measures are preferable, those that finely discriminate between degrees or states of the phenomena of interest. **Common clinical end points** in oncology trials may include survival or time to key events or response rates:
      1. **Complete response** is the percentage of patients who have complete resolution of tumor lasting at least 4 weeks.
      2. **Partial response** is defined as a 50% decrease in the sum of the products of all measurable sites of disease (as measured by physical examination or radiographs) with no new sites of disease.
      3. **Progressive disease** is defined as a 25% increase in the sum of the product of all sites of measurable disease or one or more new sites of disease.
      4. **Stable disease** is that which does not meet the definitions for response or progression.
      5. **Overall response** is the sum of partial plus complete responses. Stable disease or tumor regression may be considered responses to treatment of very aggressive cancers.
      6. **Event-free survival** is the time from a clinically significant event such as diagnosis, treatment, or transplant until some defined event, such as overall survival, disease-free or progression-free survival, time to identification of distant metastases, or local recurrence-free survival. These times may be expressed by a median for the group or a percentage at a particular time point (e.g., 1 year or 5 years).

IV. **Designing the trial**
   A. **Study population.** Equally important is defining the **target population,** which is that part of the human population to which the results will be applicable in a

clinical setting. The **sampling frame** is that part of the target population from which the study sample will be drawn. The process by which study participants are identified and recruited is the **sampling strategy.** A sound sampling strategy ensures that end points are represented fully in the study sample so that the results may be generalized to the population that may benefit from them.

B. **Reducing bias.** Bias, which is the difference between a measured estimate and the true value of the quantity being measured, can arise at any stage and must be minimized as far as possible.
   1. **Randomization.** Using a probabilistic sampling strategy, which gives each member of the sampling frame a predetermined chance of inclusion in the study, and randomization, which is the use of a formal probability model to assign participants to treatments, can reduce bias. Use of even/odd numbers, flipping a coin, or manual use of a random-number table is not sufficient. The randomization process must be documented as part of the trial and for audit if necessary. Assignments may be kept in sealed envelopes or be available from a randomization center. A randomized assignment usually is made only after the participant's eligibility is established and his or her informed consent has been given.
   2. **Blinding.** Knowledge of the treatment received by a participant can lead to significant alteration of his or her care and consequent bias of study results. Restricting knowledge of individual treatment assignments can reduce bias arising from differential care of participants. In an **unblinded, unmasked, or open-label** study, assignments are known to study participants, treating physicians, and other study personnel. In a **single-blind** study, either the study participant or the treating physician (usually the former) may be unaware of study group assignments. If both study participants and treating physicians do not know which treatment is being received, the study has a **double blind.** To maintain a double blind, it usually is necessary to extend the blind to other clinical personnel involved with participant treatment, data collection, and data management. Data analysts also may be blinded. Any document linking individuals with treatments must be inaccessible to all blinded study members. Care must be taken to design treatments and controls to be as nearly indistinguishable as possible. Unblinded study personnel must be discrete in discussing study-related information with those who are blinded.
   3. **Other means of reducing bias.** These include careful and consistent implementation of all study procedures by well-trained personnel, including maintenance of blinding (see above) and complete verified data collection. Appropriate data analysis also is needed, controlling for confounding (see later), avoiding non–hypothesis-driven searching for patterns, and including only planned interim analyses (see later). At study end, bias can be reduced by thoughtful interpretation based on observed results and publication of all results, positive and negative, as completely as possible.

C. **Eligibility and exclusion criteria.** The research hypotheses and sampling frame are used to identify characteristics of participants who may benefit from the treatment, the eligibility criteria for the trial. Characteristics of participants who are unlikely to benefit or who may be at unusually high risk if enrolled define the exclusion criteria. Eligibility and exclusion criteria are usually specific to the condition and treatment under study, although the presence of unknown or poorly estimable risks (e.g., pregnant or breast-feeding women and their offspring) also may be a reason for exclusion. Participants should never be included or excluded automatically (e.g., by age, gender, or race/ethnicity) or as a matter of convenience. A consecutive series of participants from a single clinic or practice, even if they represent “all-comers,” is biased by the nature of the clinic, its location, the mechanisms of referral, and many other factors. Such a single-institution sample may not be easily generalized to the target population, and any results may require subsequent confirmation before they are accepted.

D. **Study design.** Once the sample is defined, the study design is written. The design is a plan for assignment of participants to treatment; measurement of study end points; and collection, organization, and analysis of the resulting data. The design ensures that the results produced by the study represent its objectives in an accurate and unbiased manner in all parts of the study sample.
   1. **An observational or natural history trial** measures study end points without attempting to relate them to a baseline or alternative treatment. Such uncontrolled studies can be useful when little is known about the condition of interest in the target population. They may be used to collect data on treatment safety and study feasibility, as well as to estimate study parameters for the planning of future, controlled trials.
   2. **A controlled study** compares two or more treatments given concurrently under similar conditions. Such a study has at least two **arms,** or participant groups receiving different treatments. The control arm may receive a **placebo,** an inactive or dummy treatment that resembles as closely as possible the experimental one. Alternatively, the control arm may use an **active control,** a different but active alternative to the experimental treatment, usually the current standard therapy. Use of a placebo is ethically justified if there is no established standard of care or known effective treatment under the circumstances that surround the trial. Otherwise, it is unethical to offer any participants less than the standard of care. Patients who have been followed up for the same condition and whose outcomes are known at the outset of the study may be used as a **historical or external controls.** Conclusions from comparison with historical control are questionable because of the many unknown differences, temporal changes, and uncontrolled sources of bias that may occur between the two sets of measurements, however. A **concurrent control,** whether active or placebo, is preferred.
   3. **Covariates and confounding variables.** Study hypotheses and objectives usually will make clear which characteristics of the participants, their environment, or the condition of interest may have effects on the end points. These **covariates** often include demographic and clinical characteristics of the participants, aspects of the disease process under study, and any striking features of past or current treatments received. The study hypotheses define how covariates will be included in the analysis and interpretation of study results. If covariates of interest are related to one another, as well as to the study end points, then their interrelations may distort, mask, or **confound** their effects on the outcome measures. If these relations are understood, they can be included in and adjusted for during subsequent analyses. The term confounding also refers to the inability to separate effects of two or more covariates on an end point. If the study arms contain very unequal numbers of participants with differing disease-related characteristics, then it may be impossible to separate the effect of treatment from the effect of the characteristics. For example, if a pulmonary-function study contains one treatment group composed largely of urban residents and another of rural residents, the effect of treatment will be difficult to separate from the effect of residence. To avoid such confounding, assignment of treatments may be **stratified** so each treatment group contains approximately equal numbers of participants with each characteristic (e.g., in a two-arm study, approximately half of all urban residents and half of all rural residents will be randomized to each treatment group). Treatment effects are compared within strata. Participants also may be **matched** on the basis of covariate values (e.g., age, gender, history of treatment). Study end points are the differences observed within the matched sets. Close matching may reduce the number of participants, as appropriate matches become difficult to find. Whether covariates are effects of interest or factors to be adjusted, their definition and role need careful planning.
   4. **New drug development and trial design.** An efficient study design obtains the fullest information possible about study end points from the fewest possible study participants over the shortest possible time. A variety of formal designs are available to maximize information, observe nested effects, or manage the impact of missing data. These are routinely used in a variety of scientific disciplines and are discussed in the references. Drug studies follow steps outlined by the Food and Drug Administration (**FDA**). An Investigational New Drug Application (**IND**) includes the data collected in **preclinical trials** (*in vitro* and animal studies) and early human studies. Human trials begin with a **phase I or dose-finding trial.** In such a trial, a small cohort of patients is treated with a small dose (e.g., 10% of the dose that is lethal in rats) of the drug being studied. This cohort is observed for toxicity. In a classic phase I design, if no unacceptable or dose-limiting toxicities are observed in the first cohort, then another cohort of patients may be treated with a higher dose. This process is continued until toxicity is demonstrated. If only one patient demonstrates toxicity in a cohort, then that group may be expanded and additional patients treated before escalating the dose further. Once dose-limiting toxicity is demonstrated in more than one patient in a cohort, then the trial is completed, and the next lowest dose is considered the maximal tolerable dose (**MTD**) The MTD is recommended for further testing. Although efficacy is not a traditional end point of a phase I trial, patient responses, if observed, may indicate directions for further testing. One problem with the traditional phase I design described here is that too many patients may be treated at low doses, wasting resources by needlessly enlarging the trial and treating patients with subtherapeutic doses. This has led to increasing use of novel phase I designs with more rapid dose escalation. Studies of toxicity, absorption, activity, and clearance of the drug (**safety, pharmacokinetics, and bioavailability**) also are carried out. The participants are usually cancer patients with terminal disease for whom no standard therapy or salvage treatment exists, rather than healthy volunteers, as is often the case in other branches of medicine.
   5. **Phase II trials** enroll approximately 20 to 40 participants to investigate the drug's **efficacy** and the better to assess **toxicity** of the drug in a larger group of patients. These may be composed of a single, nonrandomized group or include one or more control groups. Study results may be analyzed before the trial is complete (**interim analysis**) to determine whether there is evidence of **benefit,** lack of benefit (**futility**), or unacceptable **toxicity.** The trial may be stopped for any of these reasons. Interim analyses and early-stopping rules must be planned before starting the trial because testing procedures and significance levels are adjusted to preserve the overall validity of the trial. Results of interim analyses are communicated in an abbreviated form to avoid alteration of treatment and bias of the final study results.
   6. **Phase III trials.** If the results are encouraging, larger, multiarm, controlled, randomized phase III trials will compare treatment effects with standard therapy.
   7. **Phase IV trials.** After a New Drug Application (**NDA**) has been approved and a drug released by the FDA, additional postmarketing phase IV trials may be carried out to observe treatment effects with long-term follow-up in a broader clinical setting or to examine issues of cost of therapy or quality of life.

E. **Power and statistical significance.** Once the design is clear, the study power and sample size can be determined. **Power** is the probability of detecting the effects of interest if they exist. The complement of power (1 – power) is the probability of failing to find an effect when one does exist, a **type II error.** Common values for type II error are 0.2 (or 1 in 5) and 0.1 (or 1 in 10), which correspond to power of 0.8 and 0.9, respectively. The study **significance level** is the probability of detecting an apparent effect when none exists and differences observed are the result of chance, a type I error. Common values for **type I error** are 0.05 (1 in 20) and 0.01 (1 in 100). Too small a sample leads to increased probability of both errors and low power. Too large a sample wastes resources, extends the study duration, and exposes participants unnecessarily to the risks associated with the trial. It also may detect differences that are statistically significant but too small to be clinically important. To calculate **sample size,** the investigator must know the desired power, significance level, and expected magnitude of the effect to be observed based on the best information available at the outset of the trial. If the required sample size is large, the

study may recruit participants from more than one institution, lengthen the recruitment time, or consider other, more information-rich end points to provide finer discrimination between effects of interest.

V. **Data collection, management, and analysis**

A. **Data-collection forms.** Once the end points and study design are defined, data-collection forms can be created. Well-designed forms smooth the daily operation of the study, save time and effort, and produce complete, clean, unambiguous data for subsequent analysis. A comparatively small investment in planning at this stage saves a great deal of time and effort later. Any discrete encounter with a participant that produces study data should have a form. Information collected at different times is kept on separate forms, so that forms are not routinely left partly blank. All forms containing information to be gathered at a particular stage of the study are gathered together into a discrete packet. Forms should be printed ahead of time, kept up to date with any changes in data collection, and made readily accessible to those who use them. Their content is determined largely by the study design. The format and organization are best worked out collaboratively with staff members experienced in data collection, entry, and analysis. If the study requires that a specific script be followed when asking questions or presenting information to participants, then the text is included at the appropriate point on the form. Individual data items are presented as clearly as possible, offering selection lists and check boxes rather than free-text fields when possible. The format and units of dates and numbers are printed on the form to reduce later confusion. Required data fields are printed in bold or otherwise clearly identified. Data items are presented as nearly as possible in the order in which they will be recorded, so that data fields are not routinely skipped. Data fields are never routinely left blank. Codes or check boxes are used to indicate why values are missing to make clear that data collection has been completed. The person filling out a form initials and dates each one in case questions arise later about the information on the form. Completed forms are sorted by participant and stage of the project and kept in locked filing cabinets in a secure area to preserve **confidentiality** of participant information.

B. **Data analysis.** Once the study hypotheses and end points are defined, a data-analysis plan specifies the exploratory analyses, comparisons, modeling procedures, and hypothesis tests to be carried out. Clinical and demographic characteristics of participants and their environment are identified, and the roles of these covariates in data analyses are specified. Those that are to be treated as confounding, adjustment, stratification, or matching variables are included the better to identify the effects of interest. For the remaining covariates, estimates of effect and variability will be made.

1. **Intent-to-treat.** The primary analysis is usually carried out on the **intent-to-treat** principle, in which each participant's results are included in estimation of the effect in the treatment group to which they were assigned, regardless of whether they actually received that, or any, treatment. Subsequent analyses may estimate effects by using only participants who actually received each treatment. Such analyses always must be interpreted with reference to intent-to-treat analyses to establish that their results are not dependent on conscious or unconscious selection of participants based on their outcomes.
2. ***Post hoc* data analyses.** Further analyses suggested by study results (for example, analysis of subsets of the study population) may be carried out to explore directions for future research. Results of such *post hoc* data analyses are regarded as hypothesis generating (supplying questions to ask in future trials) rather than definitive, regardless of the level of statistical significance or their clinical interest. Common comparisons among treatment and control groups include tests for difference of proportions (e.g., response rates), mean or median values (e.g., temperature, blood pressure), counts (e.g., episodes of toxicity), and distribution of events (e.g., time to death, disease progression, or recurrence). Unlike rates, means, or counts that are observed for all participants at specific times, events may occur after the follow-up period has ended. The time to event will be unknown for some participants (e.g., survival time for patients alive at end of study). Such values are referred to as censored and require analytic techniques such as Kaplan–Meier or Cox proportional hazards modeling.
3. **Hypothesis testing.** Comparisons are most frequently made to determine whether there is a difference between treatments, or between treatment and control, with respect to a hypothesized null value. These tests are **two-sided,** as the null hypothesis will be rejected if the observed value is greater or less than the null value (i.e., if any difference is observed). It can be argued that a treatment is of interest only if it changes clinical practice by having a favorable effect on the patient's prognosis. Tests to determine whether a treatment increases (decreases) a parameter relative to the null hypothesis that it causes no change or decreases (increases) the parameter are referred to as one-sided, because the null hypothesis is rejected only if the effect is in one direction. **One-sided** hypotheses have greater power with smaller numbers of observations but produce less information about the relation between treatments. They also are open to overgeneralization of positive results if the directionality of the test is misinterpreted. At present, two-sided tests are more commonly used.

C. **Data management.** A data-management plan and an agreement on means of protecting **participant confidentiality** follow development of data-collection forms. The process of converting written records into electronic data files is specified. Issues to consider are who will be responsible for data entry, what resources they will use, which format and software will be used for data storage, what processing or manipulation is needed before analysis, how the data will be converted into one or more files for the planned analyses, and how any personal information is to be stored.

1. **Participant confidentiality** must be protected at the time of enrollment, including any information gathered from persons who decide against participation. Confidentiality also is maintained during data collection, transfer, analysis, processing, and storage. Increasing use of Internet-based enrollment and data entry requires **encryption** as data are transferred over the web and stored on **secure servers.** Once data are stored in encrypted form, the means to access data files must be available to at least two study members, usually including the data manager or data analyst and the principal investigator. If lost, this information is not easily retrieved, so data files may become permanently inaccessible. A clear plan for long-term storage and emergency accessibility of passwords and encryption keys is needed, especially during the absence of critical study personnel. Confidentiality also is maintained by storing source documents in locked file cabinets, protection of passwords, discretion in communicating study results or individual case information, and careful dissemination of reports. In multicenter trials, centers usually have access only to their own data as the trial progresses. Secure, off-site storage also is recommended for up-to-date backup copies of data files, copies of keys to essential storage areas, passwords, and encryption keys.
2. **The informed consent** is the most important form. This form is reviewed and approved by the Internal Review Board (see later) before being put to use. Approval is normally given for 1 year and must be kept up to date. The form cannot contain any explicit or implied waiver of the participant's legal rights or any release of the investigator(s), sponsor, supporting institution, or their agents from responsibility for negligence. A legal representative may sign the form if the participant is unable to understand the contents of the form because of youth or impaired cognitive function. A legal representative also may sign the form if the participant is able to understand the conditions of the trial but is unable to read or sign and date the form because of noncognitive impairment. In the latter case, the signature of an impartial witness also is required. There is ongoing discussion concerning appropriate means of obtaining consent when it is difficult to ensure an absence of restraint or coercion, as is the case when enrolling prisoners.
3. **Source documents.** Original documents, data forms, and other records are the source of all information produced by the trial. Source documents are filed at the participating institutions and made available as needed for monitoring or auditing. The supporting institutions may make, or delegate, periodic checks to ensure that the study protocol is being followed. Sponsors may require auditing by their own independent personnel. The auditors review the progress, procedures, and results of the trial, relying heavily on source documentation.
4. **Reporting adverse events.** Any medical occurrence during a trial that causes the death of a participant, is considered life threatening, requires hospitalization or extension of existing hospitalization, or results in significant or prolonged disability or loss of capacity is a **serious adverse event (SAE).** All SAEs must be reported to participating institutions and sponsors within a fixed period, usually 24 hours. A means of observing, documenting, and communicating SAEs is established as the trial is planned. If toxicities, drug reactions, or other negative health-related occurrences (adverse events) are anticipated, a **Data Safety and Monitoring Board** or Independent Data Monitoring Committee is established. The monitoring committee is charged with providing an independent review of progress of the trial and of the safety and efficacy of its treatments. After review, the monitoring committee may recommend that the protocol be altered or the trial stopped in the participants' best interests. Efficient data collection and processing are needed to provide timely and accurate information for review. Committee members must make decisions without conflict of interest if the monitoring process is to be effective.

D. **Reporting results.** Study planning should also include an outline of expected **publications,** appropriate target audiences, media for dissemination of study results, and a list of potential study authors. Agreement on who may be included as an author and who will take the lead in writing each publication also will promote smooth and timely completion of the study.

VI. **The review process**

Before the trial can be submitted for review, all of the preceding steps are put in writing in the trial protocol. The **protocol** describes the scientific rationale, specific objectives, study design, organization, methods, and statistical analysis of the trial. It serves as a guide for conduct of the trial and is the basis of review, monitoring, and auditing of the trial. Once the protocol is complete, an in-house scientific review may take place. This includes examination of the scientific merit of the study concepts, feasibility of the study process, and adequacy of available resources. Every clinical trial is a cooperative effort, so this review serves to focus departmental resources, to obtain agreement to recruit participants, and to set priorities for managing protocols with overlapping eligibility criteria. Specific medical or surgical procedures also may have their own review committees (e.g., for the use of radioactive materials), so it is a good idea to become familiar with the practices in effect at your institution.

The Internal Review Board (**IRB;** also Institutional Review Board, Ethics Review Board, or Independent Ethics Committee) will review the protocol before any patients may be enrolled. The responsibilities and composition of an IRB are discussed in detail in Title 21, Code of Federal Regulations Part 56 (Institutional Review Boards) and Good Clinical Practice: Consolidated Guideline. In brief, an IRB is charged with minimizing risks to participants, as well as protecting their rights, safety, and welfare. Its membership must include at least five persons, at least one of whom is primarily concerned with nonscientific activities and at least one of whom is independent of the institution sponsoring the trial. Community leaders and members of religious organizations are often included. Once the

trial is under way, any amendments to the protocol also must be reviewed and approved by the IRB before being implemented. The committee charged with oversight and quality assurance of ongoing protocols may give additional, extradepartmental scientific review. If external funding is applied for, government agencies or corporate sponsors also will provide review.

VII. Management of a clinical trial

Once the trial is approved, the process of participant recruitment, treatment, and follow-up is set in place. Each clinical trial poses substantial management challenges. Smooth, effective operation depends heavily on clear definition of responsibilities, including those of physicians, nurses, clinical research assistants, data managers, and data analysts. Good communication and clear, rapid decision making are essential. Clinical responsibilities are usually heavy. Staff members are often on the move for much of the day, and decisions concerning participant care must be made quickly, so good communication may be difficult to maintain. The primary tool is a clear, written reference guide available to all study personnel. This document, the **Standard Operating Procedure** (SOP, or Manual of Procedures) outlines the events that occur as each participant passes through the trial. It details the functions and responsibilities of all trial personnel and the required or preferred ways of dealing with foreseeable contingencies. The SOP also is needed for reference when auditing occurs. Short, regularly scheduled meetings are another tool to identify and fix problems as soon as they arise. Although these meetings take time from busy schedules, they avoid a more serious burden created by neglected issues that may threaten the validity of the trial. Such meetings also may be the only face-to-face contact between trial personnel. As such, they contribute to better understanding of each other's roles and to better cooperation. Change of personnel should be taken into account, especially in projecting timelines. Trained back-up personnel should be available for all critical functions, including that of the principal investigator(s).

VIII. Study closure

Ideally, all enrolled participants are followed up to the end of the study, whether they remain on the protocol or drop out. Participants in National Cancer Institute (NCI) cooperative group therapeutic trials are followed up until death, regardless of how long after the end of the study this may occur. Once the last participant has completed the protocol, all data are entered and verified, and final data analysis is under way, source documents and other trial-related materials can be stored for future use. Source documents, the SOP, and any other information critical to correct interpretation of the study results are collected, organized, and permanently stored in clearly labeled containers. Tissue samples are stored in a licensed medical facility, and informed consent is obtained from participants before any further use. Ideally, the study materials and documents should be available for any IRB-approved replication or extension of the study.

SUGGESTED READINGS

Web sites often contain the most recently updated policy and regulatory information. At the time of writing, some useful URLs (Uniform Resource Locators) are **http://www.wma.net/** (World Medical Association, Declaration of Helsinki), **http://www.nih.gov/** (National Institutes of Health), **http://www.nci.nih.gov/** (National Cancer Institute), **http://www.fda.gov/** (Food and Drug Administration), and **www.access.gpo.gov/nara/cfr** (Code of Federal Regulations and Federal Register). Issues of study design, conduct, and analysis are regularly canvassed in major medical journals, as well as in the journals *Applied Clinical Trials, Biometrics, Biostatistics, Controlled Clinical Trials, Statistical Methods in Medical Research,* and *Statistics in Medicine.*

OTHER SUGGESTED READINGS

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CHAPTER 2. CHEMOTHERAPY: PRINCIPLES AND PHARMACOLOGY

Chris Papageorgio and Howard L. McLeod

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Consolidation/Intensification chemotherapy
Adjuvant chemotherapy
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PRINCIPLES

I. **Timing of chemotherapy**
   A. **Induction chemotherapy.** Induction chemotherapy is the use of drugs as an initial therapy, for example, in the treatment of acute leukemia to achieve significant cytoreduction (complete remission) of disease as initial therapy.
   B. **Consolidation/Intensification chemotherapy.** In consolidation/intensification treatment, given after remission, the same drugs used in induction (consolidation) or drugs that are non–cross resistant to the induction drugs (intensification) are repeated. Postremission chemotherapy is necessary to prolong remission duration and overall survival in certain hematologic malignancies such as acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML).
   C. **Adjuvant chemotherapy.** After eradication of disease with local treatment (surgical or radiation), adjuvant chemotherapy is used to treat putative microscopic disease and prevent local or distant relapse.
   D. **Neoadjuvant chemotherapy.** Before local therapy, neoadjuvant chemotherapy is given in hopes of reducing the extent of local treatment or increasing its effectiveness.
   E. **Maintenance chemotherapy.** Prolonged, low-dose outpatient chemotherapy is intended to prolong duration of remission and achieve cure in patients in remission.
   F. **Salvage chemotherapy.** After the failure of other treatments (surgery, radiation, or prior chemotherapy), salvage chemotherapy is used to control disease or provide palliation.

II. **Clinical end points in evaluating response to chemotherapy**
   A. **Induction chemotherapy**
      1. **Complete response (CR)** is the disappearance of disease on imaging studies for at least 1 month. In hematologic malignancies (e.g., in AML), a CR is defined as fewer than 5% blasts in the bone marrow (BM), no circulating blasts in the peripheral blood, and no extramedullary disease by day 14 after induction.
      2. **Partial response (PR)** is the decrease of 50% or more in the sum of the products of the biperpendicular diameters with no new sites of disease for at least 1 month.
      3. **Stable disease** is that in a patient with less than 50% response without actual progression of disease, as defined later.
      4. **Progression** is a 25% increase in the sum of the products of the biperpendicular diameters of known lesions or any new sites of disease.

B. **Adjuvant chemotherapy.** Relapse-free survival measures time from start of therapy to regrowth of tumor to detectable levels.
C. **Primary (neoadjuvant) chemotherapy** is given as with induction chemotherapy; however, the unique feature of primary chemotherapy is the ability to delineate partial responders with variable degrees of prognosis because removal of residual tumor mass and histologic examination of the tissue allow determination of the viability and character of the remaining tumor cells (pathologic response).
D. **Salvage chemotherapy.** Progression-free survival remains the major end point in patients with advanced disease and is the equivalent of relapse-free survival in the adjuvant setting.

III. **Combination chemotherapy.**

With rare exceptions, single drugs in standard doses do not cure cancer. Combination chemotherapy accomplishes not only maximal cell kill within the range of toxicity tolerated by the host for each drug, but also it provides a broader range of coverage of resistant cell lines, thus preventing or slowing the development of new resistant cells. The development of resistance by cancer cells to anticancer drugs without prior exposure to these drugs has been predicted, by the Goldie and Coldman mathematical model, to occur at population sizes between 10^3 and 10^6 tumor cells, much lower than the mass of cells considered to be clinically detectable (i.e., 10^9 cells or a 1-cm mass). Hence, as per the "Goldie–Coldman hypothesis," resistance should be a problem even with small tumors, and the maximal chance for cure occurs when all effective drugs are given simultaneously. The following principles have been useful in the selection of drugs in the most effective drug combinations.

- Only drugs known to be partially effective against the same tumor when used alone should be selected for use in combination.
- When several drugs of a class are available and are equally effective, a drug should be selected on the basis of toxicity that does not overlap with the toxicity of other drugs to be used in the combination.
- Drugs should be used in their optimal dose and schedule.
- Drug combinations should be given at consistent intervals. Because long intervals between cycles negatively affect dose intensity, the treatment-free interval between cycles should be the shortest possible time necessary for recovery of the most sensitive normal target tissue, which is usually the bone marrow.

IV. **Response to chemotherapy and the biology of human tumor growth**

Skipper et al. developed the L1210 rodent leukemia model, a rapidly growing tumor with nearly all cells actively synthesizing DNA, as measured by the uptake of tritiated thymidine (the labeling index). The L1210 leukemia has a growth fraction of 100% (i.e., all of its cells are actively progressing through the cycle), and so its life cycle is consistent and predictable, enabling Skipper et al. to show that this rodent leukemia could be cured by specifically designed doses and schedules tied to tumor volume and growth characteristics. Although the killing effects of cancer drugs in this model tumor followed log-kill kinetics (i.e., if a particular dose of an individual drug kills three logs of cells and reduces tumor burden from 10^{10} to 10^7 cells, then the same dose will reduce the tumor burden from 10^5 to 10^2 cells), human tumors appeared to follow a gompertzian model of growth and regression. The critical distinction between gompertzian and exponential growth is that in gompertzian kinetics, the growth fraction of the tumor is not constant, but decreases exponentially with time (exponential growth is matched by exponential retardation of growth). The growth fraction peaks when the tumor size is about 37% of its maximal size. In a gompertzian model, when a patient with advanced cancer is treated, the tumor mass is larger, its growth fraction is low, and the fraction of cells killed therefore is small, because response to chemotherapy depends on whether the tumor is in its phase of exponential growth. This information has been useful in the design of adjuvant chemotherapy, because it affects the patterns of regrowth of residual tumor cells.

V. **Cell cycle and therapeutic targets**

The eukaryotic cell cycle is divided into four stages: G_1, S, G_2, and M. The mechanisms that allow normal renewing cell populations of the body, like hematopoietic and gastrointestinal (GI) precursors, to monitor and repair damaged DNA or undergo cell-cycle arrest/apoptosis are responsible for the phenomenon called "the therapeutic index." The disruption of this cycle, which is a hallmark of cancer, presents numerous opportunities for targeting checkpoint controls to develop new therapeutic strategies for this disease. Such strategies include either induction of arrest at the G_1/S and/or G_2/M checkpoints (leading to cytostasis and ultimately apoptosis) or abrogation of arrest at the G_2/M checkpoint in p53-deficient cells (leading to progression of cells with damaged DNA through the cell cycle beyond the G_2/M checkpoint and ultimately apoptosis or sensitization to genotoxic stresses such as radiation). Arrest at the G_1/S checkpoint can occur only by p53-dependent mechanisms, whereas arrest at the G_2/M checkpoint can occur by either p53-dependent or -independent mechanisms. However, p53 also can activate an apoptotic response to DNA damage, especially in hematopoietic cells, which often overrides the checkpoint response. Thus in cell types programmed for apoptosis, loss of p53 function decreases sensitivity to a wide variety of DNA-damaging agents, whereas in cell types of some solid tumors not inherently programmed for apoptosis, a clear relation between p53 gene status and radiosensitivity or chemosensitivity has been more difficult to establish.

VI. **Categories of drugs by their activities relative to the cell cycle**

Cytotoxic agents can be roughly categorized by their activities relative to the cell-generation cycle.

A. **Phase-specific agents**

Phase-specific agents are effective only if present in the cancer cell during a particular phase of the cell cycle. Over a certain dosage level, further increases in drug dose will not result in more cell killing. If the drug concentration is maintained over a period of time, however, more cells will enter the specific lethal phase of the cell cycle and be killed.

1. **In the G_0 phase** (gap 0 or resting phase) cells are for the most part refractory to chemotherapy.
2. **In the G_1 phase** (gap 1 or interphase), cells synthesize proteins and RNA for specialized cell functions. In late G_1, a burst of RNA synthesis occurs, and many of the enzymes necessary for DNA synthesis are manufactured. G_1 phase–specific drugs: L-asparaginase, antisense therapies.
3. **In the S phase** (DNA synthesis), the cellular content of DNA doubles. S phase–specific drugs: procarbazine, antimetabolites, hydroxyurea, camptothecins.
4. **In the G_2 phase** (gap 2), DNA synthesis ceases, protein and RNA synthesis continues, and the microtubular precursors of the mitotic spindle are produced. G_2 phase–specific drugs: bleomycin, vinca alkaloids, taxanes.
5. **In the M phase** (mitosis), the rates of protein and RNA synthesis diminish abruptly while the genetic material is segregated into daughter cells. After completion of mitosis, the new cells enter either the G_0 or G_1 phase. M phase–specific drugs: vinca alkaloids, taxanes.

B. **Phase-nonspecific agents**

Nonspecific agents can kill either dividing cells at any point in the cell cycle (e.g., alkylating agents, platinum compounds, cell-signaling inhibitors, trastuzumab) or nondividing cells (cycle nonspecific; e.g., steroid hormones, antitumor antibiotics, except bleomycin). All phase-nonspecific drugs generally have a linear dose–response curve: the greater the amount of drug administered, the greater the fraction of cells killed.

VII. **Multiple drug resistance**

A. **Transporter-mediated resistance**

Tumor cells selected for resistance to a particular drug in the class of "natural product" or their semisynthetic analogues (topoisomerase I inhibitors, vinca alkaloids, taxanes, anthracyclines) display cross-resistance to these and other agents that have in common the following features: they are in general lipophilic, they range in molecular mass from around 300 to 900 daltons, and they appear to enter cells by passive diffusion. The accumulation and retention of these drugs is lower in the multiple drug resistant (MDR) cells than in the drug-sensitive cells from which they were derived. This alteration in cellular activity is mediated by phosphoglyceroyl phosphatase (PGP), a large transmembrane glycoprotein with molecular mass of approximately 170 kDa, consisting of two similar halves, each including six hydrophobic transmembrane segments. One of most popular hypotheses proposes that the drug molecule binds to a specific site of PGP within the lipid bilayer of the cell plasma membrane and, by means of the energy of adenosine triphosphate (ATP) hydrolysis, is transported out of the cell. PGP belongs to the super family of ABC (ATP-binding cassette) transporters, which include MDR-associated protein (MRP), breast cancer–resistance protein (BCRP, and a host of other family members with a putative role in drug resistance. In addition to membrane transporters, cytoplasmic vault proteins, such as lung resistance protein (LRP), also may contribute to resistance by diverting the chemotherapy from having its desired effect.

1. **Intrinsic multiple drug resistance**

Untreated carcinomas of the colon, kidney, hepatomas, adrenal tumors, pheochromocytomas, and some other malignancies demonstrate high levels of *MDR1* gene expression. Some hematologic malignancies (AML, chronic lymphocytic leukemia, adult T-cell lymphomas) also are usually characterized by the MDR connected with the types of cells from which a malignancy arose.

2. **Acquired multiple drug resistance**

The results suggesting the importance of PGP-MDR for outcome of tumor treatment were obtained in experiments of this kind for lung and ovarian adenocarcinomas, breast cancers, and sarcomas.

B. **MDR mediated by detoxification of the drug in the cell**

Glutathione (GSH), a nonprotein thiol, can interact with the reactive site of a drug, resulting in conjugation of the drug with glutathione. The conjugate is less active and more water soluble, and it is excluded from the cell with the participation of transporter proteins named GS-X pumps (including MRP). Increased levels of GSH were found in cell lines resistant to alkylating agents (e.g., nitrogen mustard, chlorambucil, melphalan, cyclophosphamide, 1,3-bis-[2-chloroethyl]-1-nitrosourea [BCNU]). Alkylating agents share an electrophilic nature and ability to interact spontaneously with the thiol of reduced GSH. The enzymes glutathione S-transferases (GST) catalyze the interactions between GSH and alkylating agents, increasing the rate of a drug detoxification, so activation of these enzymes can cause cellular drug resistance. Enzymes that catalyze GSH synthesis also could mediate drug resistance; however, their role in this phenomenon is not yet clear.

C. **Multiple drug resistance mediated by enhanced DNA repair**

1. **Alkylating agents (nitrosoureas)**

Most is known about the basis of resistance to the chloroethylating agents such as carmustine, BCNU, which exert cytotoxicity by the formation of intrastrand cross-links. Bifunctional intrastrand cross-links are gradually formed over time from the precurser monofunctional DNA adduct, O^6 chloroethylguanine. Resistance to these agents can be seen as the repair of the O^6 chloroethylguanine lesion before the bifunctional alkylator DNA adduct forms. Hence BCNU resistance has been correlated with tumor expression of the DNA repair enzyme O^6-alkylguanine-DNA alkyltransferase (AT), also known as methylguanine methyltransferase (MGMT), which removes alkyl adducts at the O^6 position of guanine before cross-link formation occurs, and thereby prevents nitrosourea-induced cytotoxic DNA damage. The strong correlation between AT expression and BCNU resistance has led to the development of strategies to deplete AT to reverse nitrosourea resistance. Thus to circumvent this form of resistance, one approach has been to deplete AT through the use of a methylating agent, such as streptozotocin, to form O^6-methylguanine DNA adducts, which in turn are repaired by AT and deplete the enzyme. Streptozotocin administered before BCNU was shown to decrease AT activity in peripheral mononuclear cells and colon cancer metastasis. However, residual AT levels appear to be sufficient to maintain resistance to BCNU; therefore more potent modulators of AT in tumor cells are needed to reverse clinical resistance to BCNU.

2. **Platinating agents**

Cisplatin and analogues cause interstrand *cis*-diaminedichloroplatinum (CDDP)–DNA and intrastrand cross-links. Changes in the quantities of proteins recognizing and repairing DNA injury (ERCC1, ERCC2, and ERCC3/XPB) were found in cultured cells with altered sensitivity to platinum complexes. However, resistance to these agents has been shown to be multifactorial: altered expression of oncogenes; increased repair of intrastrand cross-links; association of proteins (e.g., high-mobility group proteins HMG1 and HMG2) with CDDP-modified DNA: inactivation in the cytosol by either increased levels of metallothionine or increases in GSH, although these alterations are not seen in all CDDP-resistant cells; and decreased cellular accumulation of CDDP.

D. **Multiple drug resistance mediated by alteration of drug targets**

1. **Topoisomerases and their inhibitors**

Two types of topoisomerases exist in mammalian cells. The type I enzymes (molecular mass about 100 kDa) cut and pass single-stranded DNA, are thought to play a prominent role in transcription and are specifically inhibited by camptothecin and derivatives currently in clinical use: topotecan and irinotecan (CPT-11). All of these agents inhibit topoisomerase (topo) I by blocking the re-ligation step. The type II enzymes exist as two forms, both the products of separate genes: a (mass about 170 kDa), located on chromosome 17, and b (mass about 180 kDa), located on chromosome 3. For the type II enzymes, “classic” anthracyclines (e.g., doxorubicin and daunorubicin), the epipodophyllotoxins (etoposide and teniposide), and aminoacridines (e.g., amsacrine) all block strand re-ligation and stabilize DNA–protein complexes. In general, resistance to topoisomerase inhibitors manifests itself in two forms: decreased enzyme amount or mutation in specific domains, with the net result being a decrease in topo II activity. In some cases, the drugs that are substrates for the efflux-pump proteins, PGP (e.g., topotecan, doxorubicin, etoposide), or MRP (etoposide) elicit MDR1 or MRP expression, but in the case of the topo I inhibitors, this indirect resistance due to efflux-pump activity is probably a minor component of the phenotype.

2. **Antimetabolites**

Both the dehydrofolate reductase (DHFR) inhibitors and fluoropyrimidines target the thymidylate synthesis (TS) cycle and induce a “thymineless death” in cancer cells.

a. **Methotrexate**

Methotrexate is transported into cells by reduced folate carriers, and consequently, reduction in carrier-mediated transport frequently is seen as a basis of resistance to this drug in tumor cells. Other mechanisms of resistance to methotrexate include impaired polyglutamination and increased levels of DHFR. Methotrexate is polyglutamylated in the cell by folyl polyglutamate synthetase (FPGS), allowing its longer intracellular retention. Decreased levels of FPGS can therefore lead to methotrexate resistance. Decreased polyglutamination of methotrexate has been observed in adult patients with B-cell ALL. Increased levels of the target enzyme DHFR, often by gene amplification, is a well-documented basis of resistance to methotrexate. Mutations in the DHFR gene also have been observed to confer resistance to methotrexate by decreasing binding affinity of the drug to DHFR.

b. **5-Fluorouracil**

5-Fluorouracil (5-FU) has multiple mechanisms of action, all of which require metabolism of 5-FU to active species. Uridine, the natural nucleoside, may compete for the same metabolizing enzymes that convert 5-FU into the active moiety responsible for binding TS. Decreasing levels of the competing natural uridine nucleotides, by blocking *de novo* pyrimidine synthesis, may result in enhanced 5-FU activity.

CHEMOTHERAPEUTIC AGENTS

I. **Alkylating agents**
   A. **General mechanism of action**
      1. All these agents have in common the property of becoming strong electrophiles through the formation of carbonium ion intermediates. As a result, they form covalent linkages by alkylation of various nucleophilic moieties such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. The chemotherapeutic and cytotoxic effects, however, are directly related to the alkylation of the seven-nitrogen atom of guanine, which becomes a quaternary ammonium nitrogen, thus leading to either base pairing with thymine (substitution of AT for GC) or labilization and opening of the imidazole ring (depurination by excision of guanine residues). It appears that the selectivity of certain alkylating agents against specific malignancies may result from the capacity of normal tissues such as liver to protect themselves against cytotoxicity by further degrading the activated intermediates.
      2. The pharmacokinetics of these drugs are characterized by linear dose–response curves; more cells are killed with increasing doses (these drugs are effective only if the cells proceed through the cell cycle, but they can inflict injury at any phase of the cycle).
   B. **Nitrogen mustards**
      1. **Mechlorethamine (HN2, Mustargen)**
         a. **Indications.** Lymphomas, malignant pleural, pericardial, and peritoneal effusions.

b. **Pharmacology**
    1. **Mechanism.** Alkylation of DNA. With intracavitary use, mechlorethamine causes sclerosis and inflammatory reaction on serous membranes, leading to adherence of serosal surfaces.
    2. **Metabolism.** Native drug is highly active and is very rapidly deactivated within the blood by spontaneous hydrolysis; the elimination half-life is 15 minutes. Metabolites are excreted mostly in the urine.
c. **Toxicity.**
    1. **Dose limiting.** Myelosuppression.
    2. **Common.** Severe nausea and vomiting beginning 1 hour after administration; skin necrosis if extravasated (sodium thiosulfate may be tried); metallic taste; discoloration of the infused vein.
    3. **Occasional.** Alopecia, sterility, diarrhea, thrombophlebitis.
    4. **Rare.** Neurotoxicity (including hearing loss), angioedema, secondary neoplasms.
d. **Administration.** Patients should always be premedicated with antiemetics. The drug should be administered through the tubing of a running intravenous (i.v.) line, with extravasation precautions.
    1. **Supplied** as 10-mg vials.
    2. **Dose modification.** Hematologic; none required for hepatic or renal impairment (apparently less than .01% of the drug remains unchanged).
    3. **Dose.** From 0.2 to 0.4 mg/kg (10 mg/m^2) as a single or divided dose, monthly, or 6 mg/m^2 on day 1 and day 8 of the mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone (MOPP) regimen.

2. **Cyclophosphamide** (Cytoxan)
a. **Indications.** Used in a wide variety of conditions including ALL, AML, CML, chronic lymphocytic leukemia (CLL), and ovarian and breast cancer.
b. **Pharmacology.**
    1. **Mechanism.** Alkylation.
    2. **Metabolism.** Native drug is inactive and requires activation by liver microsomal oxidase system to form an aldehyde that decomposes in plasma and peripheral tissues to yield acrolein and an alkylating metabolite, phosphoramide mustard. The liver also metabolizes metabolites to inactive compounds. Drugs that induce microsomal enzymes (e.g., barbiturates, anticonvulsants) may enhance toxicity, whereas liver disease may decrease toxicity. Native drug is not protein bound, but active products are 50% protein bound. Active and inactive metabolites are excreted in urine.
c. **Toxicity**
    1. **Dose limiting**
        a. Myelosuppression. Leukopenia develops 8 to 14 days after administration.
        b. Effects on urinary bladder. Degradative products are responsible for hemorrhagic cystitis, which is prevented by maintaining a high urine output. Hemorrhagic cystitis is more common and can be severe when massive doses are used (e.g., for bone marrow transplantation). Bladder fibrosis with telangiectasias of the mucosa can occur (usually after long-term oral therapy) without episodes of cystitis. Bladder carcinoma has occurred.
    2. **Common.** Alopecia, stomatitis, aspermia, amenorrhea; headache (fast onset, short duration). Nausea and vomiting are common after doses of 700 mg/m^2 or more beginning 6 to 10 hours after administration.
    3. **Occasional.** Skin or fingernail hyperpigmentation; metallic taste during injection; sneezing or a cold sensation in the nose after injection; allergy, fever, dizziness, abnormal liver-function tests (LFTs).
    4. **Rare.** Transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH), especially if given with a large volume of fluid; hypothyroidism, cataracts, jaundice, cardiac necrosis, and acute myopericarditis in massive doses; secondary neoplasms (acute leukemia, bladder cancer).
d. **Administration.** The drug should be administered with a large volume of fluid in the morning or early afternoon to avoid cystitis.
    1. **Supplied** as 25-mg or 50-mg tablets; vials contain 100 to 1,000 mg.
    2. **Dose modification.** Hematologic; may be required for hepatic functional impairment.
    3. **Dose.** Cyclophosphamide is frequently used as part of combination chemotherapy regimens. Some common doses are 0.5 to 1.5 g/m^2 i.v., every 3 weeks, or 50 to 200 mg/m^2 orally for 14 days every 28 days. Bone marrow transplantation (BMT) regimens use up to 2 g/m^2 i.v., qd × 3 days.

3. **Ifosfamide (Isophosphamide, Ifex)**
a. **Indications.** A wide variety of neoplasms including lymphomas, sarcomas, head and neck carcinomas, breast carcinoma, and germ cell testicular tumors.
b. **Pharmacology**
    1. **Mechanism.** Metabolites are alkylating agents that are similar to cyclophosphamide but not cross-resistant.
    2. **Metabolism.** Like cyclophosphamide, the drug undergoes hepatic activation to an aldehyde form that decomposes in plasma and peripheral tissues to yield acrolein and its alkylating metabolite. Acrolein is highly toxic to urothelial mucosa. The chloracetaldehyde metabolite may be responsible for much of the neurotoxic effect, particularly in patients with renal dysfunction. Metabolites and unaltered drug (15% to 55%) are excreted in the urine.
c. **Toxicity**
    1. **Dose limiting.** Myelosuppression; hemorrhagic cystitis.
    2. **Common.** Alopecia, nausea, and vomiting. Neurotoxicity (especially when given in 1 day rather than 5 days and when renal dysfunction is present or when sedatives are given). Lethargy, dizziness, confusion, ataxia, and coma.
    3. **Occasional.** Salivation, stomatitis, diarrhea, constipation; urticaria, hyperpigmentation, nail ridging; abnormal LFTs, phlebitis, fever; hypotension, hypertension, hyponatremia, hypokalemia; renal tubular acidosis at higher doses.
d. **Administration.** Aggressive concomitant hydration (2 to 4 L per day) and [sodium 2-]mercaptoethanesulfonate (MESNA) are given to reduce the incidence of hemorrhagic cystitis.
    1. **Supplied** as 1- and 3-g vials; MESNA is available in 400-mg vials.
    2. **Dose modification.** Hematologic and renal dysfunction.
    3. **Dose.** From 1,000 to 1,200 mg/m^2 i.v., over 30-minute period for 5 days every 3 to 4 weeks.

        The total dose of MESNA is 60% of the ifosfamide dose. One third of the mesna dose is given just before, 4 hours after, and 8 hours after ifosfamide. The last dose of MESNA can be given orally (p.o.) to allow the patient to leave the hospital sooner. When given as a continuous infusion, MESNA and ifosfamide can be mixed in equal dosages, preceded by a MESNA loading dose of about 10% of the total ifosfamide dose.

4. **Melphalan** (Alkeran, L-sarcolysin)
a. **Indications.** Multiple myeloma, ovarian cancer, breast cancer, melanoma (the injection form is used for limb perfusion for melanoma and in BMT studies).
b. **Pharmacology**
    1. **Mechanism.** Alkylation.
    2. **Metabolism.** Acts directly. Ninety percent of the drug is bound to plasma proteins and undergoes spontaneous hydrolysis to inert products in the bloodstream. Melphalan is excreted in the urine as unchanged drug and metabolites.
c. **Toxicity**
    1. **Dose limiting.** Myelosuppression may be cumulative, and recovery may be prolonged.
    2. **Occasional.** Anorexia, nausea, vomiting, mucositis, sterility.
    3. **Rare.** Alopecia, pruritus, rash, hypersensitivity, secondary malignancies (acute leukemia), pulmonary fibrosis, vasculitis, cataracts.
d. **Administration**
    1. **Supplied** as 2-mg tablets and 50-mg vials.
    2. **Dose modification.** Hematologic; administer cautiously in patients with azotemia.
    3. **Dose.** If no myelosuppression is observed after oral dosing, poor oral absorption should be suspected. Continuous therapy: 0.10 to 0.15 mg/kg p.o., daily for 2 to 3 weeks; no therapy for 2 to 4 weeks and then 2 to 4 mg p.o. daily; or pulse therapy: 0.25 mg/kg (10 mg/m^2) p.o., daily for 4 days every 4 to 6 weeks (with prednisone for myeloma).

5. **Chlorambucil** (Leukeran)
a. **Indications.** CLL, Waldenström macroglobulinemia, indolent lymphomas, Hodgkin lymphoma, ovarian carcinoma, hairy cell leukemia, and trophoblastic tumors.
b. **Pharmacology**
    1. **Mechanism.** Alkylation.
    2. **Metabolism.** Acts directly; spontaneously hydrolyzed to inactive and active products; some also is metabolized in the liver. Native drug and metabolic products are excreted in urine.

c. **Toxicity.** Least toxic alkylating agent.
    1. **Dose limiting.** Myelosuppression (usually moderate, gradual, and reversible).
    2. **Occasional.** GI upset (minimal or absent at usual doses), mild LFT abnormalities, sterility.
    3. **Rare.** Rash, alopecia, fever; cachexia, pulmonary fibrosis, neurologic or ocular toxicity, cystitis, acute leukemia.
d. **Administration**
    1. **Supplied** as 2-mg tablets.
    2. **Dose modification.** Hematologic.
    3. **Dose.** Various dosage schedules are used alone or in combination with other antitumor agents. The prescriber may consult the medical literature as well as the manufacturer's literature in choosing a specific dosage. It is recommended that chlorambucil be discontinued if signs of pulmonary toxicity or severe skin reaction occurs.

C. **Ethylenimines**
1. **Thiotepa** (triethylenethiophosphoramide, Thio-TEPA)
    a. **Indications.** Breast, ovarian and bladder cancers; Hodgkin lymphoma; pleural and pericardial effusions.
    b. **Pharmacology**
        1. **Mechanism.** Alkylation.
        2. **Metabolism.** Rapidly decomposed in plasma and excreted largely as metabolites in the urine.
    c. **Toxicity.**
        1. **Dose limiting.** Myelosuppression.
        2. **Common.** (For intracavitary administration). Abdominal pain, hematuria, dysuria, frequency, urgency, ureteral obstruction.
        3. **Occasional.** GI upset, abnormal LFTs, rash, hives.
        4. **Rare.** Alopecia, fever, angioedema.
    d. **Administration.** It may be administered i.v., intramuscularly (i.m.), intracavitary, intrathecally, intraarterially, intravesicularly, and as an ophthalmic installation.
        1. **Supplied** as 15-mg vials.
        2. **Dose modification.** Hematologic; apnea can occur in patients receiving succinylcholine; it may increase the concentration of blood uric acid, and dosage adjustment of antigout agents may be necessary to control hyperuricemia and gout.
        3. **Dose.** i.v.: from 12 to 16 mg/m^2 every 1 to 4 weeks; intravesicular: 15 to 60 mg every week for 4 weeks.

D. **Alkyl sulfonates**
1. **Busulfan (Myleran)**
    a. **Indications.** CML (not in the blastic crisis phase), myeloproliferative disorders, BMT (high doses).
    b. **Pharmacology**
        1. **Mechanism.** Alkylation.
        2. **Metabolism.** Acts directly; catabolized in the liver to inactive products that are excreted in the urine. A clinical response usually begins within 1 to 2 weeks after initiation of therapy.
    c. **Toxicity**
        1. **Dose limiting.** Myelosuppression with slow recovery; blood counts fall for about two weeks after discontinuation of drug.
        2. **Common.** GI upset, sterility.
        3. **Occasional.** Skin hyperpigmentation, alopecia, rash, gynecomastia, cataracts, LFT abnormalities (sometimes fatal hepatovenoocclusive disease).
        4. **Rare.** Pulmonary fibrosis (“busulfan lung”), retroperitoneal fibrosis, endocardial fibrosis, Addison-like asthenia (without biochemical evidence of adrenal insufficiency), impotence, hemorrhagic cystitis, secondary neoplasms.
    d. **Administration**
        1. **Supplied** as 2-mg tablets.
        2. **Dose modification.** Hematologic.
        3. **Dose.** Usually 2 to 8 mg daily p.o., or 0.05 mg/kg/day.

E. **Nitrosoureas**
1. **Carmustine (BCNU), lomustine (CCNU)**
    a. **Indications.** Brain cancer, lymphomas, multiple myeloma (in combination with prednisone).
    b. **Pharmacology**
        1. **Mechanism.** Alkylation.
        2. **Metabolism.** Highly lipid-soluble drugs that cross the blood–brain barrier. Rapid biotransformation in the liver into active and inactive products that are excreted in the urine (some products have an enterohepatic cycle).
    c. **Toxicity**
        1. **Dose limiting.** Myelosuppression is prolonged and cumulative.
        2. **Common.** Nausea and vomiting may last 8 to 24 hours. BCNU causes local pain during injection or hypotension during a too rapid or concentrated injection.
        3. **Occasional.** Stomatitis, esophagitis, diarrhea, LFT abnormalities, alopecia, facial flushing, brown discoloration of skin, lung fibrosis with prolonged therapy and higher doses, dizziness, optic neuritis, ataxia, organic brain syndrome, renal insufficiency.
        4. **Rare.** Secondary neoplasms.
    d. **Administration**
        1. **Supplied** as 100-mg vials of BCNU; 10-, 40-, or 100-mg capsules of CCNU.
        2. **Dose modification.** Hematologic and renal.
        3. **Dose**
            a. BCNU. 150 to 200 mg/m^2 i.v. (as a single dose or divided over 2 days) every 6 to 8 weeks. Do not infuse over longer than 2 hours, owing to incompatibility of the drug with i.v. tubing. If blood and BCNU are mixed in the syringe before administration, the painfulness of injection may be decreased.
            b. **CCNU.** 100 to 130 mg/m^2 p.o., every 6 to 8 weeks.
        4. **Drug interactions.** Cimetidine decreases nitrosourea metabolism, resulting in increased hematosuppression.
2. **Streptozotocin (Zanosar)**
    a. **Indications.** Islet cell cancer of the pancreas (in combination with 5-FU), Hodgkin disease, carcinoid syndrome.
    b. **Pharmacology**
        1. **Mechanism.** Alkylating agent.
        2. **Metabolism.** Extensively metabolized in the liver and has a very short half-life. Crosses the blood–brain barrier. Excreted in urine as metabolites and unchanged drugs.
    c. **Toxicity**
        1. **Dose limiting.** Nephrotoxicity initially appears as proteinuria and progresses to glycosuria, aminoaciduria, proximal renal tubular acidosis, and renal failure if the drug is continued.
        2. **Common.** Diarrhea, abdominal cramps, LFT abnormalities.
        3. **Rare.** Central nervous system (CNS) toxicity, fever, secondary malignancies.
    d. **Administration.** Urinalysis and serum creatinine levels are monitored before each dose. Patients are routinely premedicated with antiemetics. The dose is administered slowly over a 30- to 60-minute period to avoid local pain.
        1. **Supplied** as 1-g vials.
        2. **Dose modification.** Proteinuria or elevated serum creatinine levels contraindicate use of the drug until abnormalities resolved.
        3. **Dose**
            a. From 1.0 to 1.5 g/m^2 i.v. weekly, or
            b. From 0.5 to 1 g/m^2 i.v. daily for 5 days every 3 to 4 weeks.

F. **Triazenes**
1. **Dacarbazine (DTIC)**
    a. **Indications.** Hodgkin disease, malignant melanoma, sarcomas.
    b. **Pharmacology**
        1. **Mechanisms.** Methylates the O^6 position of guanine.
        2. **Metabolism.** Native drug inactive; requires activation by oxidative N-methylation by liver microsomal oxidases. Excreted in urine predominantly; minor hepatobiliary and pulmonary excretion.
    c. **Toxicity**

1. **Dose limiting.** Myelosuppression.
2. **Common.** Nausea and vomiting often severe. Pain along the injection site, local irritant if injected subcutaneously (s.c.); not a vesicant.
3. **Occasional.** Alopecia, facial flushing, photosensitivity, abnormal LFTs, flu-like syndrome developing 1 week after treatment and lasting 1 to 3 weeks.
4. **Rare.** Diarrhea, stomatitis, cerebral dysfunction, hepatic vein thrombosis, azotemia, anaphylaxis.

d. **Administration.** Withdrawing blood into the drug-filled syringe before injecting it reduces the pain of injection.
1. **Supplied** as 100-, 200-, and 500-mg vials. Protect from sunlight.
2. **Dose modification.** Necessary for patients with impaired bone marrow, hepatic, or renal function.
3. **Dose**
a. Either 750 mg/m^2 i.v. as a single injection every 28 days, or
b. From 50 to 250 mg/m^2 i.v., daily for 5 days every 21 to 28 days or
c. From 75 to 125 mg/m^2 i.v., daily for 10 days every 28 days.

II. **Antimetabolites**

A. **General mechanism of action**
1. Their major effect is interfering with the building blocks of DNA synthesis. Their activity is therefore greatest in the S phase of the cell cycle.
2. The pharmacokinetics of these drugs are characterized by nonlinear dose–response curves; after a certain dose, no more are killed with increasing doses (5-FU and methotrexate are exceptions).

B. **Folic acid analogues**
1. **Methotrexate** (MTX, Amethopterin)
a. **Indications.**

Carcinomas of head and neck, breast and lung; leukemias, acute and meningeal.

b. **Pharmacology**
1. **Mechanism.** MTX, the 4-amino, 10-methyl analogue of folic acid, is a tight-binding inhibitor of DHFR, a critical enzyme in maintaining the intracellular folate pool in its reduced form. Tetrahydrofolates serve as one-carbon carriers for the *de novo* synthesis of thymidine 5¢-monophosphate (thymidylate, dTMP) and purine nucleotides, as well as certain amino acids. TS catalyzes the formation of dTMP from 2¢-deoxyuridine-5¢-monophosphate (deoxyuridylate, dUMP). This reaction uses 5,10-methylenetetrahydrofolate as a methyl donor and results in the oxidation of the reduced folate to dihydrofolate. The activity of the TS reaction thus creates the requirement for DHFR to maintain the intracellular reduced folate pool. Inhibition of DHFR results in accumulation of oxidized folates at the expense of reduced folates, owing to the continued synthetic function of TS. Additional metabolic effects of MTX result from its transformation to polyglutamate forms (80% of intracellular MTX), which are potent direct inhibitors of several folate-dependent enzymes including DHFR and TS. Polyglutamation occurs in tumor cells and to a lesser extent in normal tissues. Hence, metabolic inhibition caused by MTX depends not only on partial depletion of reduced folates, but also on direct inhibition of folate-dependent enzymes by the polyglutamates of both MTX and dihydrofolate that accumulate after inhibition of DHFR. The cytotoxic action of methotrexate has been referred to as “self-limiting,” because MTX also is capable of inhibiting RNA and protein synthesis and thus slowing the entry of cells into S phase.
2. **Metabolism.** MTX is readily absorbed from the GI tract at doses less than 25 mg/m^2, but larger doses are absorbed incompletely and are routinely administered intravenously. It enters cells by the same active transport mechanisms used by physiologic folates. Approximately 35% of MTX is bound to plasma proteins and may be displaced from plasma albumin by a number of drugs, including sulfonamides, salicylates, tetracycline, chloramphenicol, and phenytoin. It is metabolized minimally, and once absorbed, from 50% of a lower dose to 90% of a higher dose, is excreted unchanged in the urine within 48 hours. Reduced folates such as 5-formyltetrahydrofolate (leucovorin; LV) after high-dose MTX therapy can prevent toxicity to the BM and GI epithelium. LV is converted intracellularly to reduced folates that compete with the polyglutamates of both MTX and dihydrofolate to overcome the inhibition of TS and *de novo* purine synthesis. In addition, MTX and reduced folates compete for transport into cells and for subsequent intracellular polyglutamation. The portion of each dose of MTX that normally is excreted rapidly gains access to the urine by a combination of glomerular filtration and active tubular secretion. Therefore, the concurrent use of drugs that reduce renal blood flow (e.g., nonsteroidal antiinflammatory drugs [NSAIDs]), that are nephrotoxic (e.g., cisplatin), or that are weak organic acids (e.g., acetylsalicylic acid [ASA] or piperacillin) can delay drug excretion and lead to severe myelosuppression. MTX is entrapped in cells as polyglutamates for long periods (e.g., for weeks) in the kidneys and for months in the liver. Third body spaces such as pleural or peritoneal cavities, when expanded, can act as a site of storage and release MTX with resultant prolonged elevation of plasma concentrations and more severe toxicity.

c. **Toxicity.** LV can reverse the immediate cytotoxic effects of MTX; generally, 1 mg of LV is given for each 1 mg of MTX.
1. **Dose limiting.** Myelosuppression, stomatitis (may be preventable by sucking ice during the injection), renal dysfunction (especially in patients with dehydration or preexisting renal dysfunction).
2. **High-dose regimens.** Nausea, vomiting, renal tubular necrosis, cortical blindness.
3. **Previously irradiated areas.** Skin erythema, pulmonary fibrosis, transverse myelitis, cerebritis.
4. **Prolonged therapy.** Liver cirrhosis (subclinical and reversible hepatic dysfunction occurs with short-term intermittent therapy); osteoporosis (in children).
5. **Neurotoxicity**

C. **Pyrimidine analogues**
1. **Fluorouracil (5-FU)**
a. **Indications.** Carcinomas of the breast, stomach, pancreas, colon, and rectum.
b. **Pharmacology**
1. **Mechanism of action.** 5-FU undergoes conversion to 5-FU-5¢-monophosphate (5-F-UMP or 5-F-uridylate) either by reacting directly with 5¢-phosphoribosyl-1-pyrophosphate (PRPP) in the salvage pathway for purines or by first being converted to 5-FU and then monophosphorylated in the salvage pathway for pyrimidines (5-F-UMP may be phosphorylated to the nucleoside triphosphate 5-F-UTP and then incorporated into RNA, where it may have an inhibitory effect). Subsequently, 5-F-UMP is phosphorylated to the nucleoside diphosphate 5-F-UDP, which is then reduced by nucleoside diphosphate (NDP) reductase to the deoxynucleoside diphosphate 5-F-dUMP, which is eventually dephosphorylated to the deoxynucleoside monophosphate 5-F-dUMP. The latter (i.e., 5-F-dUMP), is the critical form of the drug that reacts with TS. The fluorine atom blocks the transfer of a methylene group to the pyrimidine ring from N^5,N^{10}-methylenetetrahydrofolate. LV enhances 5-FU cytotoxicity by stabilizing the covalent ternary complex of TS and 5-F-dUMP. The mechanism of “thymineless death” is purportedly secondary to dUMP accumulation and eventually formation of dUTP, which can be used by DNA polymerase with the same efficiency as for dTTP. Uracil in DNA is excised rapidly by uracil glycosylase, leaving an apyrimidinic site. During repair of apyrimidinic sites, in the presence of unbalanced dUTP/dTTP ratios, uracil is likely to be reinserted, causing a futile cycle of excision, repair, and reinsertion, leading to DNA strand breakage and ultimately cell death.
2. **Metabolism.** 5-FU is administered parenterally, because absorption after ingestion is unpredictable and incomplete. 5-FU is inactivated by reduction of the pyrimidine ring by dihydrouracil dehydrogenase, which is found in the liver, intestinal mucosa, and other tissues. The product of this reaction, 5-F-5,6-dihydrouracil is ultimately degraded to a-F-b-alanine plus CO_2 in the pyrimidine degradation pathway. The primary route of elimination of this drug is therefore respiratory (as CO_2). Dosage does not have to be modified in patients with hepatic dysfunction, presumably because of degradation of the drug at extrahepatic sites. 5-FU rapidly enters all tissues, including spinal fluid and malignant effusions.

c. **Toxicity** is more common in patients with inherited deficiency of dihydrouracil dehydrogenase.
1. **Dose limiting.** Myelosuppression (more common with rapid injection), mucositis, and diarrhea (more common with 5-day infusion; diarrhea may be cholera-like with high doses of LV).

2. **Cytarabine (Ara-C)**
a. **Indications.** Leukemia: AML, ALL, CML (blast phase), meningeal (prevention and treatment; intrathecal administration); lymphomas; carcinomatous meningitis.
b. **Pharmacology**
1. **Mechanism of action.** Cytarabine (1-b-D-arabinofuranosylcytosine) is an analog of 2¢-deoxycytidine with the 2¢-hydroxyl in position *trans* to the 3¢-hydroxyl of the sugar. The 2¢-hydroxyl causes steric hindrance to the rotation of the pyrimidine base around the nucleosidic bond, and thus the bases of the polyarabinonucleotides cannot stack normally. As with most purine and pyrimidine antimetabolites, Ara-C must be “activated” to the 5¢-monophosphate nucleotide (AraCMP), in this case catalyzed by deoxycytidine kinase. AraCMP can then react with appropriate nucleotide kinases to form the diphosphate and triphosphate nuclotides (AraCDP and AraCTP). Accumulation of AraCTP causes potent inhibition of DNA synthesis in many cells. The incorporation of about five molecules of AraC per 10^4 bases in DNA decreases cellular clonogenicity by about 50%. Thus inhibition of DNA synthesis by AraC without concomitant inhibition of protein and RNA syntheses can result in “unbalanced growth” (i.e., marked increases in cellular volume and in cellular death).

2. **Metabolism.** AraC and Ara-CMP are converted to nontoxic metabolites AraU and Ara-UMP by deoxycytidine deaminase and deoxycytidylate deaminase, respectively, whereas other catabolic enzymes like 5¢-nucleotidase affect Ara-C metabolite levels. When compared with other cell types, lymphocytes have high levels of deoxycytidine kinase, for which the purine deoxyribonucleosides also are substrates, and low levels of 5¢-nucleotidase. The appreciation of these pathways has prompted the development of three antilymphocyte agents that are all purine analogues: 2¢-*c*hloro*d*eoxy*a*denosine (2CDA; cladribine), 2¢-*flu*oroa*d*enine-*ara*binoside –5¢-monophosphate (fludarabine) and 2¢-deoxycoformycin (pentostatin).

c. **Toxicity**

1. **Dose limiting.** Myelosuppression (nadir is expected in 5 to 7 days, and recovery, in 2 to 3 weeks).

3. **Gemcitabine (Gemzar)**

a. **Indications.** Pancreatic adenocarcinoma and non–small cell lung cancer and carcinoma of the urinary bladder.

b. **Pharmacology**

1. **Mechanism.** Gemcitabine (2¢,2¢-difluorodeoxycytidine; dFdC) is a 2¢-deoxycytidine in which the deoxycytidine moiety contains two fluorine atoms at the 2¢-position. It is metabolized by the same salvage enzyme pathways as AraC (i.e. is phosphorylated by deoxycytidine kinase to dFdCMP and subsequently by mono- and diphosphate kinases to dFCDP and dFCTP, respectively). dFdCDP is an inhibitor of ribonucleotide reductase and thus decreases the pools of deoxyadenosine triphosphate (dATP), deoxycytidine triphosphate (dCTP), deoxyguanosine triphosphate (dGTP), and deoxythymidine triphosphate (dTTP). Depletion of dCTP as a consequence of ribonucleotide reductase inhibition leads to decreased feedback inhibition of deoxycytidine kinase and increased phosphorylation of dFdC. dFdCTP competes with dCTP for incorporation into DNA by DNA polymerase, and depletion of dCTP favors incorporation dFdCTP. DNA polymerase e is unable to remove the incorporated dFdCTP and repair the DNA strands. Thus inhibition of DNA synthesis may result from both perturbations of deoxyribonucleotide pools and inhibition of DNA synthesis.
2. **Metabolism.** dFdC undergoes deamination to an inactive uracil metabolite that is excreted through the kidneys. As is true for many other antimetabolites, the volume of distribution of dFdC is significantly affected by the duration of its infusion.

c. **Toxicity**

1. **Dose limiting.** Myelosuppression.
2. **Common.** Edema/peripheral edema; fever, usually in conjunction with other flu-like symptoms; proteinuria (cloudy urine); skin rash with or without itching; transaminasemia, nausea, vomiting.
3. **Occasional.** Bronchospasm, cardiovascular effects, and cerebrovascular accident.
4. **Rare.** Alopecia (mild); constipation or diarrhea; stomatitis.

d. **Administration**

1. **Supplied** as 200-mg or 1-g single-dose vial, respectively.
2. **Dose modification.** If ANC and PLT are less than 500×10^6/Lt and less than $50{,}000 \times 10^6$/Lt, respectively, then gemcitabine should be withheld until cell counts recover.
3. **Dose.** The usual dose in pancreatic cancer is 1,000 mg/m^2 as an i.v. bolus weekly for up to 7 weeks, followed by a week of rest before another cycle is begun.

D. **Purine analogues**

1. **6-Thiopurines**

a. **Indications.** Acute leukemia.

b. **Pharmacology**

1. **Mechanism.** 6-Mercaptopurine (6-MP) and 6-thioguanine (6-TG) are together called the 6-thiopurine analogues because they have a single substitution of a thiol group in place of the keto group on carbon 6 of the purine ring. 6-MP and 6-TG are structural analogues of hypoxanthine and guanine, respectively. Both of them are excellent substrates for hypoxanthine-guanine phosphoribosyltransferase [HGPRT; salvage pathway for the purine nucleotides inosine monophosphate and guanosine monophosphate (GMP)] and are converted to the ribonucleotides 6-thioguanosine-5¢-monophosphate (6-thioGMP) and 6-thioinosine-5¢-monophosphate (T-IMP). Because T-IMP is a poor substrate for guanyl kinase, the enzyme that converts GMP to guanosine diphosphate (GDP), T-IMP accumulates intracellularly. The accumulation of T-IMP may inhibit several vital metabolic reactions in the *de novo* pathway of purine synthesis (e.g., the oxidation of inosinate [IMP] to xanthylate [XMP]). Conversely, 6-thioGMP is slowly converted by guanyl kinase to 6-thioGDP and 6-thio-guanosine triphosphate (thioGTP), which is incorporated into DNA, causing DNA synthesis inhibition. Both 6-thioGMP and I-IMP can cause “pseudofeedback inhibition” of the first committed step in the *de novo* purine biosynthesis pathway. Inhibitors of *de novo* purine biosynthesis, such as MTX, are synergistic with 6-thiopurines because the MTX-induced block expands the PPRP required for 6-thiopurine activation in the purine salvage pathway.
2. **Metabolism.** They are degraded largely by xanthine oxidase in the liver to 6-thiouric acid, an inactive metabolite. Allopurinol, a xanthine oxidase inhibitor, increases the toxicity without apparent improvement in the therapeutic index. The polymorphic enzyme thiopurine methyltransferase (TPMT) plays a major role in 6-MP inactivation. Approximately 90% of patients have “high” TPMT activity, 10% are intermediate, and one in 300 is deficient (and at risk of severe toxicity with normal doses).

c. **Toxicity**

1. **Dose limiting.** Myelosuppression and GI toxicity (6-TG causes fewer GI side effects).
2. **Common.** Reversible cholestasis.
3. **Rare.** Stomatitis, dermatitis, fever, hematuria, Budd–Chiari-like syndrome, hepatic necrosis.

d. **Administration**

1. **Supplied** as 50-mg tablets (6-MP) and 40-mg tablets (6-TG).
2. **Dose** is reduced with impaired liver function and coadministration of allopurinol or hepatotoxic drugs.
3. **Dose**
   a. 6-MP: From 70 to 100 mg/m^2 p.o., daily until patient responds or toxic effects are seen; then adjust for maintenance therapy.
   b. 6-TG: Use 100 mg/m^2 p.o., b.i.d. for 5 days or 2 to 3 mg/kg p.o., daily until toxic effects are seen.

2. **Pentostatin (2-deoxycoformycin, dCF)**

a. **Indications.** Hairy cell leukemia; possibly cutaneous T-cell lymphoma.

b. **Pharmacology**

1. **Mechanism.** As a natural product derived from *Streptomyces,* pentostatin resembles structurally the transition state of adenosine as it is hydrolyzed by adenosine deaminase (ADA) in the purine nucleotides degradation pathway. As a result, it is a potent inhibitor of ADA, the greatest activity of which is found in cells of the lymphoid system. T cells have higher ADA activity than do B cells, and T-cell malignancies have higher activity than B-cell malignancies. The cytotoxicity that results from prevention of catabolism of adenosine or deoxyadenosine is thought to be due to elevated intracellular levels of dATP, which can block DNA synthesis through inhibition of ribonucleotide reductase.
2. **Metabolism.** The majority of dCF is excreted unchanged in the urine.

c. **Toxicity**

1. **Dose limiting.** Myelosuppression.
2. **Common.** Immunosuppression; mild nausea and vomiting, diarrhea, altered taste, fatigue, fever.
3. **Occasional.** Chills, myalgia, arthralgia; abnormal LFTs, keratoconjunctivitis, photophobia, renal failure.
4. **Rare.** Hepatitis; pulmonary infiltrates and insufficiency.

d. **Administration**

1. **Supplied** as 10-mg vials.
2. **Dose modification.** Reduce doses for renal impairment.
3. **Dose.** A 4 mg/m^2 i.v. infusion over a 20-minute period with 1 or 2 L of hydration every 2 weeks.

3. **Cladribine (2-chloro-2-deoxyadenosine; 2-CdA)**

a. **Indications.** Hairy cell leukemia, indolent lymphomas, chronic lymphocytic leukemia, mycosis fungoides.

b. **Pharmacology**

1. **Mechanism.** Antimetabolite. It blocks adenosine deaminase and inhibits RNA synthesis.
2. **Metabolism.** Plasma half-life is 7 hours.

c. **Toxicity**

1. **Dose limiting.** Myelosuppression.
2. **Common.** Nausea, skin reactions at injection site, fever, chills.
3. **Occasional.** Headache, fatigue.
4. **Rare.** Neurotoxicity, pancreatitis.

d. **Administration**

1. **Supplied** as 20-mg vials.
2. **Dose modification.** Hematologic.

3. **Dose.** Either 0.10 mg/kg/day i.v. for 7 days or 0.14 mg/kg/day i.v. over a 2-hour period for 5 days.

4. **Fludarabine (2-fluoroadenine arabinoside; Fludara)**
   a. **Indications.** Chronic lymphocytic leukemia and low-grade lymphoma.
   b. **Pharmacology**
      1. **Mechanism.** Its active metabolite, 2-fluoro-ara-A, appears to inhibit DNA primase, DNA polymerase a, and ribonucleotide reductase.
      2. **Metabolism.** The plasma half-life is 9 to 10 hours. Metabolites are excreted primarily in the urine.
   c. **Toxicity**
      1. **Dose limiting.** Myelosuppression.
      2. **Common.** Nausea and vomiting.
      3. **Occasional.** Alopecia, tumor lysis syndrome.
      4. **Rare.** Stomatitis, diarrhea, dermatitis, neurotoxicity, and chest pain.
   d. **Administration**
      1. **Supplied** as 50-mg vials.
      2. **Dose modification.** Decrease dosage by 30% for patients with creatinine clearance of less than 70 mL/minute.
      3. **Dose.** Use 25 mg/m^2 i.v. over a 30-minute period daily for 5 consecutive days every 4 weeks.

III. **Natural products**

A. **Vinca alkaloids**

1. **General mechanism of action**
   a. They bind to tubulin and block its ability to polymerize into microtubules. Through disruption of the microtubules of the mitotic apparatus, cell division is arrested in metaphase. The inability to segregate chromosomes correctly during mitosis presumably leads to cell death. In addition to the formation of mitotic spindles, microtubules are involved in many other cellular functions (e.g., axonal transport of subcellular organelles), which explains some of the other effects of vinca alkaloids (colchicine, taxanes, and podophyllotoxin also bind to tubulin but apparently at a different site from that bound by the vinca alkaloids).
   b. The pharmacokinetics of these drugs are characterized by nonlinear dose–response curves (phase-specific drugs; if the drug concentration is maintained over a period of time, more cells enter the specific phase of the cell cycle and are killed).

2. **Vinblastine (VBL)**
   a. **Indications.** Lymphomas, testicular carcinomas, a variety of other tumors, histiocytosis X.
   b. **Pharmacology**
      1. **Mechanism.** It arrests cells at G_2–M interface.
      2. **Metabolism.** Highly bound to plasma proteins and to formed blood elements, especially platelets. Metabolized by the liver. Excreted predominantly in bile.
   c. **Toxicity**
      1. **Dose limiting.** Neutropenia.
      2. **Common.** Cramps or severe pain in jaw, pharynx, back, or limbs after injection; local vesicant if extravasated.
      3. **Occasional.** Thrombocytopenia, anemia.
      4. **Rare.** Nausea, vomiting, diarrhea, mucositis, abdominal cramps, acute interstitial pneumonitis, especially when administered with mitomycin C; ischemic cardiotoxicity.
   d. **Administration**
      1. **Supplied** as 10-mg vials.
      2. **Dose modification.** Decrease dose by 50% for patients with serum bilirubin greater than 3 mg/dL.
      3. **Dose.** Use 5 mg/m^2 i.v. every 1 or 2 weeks; higher doses at 3-week intervals are used for testicular carcinomas. As a continuous infusion, 1.7 to 2 mg/m^2/day is given over a 96-hour period.

3. **Vincristine (VCR)**
   a. **Indications.** A wide variety of malignancies.
   b. **Pharmacology.** Same as VBL.
   c. **Toxicity**
      1. A dose-dependent peripheral neuropathy universally develops. It usually reverses within several months. Jaw, throat, or anterior thigh pain occurring within hours of injection disappears within days and usually does not recur.
         a. **Dose limiting.** Severe paresthesias, ataxia, foot drop (slapping gait), muscle wasting, cranial nerve palsies, paralytic ileus, obstipation, abdominal pain, optic atrophy, cortical blindness, seizures.
      2. **Common.** Tissue necrosis if extravasated alopecia.
      3. **Occasional.** Mild leukopenia, SIADH.
      4. **Rare.** Nausea, vomiting, pancreatitis, fever.
   d. **Administration.** Patients receiving VCR should be given bulk laxatives routinely.
      1. **Supplied** as 1-, 2-, and 5-mg vials.
      2. **Dose modification.** Same as for VBL.
      3. **Dose.** From 1.0 to 1.4 mg/m^2 i.v. every 1 to 4 weeks (cap dose at 2 mg); continuous-infusion regimens involve 0.5 mg/m^2/day for 4 days.

4. **Vinorelbine (VRL; Navelbine)**
   a. **Indications.** Non–small cell lung cancer; metastatic breast cancer.
   b. **Pharmacology.** Same as for VBL.
   c. **Toxicity**
      1. **Dose limiting.** Myelosuppression.
      2. **Occasional.** Chest pain, mild to moderate peripheral neuropathy, pulmonary reactions, stomatitis.
      3. **Rare.** Hemorrhagic cystitis, skin rash, anorexia, constipation.
   d. **Administration**
      1. **Supplied** as 1- and 5-mL vials.
      2. **Dose modification.** According to hematologic toxicity or hepatic insufficiency.
      3. **Dose.** Use 30 mg/m^2 once a week as a single agent. The same dose is used in combination therapy with cisplatin.

B. **Epipodophyllotoxins**

1. **General mechanism of action**
   a. Unlike podophyllotoxin, these agents do not cause mitotic arrest by binding to microtubules. Rather, at low concentrations, they block cells at S–G_2 interface of the cell cycle, and at higher concentrations, they cause G_2 arrest. They interact with the topoisomerase II–DNA complex (topoisomerase II or topo II is a chromatin scaffold protein that projects from the scaffold during replication and causes DNA double-strand breaks, moving the cleaved ends apart). This interaction prevents the resealing of the topo II–mediated DNA double-strand breaks. These breaks result in cell death only if DNA synthesis is ongoing.

2. **Etoposide (VP-16)**
   a. **Indications.** Testicular carcinoma, lung cancer, lymphoma, and a variety of other malignancies.
   b. **Pharmacology**
      1. **Mechanism.** As described earlier.
      2. **Metabolism.** Nonlinear absorption is observed at oral doses greater than 100 mg; highly bound (approximately 95%) to plasma proteins (primarily albumin); metabolized by cytochrome P450s (CYP3A4) in the liver. Excretion in urine (40%) as intact and degraded drug; excretion of the remaining 60% is uncertain; biliary excretion accounts for only a small proportion.
   c. **Toxicity**
      1. **Dose limiting.** Neutropenia.
      2. **Common.** Nausea and vomiting (with oral dosing, but uncommon with i.v. dosing); alopecia; hypotension if rapidly infused.
      3. **Occasional.** Anemia, thrombocytopenia, pain at injection site, phlebitis, abnormal LFTs, peripheral neuropathy.
      4. **Rare.** Stomatitis, dysphagia, diarrhea, constipation, parotitis, rash, radiation-recall reaction, hyperpigmentation, anaphylaxis, somnolence, vertigo, and transient cortical blindness.
   d. **Administration**
      1. **Supplied** as 50-mg capsules and 100-mg vials.
      2. **Dose modification.** Administer slowly over at least 30 minutes when given i.v. Reduce doses by 25% to 50% for creatinine clearance of less than 50 mL/minute and less than 10 mL/minute, respectively.
      3. **Dose**

a. Use 50 mg/m^2 p.o., daily for 21 days, or 50 to 120 mg/m^2 i.v., daily for 3 to 5 days.

3. **Teniposide (VM-26)**
   a. **Indications.** Acute lymphoblastic leukemia.
   b. **Pharmacology**
      1. **Mechanism.** As described earlier.
      2. **Metabolism.** Virtually all (more than 97%) of the drug is bound to protein (primarily albumin). Systemic metabolism is significant, but metabolites have not been identified. Renal excretion is only a small fraction of its clearance (less than 10%).
   c. **Toxicity**
      1. **Dose limiting.** Neutropenia.
      2. **Common.** Thrombocytopenia, hypotension with too-rapid infusion.
      3. **Occasional.** Nausea and vomiting, alopecia, abnormal LFTs, phlebitis.
      4. **Rare.** Diarrhea, stomatitis; anaphylaxis, azotemia, fever; paresthesias, seizures.
   d. **Administration.** The drug is administered by slow i.v. infusion over at least a 30-minute period.
      1. **Supplied** as 50-mg vials.
      2. **Dose.** From 20 to 60 mg/m^2/day for 5 days or 100 mg/m^2 once or twice weekly.

C. **Enzymes**

1. **L-Asparaginase (Elspar; Kidrolase)**
   a. **Indications.** ALL.
   b. **Pharmacology**
      1. **Mechanism.** Most normal tissues synthesize L-asparagine in amounts sufficient for protein synthesis. Certain neoplastic tissues, including ALL cells, require an exogenous source of this amino acid. L-Asparaginase deprives these cells of the asparagine available from extracellular fluid by catalyzing the hydrolysis of L-asparagine to aspartic acid and ammonia. There may be striking synergistic effects when L-asparaginase is used in combination with drugs such as MTX or cytarabine. The sequence of the administration is crucial (e.g., synergistic cytotoxicity is seen when MTX is administered before L-asparaginase). It appears to be cell-cycle specific for the G_1 phase of cell division.
      2. **Metabolism.** Unknown. Only trace amounts are recovered in the urine.
   c. **Toxicity**
      1. **Dose limiting.** Allergic reactions (they usually develop within 1 hour of dosing and are most likely to occur after several doses are given, particularly if the last dose was given more than 1 month previously and if the drug is administered i.v. rather than i.m.) Patients who respond to *Escherichia coli* asparaginase but develop allergic reactions may be treated relatively safely with another source of the enzyme.
      2. **Common**
         a. **Encephalopathy** in 25% to 50% of patients. Lethargy, somnolence, and confusion tend to occur within the first few days of therapy reverse after completion of therapy and are rarely a cause for discontinuing treatment. Hemorrhagic and thrombotic CNS events occur later and are associated with the induced imbalances in the coagulation and fibrinolytic systems.
         b. **Nausea, anorexia, and vomiting (60%).**
         c. **Hepatitis** (abnormal LFTs in more than 50% of treated patients but rarely severe); pancreatitis (10%).
         d. **Coagulation defects** associated with decreased synthesis of clotting factors especially fibrinogen and antithrombin III.
         e. **Prerenal azotemia (65%).**
         f. **Hyperglycemia.**
      3. **Rare.** Myelosuppression, diarrhea, severe renal failure, hyperthermia.
   d. **Administration.** Administer a small (two-unit) intradermal test dose to check for hypersensitivity. Epinephrine (1 mg, 1:1,000), hydrocortisone (100 mg), and diphenhydramine (50 mg) should be readily available to treat anaphylaxis to each time the drug is given.
      1. **Supplied** as 10,000-IU vials.
      2. **Dose modification.** For hepatic dysfunction or pancreatitis.
      3. **Dose.** Usually administered in combination with VCR and prednisone at a dose of 6,000 IU/m^2 i.m. 3 times weekly for nine doses.

D. **Antibiotics: general mechanism of action**

Antitumor antibiotics generally are drugs derived from microorganisms. They usually are cell cycle–nonspecific agents that are especially useful in slow-growing tumors with low growth fractions.

1. **Actinomycin D** (Dactinomycin)
   a. **Indications.**

      Ewing sarcoma, testicular carcinoma, Wilms tumor, rhabdomyosarcoma, and trophoblastic tumors.

   b. **Pharmacology**
      1. **Mechanism.** It intercalates between base pairs and inhibits DNA-dependent RNA synthesis.
      2. **Metabolism.** Unknown; extensively bound to tissues resulting in long (36 hours) half-life in plasma and tissue. Excreted in bile and urine as unchanged drug.
   b. **Toxicity**
      1. **Dose limiting.** Myelosuppression.
      2. **Common.** Nausea and vomiting, alopecia, acne, erythema, desquamation, hyperpigmentation, radiation-recall reaction (i.e., darkening of skin if patient has received previous radiation therapy). It is a vesicant that can cause necrosis if extravasated.
      3. **Occasional.** Stomatitis, cheilitis, glossitis, proctitis, diarrhea; vitamin K antagonism.
      4. **Rare.** Anaphylaxis; hepatotoxicity including ascites, hepatomegaly, hepatitis, and LFT abnormalities; hyperuricemia (joint pain; lower back or side pain); hypocalcemia; lethargy.
   c. **Administration.** Premedication with antiemetics and extravasation precautions are of utmost importance.
      1. **Supplied** as 0.5-mg vials.
      2. **Dose modification.** Reduce by 50% in the presence of renal or hepatic functional impairment.
      3. **Dose**
         a. From 0.25 to 0.60 mg/m^2 i.v. daily for 5 days every 3 to 4 weeks or
         b. From 1 to 2 mg/m^2 i.v. single dose every 3 to 4 weeks.
2. **Daunorubicin**
   a. **Indications.** ALL or AML.
   b. **Pharmacology**
      1. **Mechanism.** Daunorubicin is an anthracycline glycoside. It is most active in the S phase of cell division, but as is the case usually with the antitumor antibiotics, is not cell cycle–phase specific. Its exact mechanism of antineoplastic action is unknown but may involve binding to DNA by intercalation between base pairs and inhibition of DNA and RNA synthesis by template disordering and steric obstruction.
      2. **Metabolism.** It is rapidly biotransformed in the liver within 1 hour to produce an active metabolite, daunorubicinol. Further metabolism is hepatic, and an estimated 40% is eliminated by biliary excretion.
   c. **Toxicity**
      1. **Dose limiting.**
         a. **Myelosuppression,** especially leukopenia that may be asymptomatic or present as an infection (fever or chills, cough or hoarseness, painful or difficult urination).
         b. **Esophagitis or stomatitis** (sores in mouth and on lips).
         c. **Cardiotoxicity** in the form of congestive heart failure (irregular heart beat; shortness of breath; swelling of feet and lower legs). Incidence of cardiotoxicity is more frequent in adults receiving a total cumulative dosage of more than 550 mg/m^2 of body surface (450 mg/m^2 in patients who have received previous chest irradiation), in the elderly, and in patients with a history of cardiac disease or mediastinal radiation. It usually appears within 1 to 6 months after initiation of therapy. It may develop suddenly and may not be detected by routine electrocardiogram (ECG). It may be irreversible and fatal, but responds to treatment if detected early.
      2. **Common**
         a. **Hyperuricemia or uric acid nephropathy** (joint pain, lower back or side pain) occurs most commonly during initial treatment of patients with leukemia as a result of rapid cell breakdown, which leads to elevated serum uric acid concentrations.

b. **Nausea and vomiting.**
c. **Loss of hair and reddish urine** (reddish urine usually clears within 48 hours).

3. **Occasional**
a. **Allergic reaction** (skin rash or itching).
b. **Cardiotoxicity** in the form of pericarditis–myocarditis.

4. **Rare.** Darkening or redness of skin if patient has received previous radiation therapy; diarrhea.

d. **Administration.** It is recommended that the patient be hospitalized at least during initial treatment. Care must be taken to avoid extravasation during i.v. administration. Facial flushing or erythematous streaking along the vein indicates overly rapid injection.

1. **Supplied** as 20-mg vials.
2. **Dose modification.** Up to a total lifetime dose of 550 mg/m^2 of body surface, 450 mg/m^2 in body surface in patients who have received previous chest irradiation (to reduce risk of cardiotoxicity).
3. **Dose**
a. **ALL:** 45 mg/m^2 of body surface on days 1, 2, and 3 of a 32-day course in combination with VCR, prednisone, and asparaginase.
b. **AML:** 45 mg/m^2 of body surface on days 1, 2, and 3 of the first course and days 1 and 2 of the second course in combination with cytarabine.

3. **Doxorubicin (Adriamycin)**
a. **Indications.** ALL, AML, breast cancer, gastric cancer, small-cell lung cancer, epithelial ovarian cancer, thyroid cancer, neuroblastoma, Wilms tumor, and bladder carcinoma.
b. **Pharmacology**
1. **Mechanism.** Doxorubicin is an anthracycline glycoside. It is cell-cycle specific for the S phase of cell division. Its mechanism of action may involve binding to DNA by intracalation between base pairs and inhibition of DNA and RNA synthesis by template disordering and steric obstruction. Other possible mechanisms of action may include binding to cell-membrane lipids and interacting with topo II to form DNA-cleavable complexes.
2. **Metabolism.** It is biotransformed rapidly within 1 hour in the liver to produce an active metabolite, doxorubicinol. The enzymatic reduction of doxorubicin by oxidases, reductases, and dehydrogenases results in the production of free radicals, which may contribute to cardiotoxicity.
3. **Excretion.** An estimated 40% of the drug is excreted unchanged in the bile over a 5-day period. An estimated 5% to 12% of doxorubicin and metabolites appear in urine for 5 days, imparting a red tinge to the urine.

c. **Toxicity**
1. **Dose limiting**
a. **Myelosuppression,** particularly leukopenia, which reaches nadir in 10 to 15 days.
b. **Cardiomyopathy** with congestive heart failure that may be refractory is more frequent in patients receiving total dosages of more than 550 mg/$m^2$of body surface area (400 mg/m^2 of body surface area in patients who have previously received chest irradiation or medication increasing cardiotoxicity) and in patients with a history of cardiac disease or mediastinal radiation. Cardiotoxicity usually appears within 1 to 6 months after initiation of therapy. Cardiomyopathy has been reported to be associated with persistent voltage reduction in the QRS wave, systolic-interval prolongation, and reduction of ejection fraction. It may develop suddenly and may not be detected on routine ECG. It may be irreversible and fatal, but responds to treatment if detected early. Monitoring the left ventricular ejection fraction (LVEF) with radionuclide techniques is mandatory, particularly when the cumulative dose exceeds 300 mg/m^2 and when it exceeds 450 mg/m^2. Current data suggest that once the maximal cumulative dose has been reached, the drug can never be safely resumed. The drug should be discontinued if any of the following occurs: congestive heart failure, ECG changes, decreased LVEF to less than 50% or at least by 10%.
2. **Common**
a. **Alopecia** (in nearly 100% of patients when administered as a bolus every 3 to 4 weeks, but minimal when the dose is divided and given weekly), nausea and vomiting (mild to severe), stomatitis.
b. **Extravasation** of the drug results in severe ulceration and necrosis.
c. **Previously irradiated skin sites** may become erythematous and desquamate when the drug is started (“radiation-recall reaction” can occur years after radiation was given).
3. **Occasional.** Diarrhea, hyperpigmentation of nail beds and dermal creases, facial flush, conjunctivitis, lacrimation, red urine.
4. **Rare.** Anaphylaxis, activation of fibrinolysis, fever, chills.

d. **Administration.** The drug must be slowly pushed through a running i.v. line over a 2- to 5-minute period or continuously infused through a central venous line. Rapid infusion may induce serious arrhythmias, flushing, or syncope; protect drug from sunlight.

1. **Supplied** as 10-, 20-, 50-, 100-, and 150-mg vials.
2. **Dose modification.** The risk of developing congestive heart failure is estimated to be 1% to 2% at a total cumulative dosage of 300 mg/m^2 of body surface area, 2% to 3% at a total cumulative dosage of 400 mg/m^2 of body surface area, 5% to 8% at a total cumulative dosage of 450 mg/m^2, and 6% to 20% at a total cumulative dosage of 500 mg/m^2. This toxicity may develop at lower cumulative dosages in patients who have previously received chest irradiation, patients who have received medications increasing cardiotoxicity, or patients with dosage for preexisting heart disease. Doxorubicin should not be given to patients with congestive heart failure from any cause.
3. **Dose**
a. From 50 to 75 mg/m^2 i.v. bolus or continuous infusion over a 2- to 4-day period every 3 to 4 weeks.
b. Use 30 mg/m^2 i.v. daily for 3 days every 3 to 4 weeks.
c. From 10 to 20 mg/m^2 i.v. weekly.

4. **Idarubicin** (Idamycin)**/epirubicin** (Ellence)
a. **Indications.** AML.
b. **Pharmacology.** Idarubicin and epirubicin are anthracycline glycosides. They may intercalate DNA strands, inhibit DNA synthesis, interact with RNA polymerases, and inhibit topo II. They are more lipophilic than other anthracycline antibiotics.
c. **Toxicity** similar to that of doxorubicin.
d. **Administration.** Again like doxorubicin, a slow i.v. injection over a 5-minute period with extravasation precautions is mandated.
1. **Supplied** as idarubicin in 5- and 10-mg vials; epirubicin, 50- and 200-mg vials.
2. **Dose modification.** Same as doxorubicin.
3. **Dose.** Idarubicin, 12 mg/m^2 i.v. daily for 3 days; epirubicin, 100 mg/m^2 every 21 days.

5. **Bleomycin (Blenoxane)**
a. **Indications.** Head and neck carcinoma; laryngeal carcinoma; vulvar carcinoma or testicular carcinoma; Hodgkin lymphoma and non-Hodgkin lymphomas.
b. **Pharmacology**
1. **Mechanism.** Although bleomycin is effective against both cycling and noncycling cells, it seems to be most effective in the G_2 phase of cell division. It causes DNA strand cleavage by free radicals and inhibits DNA repair by marked inhibition of DNA ligase.
2. **Metabolism.** Biotransformation is unknown; probably by enzyme degradation in tissues, based on animal studies. It is not known whether any metabolites are active. Both free drug and metabolic products are excreted into the urine.

c. **Toxicity**
1. **Dose limiting**
a. **Fever and chills** occur in approximately 20% to 60% of patients, usually 3 to 6 hours after administration, last 4 to 12 hours, and become less frequent with continued use. An unusual idiosyncratic reaction (confusion, faintness, fever and chills, wheezing) occurs in approximately 1% of treated patients) but in approximately 1% to 6% of lymphoma patients. If not promptly treated, it may progress to sweating, dehydration, hypotension, and renal failure or cardiorespiratory collapse. It usually occurs at doses of 25 units per m^2 or greater, although it has occurred with a dose of 7.5 units. It may be immediate or delayed by several hours and occurs after the first or second dose.
b. **Pulmonary toxicity** occurs in 10% to 40% of treated patients, usually 4 to 10 weeks after initiation of treatment; approximately 1% of treated patients have died of pulmonary fibrosis. Pulmonary toxicity is age and dose related, occurring most frequently in patients older than 70 years and/or receiving a total dose of more than 400 units (although it has been reported with doses as low as 20 to 60 units). It may be irreversible and fatal; however, there is some evidence that in patients who survive that symptoms and pulmonary-function parameters return to normal in approximately 2 years. It occurs at lower doses in patients who have received other antineoplastics or thoracic irradiation; mortality may be as high as 10% in patients who have received pulmonary irradiation. A low-dose allergic pneumonitis also has been reported. The earliest signs of pulmonary toxicity are a decrease in diffusion capacity and fine rales. On chest radiograph, pneumonitis is seen as nonspecific patchy opacities, usually of the lower lung fields. Pulmonary-function tests show a decrease in total lung volume and a decrease in vital capacity.
2. **Common**
a. **Sensitizes tumor and normal tissues to radiation.**
b. **Dermatologic (50% of patients):** hyperpigmentation of skin stretch areas (e.g., knuckles, elbows); hardening tenderness or loss of fingernails;

hyperkeratosis of palms and fingers, scleroderma-like changes; skin tenderness, pruritus, or urticaria, erythroderma, desquamation, alopecia. Of note is that skin toxicity occurs in 25% to 50% of treated patients, usually 2 to 4 weeks after initiation of therapy. It appears to be related to cumulative dose and usually develops after 150 to 200 units has been given.

c. **Anorexia;** a rancid smell (like old gym socks) beginning about 10 seconds after injection.

3. **Occasional.** Nausea, vomiting, mild reversible myelosuppression, Raynaud phenomenon, phlebitis, pain at injection site.

d. **Administration.** A 2-unit test dose is given before the first treatment, followed by a 1- to 2-hour observation period.

1. **Supplied** as a 15-unit vial.
2. **Dose modification.** It is recommended that the dosage of bleomycin be reduced in patients with renal-function impairment (creatinine clearance less than 25 to 35 mL/minute). It also is recommended that equipment and medications (including epinephrine, oxygen, diphenhydramine, and i.v. corticosteroids) necessary for treatment of a possible anaphylactic reaction be readily available at each administration of bleomycin. The drug should not be given to patients with symptomatic chronic obstructive lung disease. It must be discontinued in patients who have erythroderma (continued treatment may lead to fatal exfoliative dermatitis). The drug also must be discontinued if there are symptoms or signs of interstitial lung disease. Routine pulmonary function tests are generally not helpful; some authorities recommend monitoring carbon monoxide diffusing capacity.
3. **Dose.** Avoid cumulative dosage of more than 400 units; some physicians limit the total dose to 300 units.
   a. From 10 to 20 units/m^2 i.m., i.v., or s.q. once or twice weekly (twice-weekly dose is higher than 20 units each or likely to cause serious toxic reactions of the skin) or
   b. Use 15 to 20 units/m^2 daily for 3 to 7 days by continuous infusion or
   c. Use 60 units/m^2 dissolved in 100 mL of normal saline for intracavitary therapy.

6. **Mitomycin (Mutamycin)**

a. **Indications.** Gastric carcinoma, pancreatic carcinoma.

b. **Pharmacology**

1. **Mechanism.** After enzyme activation in the tissues, it functions as a bifunctional or trifunctional alkylating agent. It causes cross-linking of DNA, inhibits DNA synthesis, and to a lesser extent also inhibits RNA and protein synthesis.
2. **Metabolism.** Metabolized predominantly in the liver. Free drug and metabolites are excreted in the urine. The percentage of a dose excreted in urine increases with increasing doses because of saturation of metabolic pathways at relatively low doses.

c. **Toxicity**

1. **Dose limiting.** Cumulative myelosuppression, which may be severe and prolonged (particularly thrombocytopenia with unusual bleeding or bruising, black tarry stools, blood in urine or stools, pin-point red spots on skin). It may occur up to 8 weeks after initiation of therapy, and counts return to normal within 10 weeks after therapy stops, although in about 25% of episodes, counts do not recover. Severity of bone marrow depression varies and determines subsequent dosage of mitomycin.
2. **Common.** Mild nausea and vomiting, anorexia; vesicant drug that can cause necrosis if injected s.q. (skin erythema and ulceration can occur weeks to months after administration and may appear at a site distant from the site of injection).
3. **Occasional.** Alopecia, stomatitis, skin rashes, photosensitivity, pain at site of injection, phlebitis; hemolytic uremia–like syndrome (blood in urine, decreased urination, shortness of breath, swelling of feet or lower legs).
4. **Rare.** Acute interstitial pneumonitis, especially when given with VBL (cough, shortness of breath; it usually occurs after several doses, but it can be severe, and it may be life threatening). Renal toxicity (blood in urine, decreased urination, shortness of breath).

d. **Administration.** Administered through i.v. infusion with extravasation precautions.

1. **Supplied** as 5-, 20-, and 40-mg vials.
2. **Dose modification.** Reduce dose by 50% to 75% for patients who were previously treated with extensive irradiation or developed white blood cell count (WBC) less than 2,000/µL with prior doses of mitomycin. An additional course of mitomycin should be given only after circulating blood elements have returned to acceptable levels (e.g., WBC more than 3,000/µL and platelets more than 75,000/µL.
3. **Dose**
   a. **Single agent:** 10 to 20 mg/m^2 i.v. every 6 to 8 weeks.
   b. **In combination:** 5 to 10 mg/m^2 i.v. every 6 weeks.
   c. **For bladder installation:** 20 to 40 mg every 1 to 2 weeks.

7. **Plicamycin (mithramycin)**

a. **Indications.** Testicular carcinoma; hypercalcemia and hypercalciuria associated with neoplasms, although it has generally been replaced by other agents.

b. **Pharmacology**

1. **Mechanism.** It has been shown that plicamycin forms a complex with DNA in the presence of magnesium or other divalent cations, thereby inhibiting DNA-dependent or DNA-directed RNA synthesis. It also may act by blocking the hypercalcemic action of vitamin D or by inhibiting the effect of parathyroid hormone on osteoclasts. The plicamycin inhibition of DNA-dependent RNA synthesis appears to render osteoclasts unable to respond fully to parathyroid hormone with a biosynthesis necessary for osteolysis.
2. **Metabolism.** Unknown; eliminated in the urine (40%).

c. **Toxicity.** Renal and hepatic damage are rare with dosage schedules used for hypercalcemia.

1. **Dose limiting.** Thrombocytopenia; coagulation defects may occur in the absence of thrombocytopenia and result in a severe hemorrhagic diathesis (usually with frequent doses).
2. **Common.** Nausea and vomiting; hypocalcemia, hypophosphatemia, hypokalemia, hypomagnesemia, rebound hypercalcemia; abnormal LFTs (including prothrombin time); azotemia, skin and soft-tissue necrosis if extravasated.
3. **Occasional.** Leukopenia, anemia, stomatitis, diarrhea, hyperpigmentation, acneform rash, headache, dizziness, drowsiness, nervousness.
4. **Rare.** Toxic epidermal necrolysis, fever, lethargy, periorbital pallor.

d. **Administration.** It is recommended that plicamycin be administered by i.v. infusion only to hospitalized patients by or under the supervision of a physician experienced in the use of cancer chemotherapeutic agents because of the possibility of severe reactions. Rapid direct i.v. injection of plicamycin should be avoided.

1. **Supplied** as 2.5-mg vials.
2. **Dose modification.** The drug should be withheld if studies show liver or renal damage, prolonged prothrombin time, serious thrombocytopenia, or normal or low calcium levels.
3. **Antineoplastic dose.** From 25 to 30 µg (0.025 to 0.03 mg)/kg i.v. daily, administered over a period of 4 to 6 hours for 8 to 10 days; additional courses of therapy may be administered at 1-month intervals.
4. **Antihypercalcemic.** From 15 to 25 µg (0.015 to 0.025 mg)/kg i.v. daily, over a period of 4 to 6 hours for 3 to 4 days, the dose to be repeated at 1-week or greater intervals if necessary until the desired response is obtained (the same dose may be given by i.v. push over a 20- to 30-minute period to reduce the risk of extravasation).

E. **Camptothecin analogues: general mechanism of action.** The two camptothecin analogues approved for clinical use are topotecan and irinotecan. They contain the camptothecin pentacyclic structure with a closed lactone ring moiety in the E ring, which is essential for cytotoxicity. They both interact with topoisomerase I (topo I) and prevent the resealing of the topo I–mediated DNA single-strand breaks. These strand breaks result in cell death only if DNA synthesis is ongoing: a division between the advancing replication fork and the drug-stabilized single-strand break in DNA result in replication-fork breakage and double-strand breaks in the DNA. Treatment of mammalian cells with topo I inhibitors induces inhibition of DNA synthesis, cell-cycle arrest in G_2, and cell death by apoptosis. Drug-induced G_2 arrest has been associated with a failure to activate cdc2 kinase. Because the cytotoxicity associated with topo I–interactive agents is highly dependent on DNA synthesis, any deregulation of cyclins, cell cycle–regulated kinases, or phosphatases may influence the cytotoxicity of topo I–interactive agents.

1. **Topotecan** (Hycamtin)

a. **Indications.** Ovarian carcinoma, small cell lung carcinoma.

b. **Pharmacology**

1. **Mechanism.** Topo I inhibitor, as outlined earlier.
2. **Metabolism.** Topotecan undergoes reversible, pH-dependent hydrolysis of the active lactone moiety, forming an inactive open-ring hydroxyacid. Neither the lactone nor the hydroxyacid form of topotecan is metabolized to a significant extent. Approximately 30% of the dose is eliminated through the kidneys, and a lower percentage of the dose, via the biliary route.

c. **Toxicity**

1. **Dose limiting.** Myelosuppression.
2. **Common.** Nausea or vomiting, anorexia, constipation or diarrhea, neurologic effects including muscle weakness or paresthesia.
3. **Rare.** Allergic reactions including anaphylactoid reactions.

d. **Administration.** Topotecan should be administered only under the supervision of a physician experienced in cancer chemotherapy. It is to be administered only by i.v. infusion.

1. **Supplied** as a 4-mg vial.
2. **Dose modification.** For patients with moderate renal function impairment (creatinine clearance, 20 to 39 mL/minute). A reduction in dose to 0.75 mg/m^2 is recommended.
3. **Dose**
   a. **Ovarian carcinoma:** Use 1.5 mg/m^2 daily for 5 consecutive days, repeated every 21 days.
   b. **Small-cell lung carcinoma:** From 1.25 to 2 mg/m^2 daily for 5 consecutive days, repeated every 21 days.

2. **Irinotecan (Camptosar or CPT-11)**
   a. **Indications.** Colorectal carcinoma (metastatic).
   b. **Pharmacology**
      1. **Mechanism.** Irinotecan and its active metabolite, SN-38, inhibit the action of topo I. The precise contribution of the metabolite to the activity of irinotecan in humans is not known because its protein binding is significantly higher and its area under the plasma concentration–time curve (AUC) is much lower than those of irinotecan (although SN-38 is approximately 1,000 times more potent than the parent compound in various *in vitro* cytotoxicity assays).
      2. **Metabolism.** Primarily hepatic. Up to 11% to 20% of a dose is excreted through the kidneys as unchanged irinotecan, whereas less than 1% of a dose is excreted as SN-38. The effect of hepatic- or renal-function impairment on elimination of irinotecan and its metabolites has not been formally studied.
   c. **Toxicity**
      1. **Dose limiting.** Myelosuppression: diarrhea possibly preceded by abdominal cramping and/or sweating (diarrhea occurring within 24 hours after administration of irinotecan is cholinergic, whereas diarrhea occurring more than 24 hours after administration of irinotecan may be severe and prolonged enough to cause life-threatening dehydration and may be associated with ulceration of the colon and sometimes with bleeding).
      2. **Common.** Dyspnea (it may be associated with pulmonary metastasis or other preexisting lung disease), nausea and vomiting, weakness, constipation.
      3. **Occasional.** Bloated feeling or gas, headache, indigestion, rhinitis, skin rash, flushing.
   d. **Administration.** It is recommended that irinotecan be administered to patients only under the supervision of a physician experienced in cancer chemotherapy and only by i.v. infusion, taking extravasation precautions.
      1. **Supplied** as 40 mg/2-mL and 100 mg/5-mL single-use vials.
      2. **Dose modification.** A lower initial dose of 100 mg/m^2 once a week should be considered for patients with a combined history of pelvic–abdominal irradiation and modestly elevated total serum bilirubin concentrations (1 to 2 mg/dL) because of the increased likelihood of first-course grade 3 or 4 neutropenia.
      3. **Dose.** Use 125 mg/m^2 i.v. once a week for 4 weeks, followed by a rest period of 2 weeks.

F. **Taxanes: general mechanism of action.** The taxanes bind to tubulin polymers (microtubules) at binding sites that are distinct from exchangeable GTP, colchicine, podophyllotoxin, and vinca alkaloids. Paclitaxel binds preferentially to the N-terminal 31 amino acids of the b-tubulin subunit. Docetaxel, which most likely shares the same tubulin-binding site as paclitaxel, appears to have a 1.9-fold higher affinity for this site. However this difference might not translate into greater therapeutic index for docetaxel in the clinic, as greater potency also may lead to more severe toxicity at identical drug concentrations *in vivo.* Nevertheless, the results of both preclinical and clinical studies suggest that the taxanes may not be completely cross-resistant. Although the precise mechanism by which microtubule disturbances lead to apoptosis has not been determined, the taxanes interact with numerous substances including regulatory molecules and oncogenes that bind to the mitotic apparatus.

1. **Paclitaxel (Taxol)**
   a. **Indications.** Ovarian carcinoma; breast carcinoma; Kaposi sarcoma; non–small cell lung carcinoma.
   b. **Pharmacology**
      1. **Mechanisms.** Antimicrotubule agent as outlined earlier.
      2. **Metabolism.** Nearly totally protein bound and distributed well in body fluids (including effusions), with a plasma half-life of about 5 hours. It has substantial hepatic metabolism, biliary excretion, and fecal elimination.
   c. **Toxicity**
      1. **Dose limiting**
         a. **Neutropenia,** particularly patients who were previously heavily treated or who received cisplatin just before paclitaxel.
         b. **Hypersensitivity** (3%) is manifested by cutaneous flushing, hypotension, bronchospasm, urticaria, diaphoresis, pain, or angioedema. Reactions usually develop within 20 minutes of starting the treatment; 90% of hypersensitivity reactions develop after the first or second dose.
         c. **Peripheral neuropathy,** particularly in the higher-dosage (more than 170 mg/m^2) schedules and in patients with concomitant etiologies for peripheral neuropathy. The distribution is usually “stocking–glove” and consists of dysesthesias, paresthesias, and loss of proprioception.
      2. **Common.** Alopecia (usually total and sudden, within 3 weeks of treatment), thrombocytopenia (usually not severe); transient arthralgias and myalgias within 3 days of treatment (often requiring narcotics and ameliorated by NSAIDs and prednisone), transient bradycardia (usually asymptomatic).
      3. **Occasional.** Nausea and vomiting, taste changes, mucositis, diarrhea; atrioventricular conduction defects, ventricular tachycardia, cardiac angina; necrosis when extravasated.
      4. **Rare.** Paralytic ileus, generalized weakness, seizures; myocardial infarction.
   d. **Administration.** Paclitaxel should be given before cisplatin, in combination regimens in which both are administered. Patients who were heavily previously treated may require support with granulocyte–colony-stimulating factor. Cardiac monitoring is recommended for patients taking cardiac medications or with a history of cardiac disease. Administer with extravasation precautions.
      1. **Supplied** as 30-mg vials.
      2. **Dose modification.** Hematologic.
      3. **Dose.** From 135 to 175 mg/m^2 infused over a 3- to 24-hour period.

2. **Docetaxel (Taxotere)**
   a. **Indications.** Breast carcinoma, non-small cell lung cancer.
   b. **Pharmacology.** As outlined for paclitaxel.
   c. **Toxicity**
      1. **Dose limiting.** Anemia and neutropenia.
         a. **Fluid retention** that usually begins in the lower extremities but may become generalized and lead to pleural effusions, pericardial effusions, or ascites (prophylactic corticosteroid administration decreases incidence and severity of this complication and increases the median cumulative dose at which moderate or severe edema occurs). The fluid retention is secondary to increased capillary permeability rather than hypoalbuminemia or cardiac, hepatic, or renal damage. Fluid retention is usually reversible after treatment is discontinued.
         b. **Hypersensitivity reactions** are most likely to occur during the first two cycles of docetaxel treatment, generally within the first few minutes after the infusion has started. If a severe reaction occurs, the infusion should be discontinued immediately, and aggressive treatment instituted.
         c. **Peripheral neuropathy.** Rarely neurologic effects may result in moderate to severe neuropathy, leading to decreased dexterity and/or disturbances in gait, usually after accumulative doses of 600 mg/m^2 have been given.
      2. **Common.** Mild cutaneous reaction, diarrhea, stomatitis.
      3. **Occasional.** Arthralgias or myalgias; headache; infusion-site reactions; nail disorder that is discoloration of fingernails or toenails; vomiting.
      4. **Rare.** Cardiovascular effects, including angina, arrhythmia, heart failure, hypertension.
   d. **Administration.** Docetaxel should be administered only under the supervision of a physician experienced in cancer chemotherapy. Pretreatment administration of an oral corticosteroid is recommended to decrease the frequency and severity and delay the onset of docetaxel-induced fluid retention. Pretreatment administration of an oral corticosteroid with or without antihistamines also reduces the severity of docetaxel-induced hypersensitivity reactions and cutaneous toxicity. Docetaxel is not highly emetogenic, and routine prophylaxis with antiemetics is generally not required.
      1. **Supplied** as 20 mg per 0.5-mL vial and 80 mg per 2-mL vial.
      2. **Dose modification.** A reduction in subsequent doses is recommended for patients in whom severe neutropenia develops (neutrophil count less than 500/µL that persists for 7 days or more). Docetaxel is not recommended for patients with hepatic-function impairment, especially moderate to severe impairment, because of the considerably higher risk of severe toxicity.
      3. **Dose.** From 60 to 100 mg/m^2 i.v., administered as a 1-hour infusion every 3 weeks.

IV. **Miscellaneous**

A. **Platinum coordination complexes**

1. **Cisplatin** (Platinol; Platinol-AQ)
   a. **Indications.** Bladder carcinoma; ovarian carcinoma; testicular carcinoma (cisplatin is used for a wide variety of malignancies such as breast, gastric, lung; however, these indications are not included in the United States product labeling).

b. **Pharmacology**
   1. **Mechanism of action.** Cisplatin resembles an alkylating agent. Although the exact mechanism of action is unknown, action is thought to be similar to that of the bifunctional alkylating agents; that is, possible cross-linking and interference with the function of DNA and a small effect on RNA. It is cell-cycle phase nonspecific. Stimulation of the host immune system also is possible.
   2. **Metabolism.** By rapid nonenzymatic conversion to inactive metabolites. It is eliminated up to 27% to 43% via the kidneys. (Platinum may be detected in tissues for 4 months or more after administration.)

c. **Toxicity**
   1. **Dose limiting**
      a. **Cumulative renal insufficiency** is about 5% with added hydration measures and 25% to 45% without hydration measures. Nephrotoxicity (and perhaps ototoxicity) is increased by concurring administration of nephrotoxic drugs such as aminoglycoside antibiotics, MTX, or amphotericin B.
      b. **Peripheral sensory neuropathy** develops after administration of 200 mg/m^2 and can become dose limiting when the cumulative cisplatin dose exceeds 400 mg/m^2. Symptoms may progress after treatment is discontinued and include loss of proprioception and vibratory senses, hyporeflexia, and Lhermitte sign. Symptoms may resolve slowly after many months but are aggravated by further dosing.
      c. **Ototoxicity** with tinnitus and high-frequency hearing loss occurs in 5% of patients. Ototoxicity occurs more commonly in patients receiving doses more than 100 mg/m^2 by rapid infusion or high cumulative doses.
   2. **Severe.** Nausea and vomiting occur in all treated patients and last more than 24 hours without use of effective preventive antiemetic regimens. Hypokalemia, hypomagnesemia (occasionally difficult to correct), and mild myelosuppression.
   3. **Occasional.** Alopecia, loss of taste, vein irritation, abnormal LFTs, SIADH, hypophosphatemia, myalgia, and fever.
   4. **Rare.** Altered color perception and reversible focal encephalopathy that often causes cortical blindness. Raynaud phenomenon, bradycardia, bundle-branch block, congestive heart failure; anaphylaxis, tetany.

d. **Administration**
   1. **Supplied** as 10- to 50-mg vials.
   2. **Dose modification.** Renal function must return to normal before cisplatin can be given. Many physicians avoid using cisplatin when the creatinine clearance is less than 40 mL/minute. Cisplatin is relatively contraindicated in patients with documented hearing impairment.
   3. **Dose**
      a. From 40 to 120 mg/m^2 or more i.v. every 3 to 4 weeks or
      b. From 20 to 40 mg/m^2 i.v. daily for 3 to 5 days every 3 to 4 weeks.
   4. **Method.** The principles of cisplatin administration are as follows.
      a. **Monitoring.** Serum creatinine, electrolytes, magnesium, and calcium levels should be measured daily during therapy. Audiometry is usually not necessary.
      b. **Antiemetics.** Patients should be given antiemetics such as ondansetron and dexamethasone before, during, and after cisplatin infusion.
      c. **Hydration and diuresis** are required when 40 mg/m^2 or more of cisplatin is given as a short infusion to maintain a urine output of 100 to 150 mL/hour before administration of the drug.
         i. From 1.5 to 2.0 L of 5% dextrose in 0.45% NaCl-containing $MgSO_4$ and KCl should be administered before cisplatin treatment. The same volume and composition of fluids also is given after cisplatin.
         ii. Furosemide, 40 mg i.v., should be given if needed to prevent a fluid overload.
         iii. Mannitol, 12.5 to 37.5 g, should be administered before cisplatin if urine output is insufficient.

2. **Carboplatin (Paraplatin; Paraplatin-AQ).**
   a. **Indications.** Ovarian carcinoma. Other indications such as for endometrial or lung carcinoma are not included in the United States product labeling. Carboplatin may be an alternative to cisplatin when renal or neural toxicity are dose-limiting considerations.
   b. **Pharmacology**
      1. **Mechanism.** Similar to cisplatin. Cisplatin and carboplatin exhibit substantial clinical cross-resistance.
      2. **Metabolism.** Bihydrolysis in solution (aquation) at rates lower than occurs with cisplatin to the active species that reacts with DNA. Plasma half-life of only 2 to 3 hours. Excreted in the urine as unchanged drug (60%) and metabolites.
   c. **Toxicity**
      1. **Dose limiting.** Myelosuppression, especially thrombocytopenia with cumulative suppression of erythropoiesis.
      2. **Common.** Nausea and vomiting (less severe than with cisplatin); pain at injection site.
      3. **Occasional.** Abnormal LFTs; azotemia.
      4. **Rare.** Alopecia, rash, flu-like syndrome, hematuria, hyperamylasemia; peripheral neuropathy (especially in patients older than 65 years) hearing loss, optic neuritis.
   d. **Administration**
      1. **Supplied** as 50-, 150-, and 450-mg vials.
      2. **Dose modification.** Reduced dosage for creatinine clearance of 60 mL/minute or less. Be cautious when concomitantly administering other myelosuppressive or nephrotoxic drugs.
      3. **Dose.** From 300 to 400 mg/m^2 i.v. over 15 to 60 minutes every 4 weeks. Increasingly used is the Calvert formula which yields a dose that will achieve a targeted area under the concentration-time (AUC)—usually 5–7. Dose (in mg) = [Creatinine Clearance + 25] × AUC target.

B. **Anthracenedione**
   1. **Mitoxantrone (Novantrone)**
      a. **Indications.** Advanced hormone-refractory prostate cancer; AML.
      b. **Pharmacology**
         1. **Mechanism of action.** Mitoxantrone appears to be most active in the late S phase of cell division, but is not cycle-phase specific. Although the exact mechanism of action is unknown, evidence seems to indicate involvement of binding to DNA by intercalation between base pairs and a nonintercalative electrostatic interaction, resulting in inhibition of DNA and RNA synthesis. Mitoxantrone is in the anthracenedione class of compounds, which are analogues to the anthracyclines. In general mechanism of action and of metabolism, are similar but not identical to doxorubicin. Mitoxantrone lacks the ability to produce the quinone-type 3 radicals that are responsible for anthracycline-associated cardiac toxicity (they have obtained the planar polycyclic aromatic ring structure that permits its intercalation into DNA).
         2. **Metabolism.** Metabolized by the liver. Excreted into bile and urine as metabolites and unchanged drug.
      c. **Toxicity.** Compared with the anthracyclines, mitoxantrone is associated with less cardiotoxicity, less nausea and vomiting, and decreased potential for extravasation injury.
         1. **Dose limiting.** Bone marrow suppression.
         2. **Common.** Mild nausea and vomiting, mucositis; alopecia (usually mild); blue discoloration of the urine, sclerae, fingernails and over venous site of injection that may last 48 hours.
         3. **Occasional.** Cardiomyopathy (most well defined for patients who have previously received doxorubicin; appears to be less cardiotoxic than doxorubicin) pruritus, LFT abnormalities, allergic reactions.
         4. **Rare.** Jaundice, seizures, pulmonary toxicity.
      d. **Administration.** 30-minute infusion; rarely causes extravasation injury if infiltrated.
         1. **Supplied** as 20-, 25-, and 30-mg vials.
         2. **Dose modification.** Hematologic.
         3. **Dose** is 10 to 12 mg/m^2 i.v., given every 3 weeks for solid tumors or daily for 5 days in combination with cytarabine for acute leukemia.

C. **Substituted urea**
   1. **Hydroxyurea** (Hydrea)
      a. **Indications.** Epithelial ovarian carcinoma; CML.
      b. **Pharmacology**
         1. **Mechanism.** Hydroxyurea also can be classified as an antimetabolite. It is thought to be cell-cycle specific for the S phase of cell division. The exact mechanism of antineoplastic activity is unknown, but it is thought to involve interference with synthesis of DNA with no effect on the synthesis of RNA or protein.
         2. **Metabolism.** Crosses the blood–brain barrier. Half of the drug is rapidly degraded into inactive compounds. Inactive products and unchanged drug (50%) are excreted in urine.
      c. **Toxicity**
         1. **Dose limiting.** Myelosuppression, which recovers rapidly when treatment is stopped (prominent megaloblastosis resembling pernicious anemia, probably due to delaying of the rate of iron utilization by erythrocytes).
         2. **Occasional.** Nausea and vomiting; skin rash, facial erythema, hyperpigmentation, azotemia, or uric acid nephropathy. Most commonly during the initial treatment of patients with leukemia secondary to rapid cell breakdown; transient LFT abnormalities; radiation-recall phenomenon.

3. **Rare.** Alopecia, mucositis, diarrhea, constipation; neurologic events; pulmonary edema; flu-like syndrome.

d. **Administration**

1. **Supplied** as 500-mg capsules.
2. **Dose modification.** The drug should be given cautiously in the presence of liver dysfunction or when combined with other antimetabolites. Dosage should be reduced for creatinine clearance less than 50 ml/minute and when given with concomitant radiotherapy.
3. **Dose**
   a. **CML:** From 15 to 30 mg/kg p.o. every day or
   b. **Solid tumors:** Use 80 mg/kg p.o. every 3 days.

D. **Methylhydrazine derivative**

1. **Procarbazine** (Matulane; Natulan).

a. **Indications.** Hodgkin lymphoma.

b. **Pharmacology**

1. **Mechanism.** DNA alkylation and depolymerization. It is cell-cycle specific for the S phase of cell division. Inhibits DNA, RNA, and protein synthesis.
2. **Metabolism.** Metabolic activation of the drug is required. Readily enters the cerebrospinal fluid (CSF). Degraded in the liver to active compounds, which are excreted in urine (70%).

c. **Toxicity**

1. **Dose limiting.** Myelosuppression, which may not begin until several weeks after starting treatment.
2. **Common.** Nausea and vomiting, which decrease with continued use; myalgia, arthralgia; sensitizes tissue to radiation.
3. **Occasional.** Dermatitis, hyperpigmentation, photosensitivity; stomatitis, dysphagia, diarrhea; hypotension, tachycardia; urinary frequency, hematuria; gynecomastia, steriolytic.
4. **Neurologic.** Procarbazine may result in disorders of consciousness or mild peripheral neuropathies in about 10% of cases. These abnormalities are reversible and rarely serious enough to alter drug dosage. Manifestations of toxicity include sedation, depression, agitation, psychosis, decreased deep-tendon reflexes, paresthesias, myalgias, and ataxia.
5. **Rare.** Xerostomia, retinal hemorrhage, photophobia, papilledema; allergic pneumonitis, secondary malignancy.

d. **Administration**

1. **Supplied** as 50-mg capsules.
2. **Dose modification** reduced dose in patients with hepatic, renal, or bone marrow dysfunction.
3. **Dose.** Use 100 mg/m^2 p.o. daily for 14 days in combination regimens.
4. **Drug interactions.** Procarbazine is a monoamine oxidase (MAO) inhibitor and interacts with the following.
   a. **Alcohol,** causing disulfiram (Antabuse)-like reactions.
   b. **CNS depressants** synergistically (antihistamines, phenothiazines, barbiturates).
   c. **Tricyclic antidepressants and monoamine oxidase inhibitors,** causing hyperpyrexia, convulsions.
   d. **Meperidine and other narcotics,** causing hypertension, hypotension, and coma.
   e. **Hypoglycemic agents,** increasing hypoglycemia.
   f. **Sympathomimetic amines and tyramine-containing foods,** causing hypertensive crisis (after dosage is stopped, MAO inhibitor effects of this medication may persist for up to 2 weeks after discontinuation, which is the time required for regeneration of the enzyme; hence during this period, food and drug contraindications must be observed).

E. **Adrenocortical suppressants**

1. **Mitotane (Lysodren)**

a. **Indications.** Adrenocortical carcinoma.

b. **Pharmacology**

1. **Mechanism.** Causes adrenocortical atrophy by inhibiting mitochondria (the exact mechanism is unknown). Blocks adrenocorticoid synthesis in normal and malignant cells. Aldosterone synthesis is not affected.
2. **Metabolism.** Degraded slowly in the liver and extensively distributed in fatty tissues. Its action is antagonized by spironolactone; the two drugs should not be administered together. Metabolites are excreted in the bile and the urine.

c. **Toxicity**

1. **Dose limiting.** Nausea and vomiting.
2. **Common.** Diarrhea, depression, lethargy, maculopapular rash, and hypercholesterolemia.
3. **Occasional.** Orthostatic hypotension, hypertension; abnormal LFTs; irritability, confusion, tremors; shortness of breath, and wheezing.
4. **Rare.** Permanent brain damage, myelosuppression, other dermatologic problems, visual disturbances, hemorrhagic cystitis, and fever.

d. **Administration.** Plasma cortisol levels should be monitored periodically to assess the effectiveness of treatment and the possible development of adrenal insufficiency. Glucocorticoid and mineralocorticoid replacement therapy may be necessary.

1. **Supplied** as 500-mg tablets.
2. **Dose modification.** Reduce dose for patients with hepatic impairment.
3. **Dose.** From 4 to 6 g p.o. daily in three divided doses; increased to 10 g daily, as tolerated. Duration of treatment depends on clinical response. Only 10% of patients showing no response after 3 months of treatment at the maximal tolerated dose will show a response to continued therapy. It is recommended that mitotane be temporarily discontinued immediately after shock or severe trauma and that steroids be administered because adrenal suppression may prevent the normal response to stress.

2. **Aminoglutethimide** (Cytadren)

a. **Indications.** Cushing syndrome; breast carcinoma; prostatic carcinoma.

b. **Pharmacology**

1. **Mechanism.** An aromatase enzyme inhibitor that inhibits adrenocortical conversion of cholesterol to pregnenolone and blocks peripheral conversion of androgens to estrogens.
2. **Metabolism.** Approximately 25% of drug is bound to plasma proteins. Metabolized by the liver, excreted in the urine primarily as unchanged drug (50%).

c. **Toxicity**

1. **Dose limiting.** Adrenal insufficiency; postural hypotension (hypoaldosteronism).
2. **Common.** Mild GI upset; transient maculopapular eruptions associated with fever (these remit in about 4 days without stopping the drug); transient fatigue; and lethargy (results about 6 weeks after starting treatment).
3. **Occasional.** Cerebellar signs, hypercholesterolemia, virilization, myalgia, fever, and leg cramps.
4. **Rare.** Myelosuppression, desquamation, oral ulcers, hyperthyroidism, lupus, and hepatitis-like syndrome.

d. **Administration**

1. **Supplied** as 250-mg tablets.
2. **Dose.** Use 250 mg p.o. b.i.d. (with hydrocortisone, 100 mg/day) for 2 weeks. Then increase the dose to 250 mg p.o. q.i.d., and decrease hydrocortisone to 10 mg in the morning and at noon and 20 mg at bedtime. The hydrocortisone prevents overriding of the adrenal blockade by inhibiting the pituitary adrenocorticotropic hormone (ACTH) secretion. Occasionally a mineralocorticoid also is needed (fludrocortisone, 0.1 mg/day p.o.).
3. **Drug interactions.** Aminoglutethamide (Cytadren) induces the metabolism of warfarin, theophylline, digoxin, dexamethasone, and medroxyprogesterone: larger doses of these drugs may be needed.

F. **Estradiol–mustard ester**

1. **Estramustine** (Emcyt)

a. **Indications.** Prostate carcinoma.

b. **Pharmacology.** Classified as a hormone (effects are similar to those of estrogen) but also may be an antimicrotubule agent. Estramustine is highly localized in prostatic tissue because of binding to an estramustine-specific protein. Estramustine is a phosphorylated combination of estradiol and mechlorethamine (nitrogen mustard).

c. **Toxicity.** Similar to estrogens (see later).

d. **Administration**

1. **Supplied** as 140-mg capsules.
2. **Dose** is 15 mg/kg/day in three divided doses taken on an empty stomach.

V. **Hormonal agents**

A. **Antiestrogens**

1. **Tamoxifen** (Nolvadex)

a. **Indications.** Breast carcinoma (treatment and prophylaxis).
b. **Pharmacology**
    1. **Mechanism.** Tamoxifen is a nonsteroidal antiestrogen agent that also has weak estrogenic effects. The exact mechanism of antineoplastic action is unknown but may be related to its antiestrogen effects; tamoxifen blocks uptake of estradiol.
    2. **Metabolism.** Tamoxifen is eliminated via the biliary/fecal route primarily, mostly as metabolites. An objective response usually occurs within 4 to 10 weeks of therapy but may take several months in patients with bone metastasis.
c. **Toxicity**
    1. **Common.** Thrombocytopenia (mild and transient), hot flashes, menstrual changes, uterine bleeding; reduced serum cholesterol (especially low-density cholesterol) while receiving tamoxifen.
    2. **Occasional.** Retinopathy or keratopathy (5%; reversible), cataracts; leukopenia, anemia; nausea and vomiting, hair loss (mild), rash; thrombophlebitis, thromboembolism; “tamoxifen flare” in first month of therapy (bone pain; it also may consist of hypercalcemia and/or spinal cord compression, as well as a sudden increase in the size of preexisting lesions in patients with soft-tissue disease; sometimes associated with marked erythema within and surrounding the lesions and/or the development of the new lesions; transient local disease flare usually subsides within 1 to 2 weeks).
    3. **Rare.** Abnormal LFTs; altered mental state; slightly increased occurrence of endometrial adenocarcinoma on prolonged use.
d. **Administration**
    1. **Supplied** as 10- and 20-mg tablets.
    2. **Dose** is 20 mg p.o. daily.

B. **Estrogens** (conjugated estrogens; diethylstilbestrol; esterified estrogens; estradiol; estrone; estropipate; ethinyl estradiol).
a. **Indications.** Breast and prostatic carcinoma.
b. **Pharmacology**
    1. **Mechanism.** At the cellular level, estrogens increase the synthesis of DNA, RNA, and various proteins in target tissues. Pituitary mass also is increased. Estrogens reduce the release of gonadotropin-releasing hormone from the hypothalamus leading to a reduction in release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary.
    2. **Metabolism.** From 50% to 80% estrogens are bound to albumin and sex hormone–binding globulin. Estrogens are distributed to most tissues, especially breast, uterine, vaginal, hypothalamic, and pituitary; they have a high affinity for adipose tissue. Estrogens are excreted primarily through the kidneys as metabolites.
c. **Toxicity**
    1. Nausea, feminization, uterine bleeding.
    2. **Hypercalcemic flare** in patients with breast cancer.
    3. **Vaginal carcinoma** in offspring if used during pregnancy.
    4. **Painful gynecomastia** (preventable in men with low-dose breast irradiation).
    5. **Thromboembolic disorders** (especially with doses more than 3 mg/ day).
    6. Abnormal LFTs, cholestatic jaundice (rare).
    7. Chloasma, optic neuritis, retinal thrombosis; rash, pruritus.
    8. Fluid retention, hypertension, headache, dizziness, hypertriglyceridemia.
    9. Increased cardiovascular and cerebrovascular deaths in men with prostatic carcinoma.
d. **Administration**
    1. **Conjugated estrogens**
        a. **Supplied** as 0.3- and 0.625-mg tablets.
        b. **Dose**
            i. **Breast carcinoma** (inoperable and progressing in selected men and postmenopausal women): 10 mg p.o. t.i.d. for at least 3 months.
            ii. **Prostatic carcinoma** (inoperable and progressing): 1.25 to 2.25 mg p.o. t.i.d.
    2. **Diethylstilbestrol**
        a. **Not commercially available in the United States.**
    3. **Esterified estrogens**
        a. **Supplied** as 0.3-, 0.625-, 1.25-, and 2.5-mg tablets.
        b. **Dose**
            i. **Breast carcinoma** (inoperable and progressing in selected men and postmenopausal women): 10 mg p.o. t.i.d. for at least 3 months.
            ii. **Prostatic carcinoma** (inoperable and progressing): 1.25 to 2.5 mg p.o. t.i.d.
    4. **Estradiol**
        a. **Supplied** as 0.5-, 1-, and 2-mg tablets.
        b. **Dose**
            i. **Breast carcinoma** (inoperable and progressing in selected men and postmenopausal women): 10 mg p.o. t.i.d. for at least 3 months.
            ii. **Prostatic carcinoma** (inoperable and progressing): 1 to 2 mg p.o. t.i.d.
    5. **Estrone**
        a. **Supplied** as 2- and 5-mg/mL solution.
        b. **Dose**
            i. **Prostatic carcinoma** (inoperable and progressing): 2 to 4 mg i.m., 2 or 3 times a week.

C. **Aromatase inhibitors** (anastrozole or Arimidex; letrozole or Femara).
1. **Indications.** Advanced breast carcinoma in postmenopausal women.
    a. **Pharmacology**
        1. **Mechanism.** Both anastrozole and letrazole are nonsteroidal competitive inhibitors of aromatase and thus in postmenopausal women inhibit conversion of adrenal androgens (primarily androstenedione and testosterone) to estrogens (estrone and estradiol) in peripheral tissues and cancer tissue. As a result, they interfere with estrogen-induced stimulation or maintenance of growth of hormonally responsive (estrogen- and/or progesterone-receptor positive or receptor unknown) breast cancer.
        2. **Metabolism.** Metabolism is primarily hepatic by the CYP isoenzymes. Approximately 90% of the dose is eliminated via the kidneys as glucuronide conjugates of the inactive metabolite.
    b. **Toxicity**
        1. **Indicating need for medical attention.**
            a. **Incidence less frequent (less than 10%):** chest pain; shortness of breath; edema of feet or lower legs; hypertension; mental depression.
            b. **Incidence rare:** thromboembolism; vaginal bleeding.
        2. **Indicating need for medical attention only if they continue or are bothersome.**
            a. **Incidence more frequent (more than 10%):** nausea.
            b. **Incidence less frequent (less than 10%):** anorexia; anxiety; arthralgia; asthenia; constipation; cough; diarrhea; dizziness; headache; hot flushes; increased sweating; myalgia; skin rash or itching; sleepiness; stomach pain or upset; unusual tiredness; vomiting; weight gain.
        3. **Not indicating need for medical attention.**
            a. **Incidence less frequent (less than 10%):** alopecia.
    c. **Administration**
        1. **Anastrozole**
            a. **Supplied** as 1-mg tablets.
            b. **Dose:** Use 1 mg p.o. qd.
        2. **Letrazole**
            a. **Supplied** as 2.5-mg tablets.
            b. **Dose:** Use 2.5 mg p.o. qd.

D. **Gonadotropin-releasing hormone analogues**
1. **Leuprolide (Leupron); others**
    a. **Indications.** Prostatic carcinoma.
    b. **Pharmacology**
        1. **Mechanism** like naturally occurring luteinizing hormone–releasing hormone (LHRH), initial or intermittent administration of leuprolide stimulates release of LH and FSH from the anterior pituitary. However, continuous administration of leuprolide in the treatment of prostatic carcinomas suppresses the secretion of gonadotropin-releasing hormone with a resultant decrease in testosterone concentrations and pharmacologic castration.

2. **Metabolism.** Less than 5% of a 3.75-mg dose is recovered in the urine as parent drug and metabolite. Transient increases in testosterone and estradiol concentrations occur within the first week of therapy; and decline to castrated and postmenopausal levels, respectively, occurs within 2 to 4 weeks.

c. **Toxicity**
1. **Common.** Hot flashes, decreased libido; impotence and gynecomastia in men; amenorrhea and uterine bleeding in women.
2. **Occasional.** Hypercholesterolemia, local discomfort at site of injection.
3. **Rare.** GI upset, rash, hypertension, azotemia, headache, depression.

d. **Administration**
1. **Leuprolide** (Lupron)
a. **Supplied** as 3.75- and 7.5-mg vials and a kit (14-mg mount a dose vial with syringes).
b. **Dose:** Use 7.5 mg of depot suspension i.m. or s.c. monthly or 1 mg s.c. daily.
2. **Goserelin** (Zoladex)
a. **Supplied** as 3.6- and 10.8-mg preloaded in special single-use syringes.
b. **Dose:** Use 3.6 mg s.c. monthly or 10.8 mg every 3 months.
3. **Buserelin** (Suprefact)
a. **Supplied** as 1-mg/mL injectable solution or nasal spray.
b. **Dose:** By s.c. injection: 0.5 mg s.c. t.i.d. for the first week, and then 0.2 mg daily. By intranasal inhalation: 0.8 mg t.i.d. for 1 week, and then 0.4 mg t.i.d.

E. **Antiandrogens**
1. **Bicalutamide; flutamide; nilutamide.**
a. **Indications.** Prostatic carcinoma in combination with an LHRH analogue; nilutamide is indicated in conjunction with bilateral orchiectomy).
b. **Pharmacology**
1. **Mechanism.** Nonsteroidal antiandrogens bind to cytosol androgen receptors and competitively inhibit the uptake and/or binding of androgens in target tissues, thereby interfering with the actions of androgens at this cellular level. Prostatic carcinoma is androgen sensitive; ablation of endogenous androgen activity inhibits tumor growth and causes tumor suppression. The antiandrogenic effect of these medications complements medical or surgical treatments (LHRH analogue therapy or bilateral orchiectomy) that result in inhibition or cessation of testicular (but not adrenal) androgen production.
2. **Metabolism.** All three drugs have extensive hepatic metabolism and primarily renal elimination as glucuronide derivatives. All three are extensively bound to plasma proteins, and those significant quantities are not likely to be removed from the circulation by dialysis.
c. **Toxicity.** Slight adverse effects listed later for bicalutamide and for flutamide were reported during concurrent use of the antiandrogen LHRH analogue. Nilutamide may be less expensive, but it has two unique toxicities, night blindness and pulmonary toxicity, which limit its utility.
1. **Common.** Gynecomastia.
2. **Occasional.** Galactorrhea, impotence, myalgia, nausea, and vomiting.
3. **Rare.** Hematosuppression, methemoglobinemia, diarrhea, abnormal LFTs.
d. **Administration**
1. **Bicalutamide**
a. **Supplied** as 50-mg tablets bicalutamide (Casodex).
b. **Dose:** Use 50 mg p.o. qd.
2. **Flutamide**
a. **Supplied** as 125-mg capsules flutamide (Eulexin).
b. **Dose:** Use 250 mg p.o. t.i.d.
3. **Nilutamide**
a. **Supplied** as 50-mg tablets (Nilandron).
b. **Dose:** Use 300 mg p.o. qd for 30 days and then 150 mg p.o. qd thereafter.

F. **Other hormonal therapies**
1. **Progestins.** (hydroxyprogesterone, levonorgestrel, medroxyprogesterone, megestrol, norethindrone, norgestrel, and progesterone).
a. **Indications.** Treatment of anorexia or cachexia or weight loss; breast carcinoma; endometrial carcinoma; prostatic carcinoma; renal carcinoma; endometriosis.
b. **Pharmacology**
1. **Mechanism.** Progestins enter target cells by passive diffusion and bind to cytosolic (soluble) receptors that are loosely bound in the nucleus. The steroid–receptor complex initiates transcription, resulting in an increase in protein synthesis. Estrogenic effects are modified by the progestins either by reducing the availability or stability of the hormone–receptor complex or by turning off specific hormone-responsive genes by direct interaction with the progestin receptor in the nucleus. Hormonal effects such as estrogenic-, anabolic-, androgenic-, or glucocorticoid-inducing or suppressing effects are demonstrated to different degrees and depend on the progestin type and dose. Whereas the progestational effects dominate, the other effects can become important when choosing the appropriate progestin or monitoring side effects. Megestrol appears to have appetite-stimulant and metabolic effects that result in weight gain while causing minimal fluid retention. In certain doses, progestins can produce a diminished response to endogenous hormones in tumor cells by decreasing the number of steroid hormone receptors (estrogen, progesterone, androgen, and glucocorticoid). The suppression of the growth hormone–sensitive cells may be due to a direct cytotoxic effect or antiproliferative effects on cell-cycle growth and an increased terminal cell differentiation. At higher doses, some progestins compete for the glucocorticoid receptor, resulting in suppressed adrenal production of estradiol and androstenedione.
c. **Toxicity**
1. **Indicating need for medical attention**
a. **Incidence more frequent:** amenorrhea; breakthrough menstrual bleeding or amino menometrorrhagia; hyperglycemia.
b. **Incidence less frequent:** galactorrhea; mental depression; skin rash.
c. **Incidence rare:** adrenal suppression or insufficiency or hypotension; Cushing syndrome; thromboembolism, or thrombus formation.
2. **Indicating the need for medical attention only if they continue or are bothersome.**
a. Abdominal pain or cramping; dizziness; drowsiness for progesterone only; edema of ankles or feet; headache mild; mood changes with nervousness; ovarian enlargement; ovarian cyst formation (abdominal pain); pain, redness, or skin irritation at the site of infection.
b. **Incidence less frequent:** acne; breast pain or tenderness; hot flashes; insomnia; libido decrease; melasma (i.e., brown spots on exposed skin, which may persist after treatment stops); nausea.
d. **Administration**
1. **Medroxyprogesterone**
a. **Supplied** as 2.5-, 5-, and 10-mg tablets (Provera) or vials containing 400 mg/mL medroxyprogesterone (Depo-Provera).
b. **Dose**
i. Use 1 g i.m. weekly for six doses and then monthly, or
ii. Use 200 to 800 mg p.o. daily.
2. **Megestrol acetate** (Megace)
a. **Supplied** as 20- and 40-mg tablets and 40 mg/ml liquid.
b. **Dose:** Use 40 mg p.o. q.i.d. for breast cancer and 80 mg q.i.d. for endometrial cancer; 160 to 1,600 mg/day has been used as an appetite stimulant.

2. **Octreotide (Sandostatin)**
a. **Indications.** GI endocrine tumors such as carcinoid or vasoactive intestinal peptide (VIP)omas; cholera-like diarrhea caused by chemotherapeutic agents.
b. **Pharmacology**
1. **Mechanism.** The action of octreotide is similar to that of naturally occurring somatostatin but with a prolonged duration. Like the naturally occurring hormone, octreotide suppresses secretion of serotonin and gastroenteropancreatic peptides including gastrin, motilin and secretin, stimulates fluid and electrolyte absorption from the GI tract, and prolongs intestinal transit time. It blocks a carcinoid flush, decreases circulating concentrations of serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and controls other symptoms associated with a carcinoid syndrome.
2. **Metabolism.** The elimination half-life is 1.5 hours, and the duration of action is about 12 hours; 30% of the drug is excreted unchanged in the urine.
c. **Toxicity**
1. **Dose limiting.** Abdominal pain, vomiting, and loose stools.
2. **Dermatologic.** Injection-site pain or other reactions, hair loss, rash, thinning of skin, hyperhidrosis.

3. **Occasional.** Hypoglycemia; hypertension; hypotension, thrombophlebitis, cardiac ischemia or failure; fat malabsorption, abnormal LFTs; visual disturbance, rhinorrhea, dry mouth, throat discomfort, prostatitis, chills, fever.
4. **Rare.** GI bleeding, cholelithiasis, hepatitis.

d. **Administration**

1. **Supplied** as 1-mg ampules containing 0.05, 0.1, and 0.5 mg/mL.
2. **Dose.** From 100 to 600 µg s.c./day in two to four divided doses.

CHAPTER 3. FUNDAMENTALS OF PATIENT MANAGEMENT IN RADIATION ONCOLOGY

Jeffrey D. Bradley and Carlos A. Perez

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Goals of radiation therapy
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Radiobiologic principles
Probability of tumor control
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I. Introduction

Optimal care of patients with malignant tumors is a multidisciplinary effort that may combine two or more of the classic disciplines: surgery, radiation therapy, and chemotherapy. Pathologists, radiologists, clinical laboratory physicians, and immunologists are integral members of the team that renders the correct diagnosis. Many professionals, including physicists, laboratory scientists, nurses, social workers, and others, are intimately involved in the care of the patient with cancer.

Radiation oncology is a clinical and scientific discipline devoted to management of patients with cancer and other diseases by ionizing radiation, alone or combined with other modalities, investigation of the biologic and physical basis of radiation therapy, and training of professionals in the field. The aim of radiation therapy is to deliver a precisely measured dose of irradiation to a defined tumor volume with as minimal damage as possible to surrounding healthy tissue, resulting in eradication of the tumor, a high quality of life, and prolongation of survival at competitive cost. In addition to curative efforts, radiation therapy plays a major role in the effective palliation or prevention of symptoms of cancer including pain, restoring luminal patency, skeletal integrity, and organ function with minimal morbidity.

The radiation oncologist, like any other physician, must assess all conditions relative to the patient and the tumor under consideration for treatment, systematically review the need for diagnostic and staging procedures, and determine the best therapeutic strategy.

II. Types of irradiation

Many types of irradiation are used for treatment of both benign and malignant disease. The most common form of irradiation is by use of external beam photons or electrons. Photons are x-rays or g-rays and may be considered as bundles of energy that deposit dose as they pass through matter. The modern radiotherapy unit, a linear accelerator, produces both x-rays and electrons. Accelerating electrons between a cathode and anode in an x-ray tube generates x-rays. When the electrons strike a tungsten target at the end of the tube, x-rays are generated. Removing the tungsten target allows electrons to pass freely and be shaped to strike the targeted tissue. Radiotherapy units used in x-ray therapy are contact (40 to 50 kilovoltage potential or kV), superficial (50 to 150 kV), orthovoltage units (150 to 500 kV), and linear accelerators (4 to 25 million volts or MV). X-rays measured in kV, have a limited range, and are used to treat superficial tissues such as skin or mucosa. X-rays measured in MV are used when treating deeper targets (beyond 3- to 4-cm depth) and have “skin sparing” qualities. Electrons deposit their maximal energy slightly beyond the skin surface and have a sharp fall-off beyond their range. The electron depth–dose curve has a tail representing a component of photons within the electron beam. Electrons are used mainly for treating skin or superficial tissues. g-Rays are generated from isotopes. The most common source of g-rays for external beam radiotherapy is cobalt 60. Most radiotherapy facilities no longer use g-rays because of the need to replace or recalculate for decaying sources. An exception is the gamma knife unit used for stereotactic radiosurgery, which houses 201 cobalt 60 sources.

Other sources of external-beam irradiation are protons and neutrons. Protons are charged particles that have the advantage of depositing dose at a constant rate over the majority of the beam, but depositing the majority of dose at the end of their range, creating a Bragg peak. The advantage of protons over photons is that beyond the Bragg peak, protons fall off rapidly and avoid dose deposition beyond the target. This vastly limits radiation dose to normal tissues beyond the target. Because of the expense of protons, only three radiotherapy facilities in the United States currently have proton units available for patient treatment. Neutrons are uncharged heavy particles that are produced by a variety of mechanisms. The most common interaction producing neutrons is by accelerating protons to strike a beryllium target. Neutrons are neutral in charge and lose their energy primarily by striking protons in the cell nucleus. These nuclear events result in recoil protons and charged nuclear fragments that deposit large amounts of energy very close to the site of the initial interaction. Neutrons and protons have a relatively high relative biologic effectiveness (RBE) compared with photons, meaning they have an efficient cell kill per unit dose. Experience with neutrons has been limited to a few centers because of the cost of producing and maintaining these radiotherapy units. Clinical trials are under way to investigate other areas in which neutrons may provide an advantage over photons. An example of depth dose characteristics for photons, electrons, protons, and neutrons is shown in Fig. 3.1.

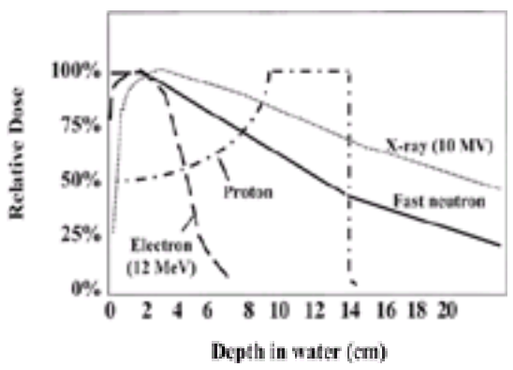

FIG. 3.1. Depth–dose curves for photons (x-rays), electrons, protons, and neutrons at energies used in radiation therapy.

Brachytherapy is an alternative method of irradiating targeted tissues. *Brachy* is translated from Greek, meaning short distance. In brachytherapy, sealed or unsealed radioactive sources are placed very close to or in contact with the targeted tissue. Because the absorbed dose falls off rapidly with increasing distance from the source (1/radius^2 for a point source and 1/radius for a line source), higher doses can be delivered safely to the targeted tissue over a short time. Prescribed brachytherapy doses are generally delivered in days for low dose rate (LDR) or minutes for high dose rate (HDR). Brachytherapy sources can be

placed temporarily, such as the use of iridium 192 for HDR applications in cervix cancer, or permanently, such as the use iodine 125 applications for prostate cancer. Unsealed sources are liquid and are used in radiopharmaceutical therapy. An example is iodine 131 for thyroid cancer. Commonly used sealed brachytherapy sources include cesium 137, iridium 192, iodine 125, palladium 103, gold 198, and strontium 90. Commonly used unsealed sources include iodine 131, phosphorus 32, strontium 89, and samarium 153.

III. Goals of radiation therapy

The clinical use of irradiation is a complex process that involves many professionals and a variety of interrelated functions. The aim of therapy should be defined at the onset of the therapeutic intervention:

1. **Curative:** the patient has a probability of long-term survival after adequate therapy. Oncologists may be willing to risk both acute and chronic complications as a result of therapy in an attempt to eradicate the malignant disease.
2. **Palliative:** there is no hope that the patient will survive for extended periods; symptoms that produce discomfort or an impending condition that may impair the comfort or self-sufficiency of the patient require treatment.

In curative therapy, some side effects of therapy, even though undesirable, may be acceptable. However, in palliative treatment, no major side effects should be seen. In palliation of epithelial solid tumors causing complications due to mass effect or pain, relatively high doses of irradiation (sometimes 75% to 80% of curative dose) are required to control the tumor for the survival period of the patient. There are some exceptions to high-dose palliative radiotherapy, including patients with lymphoma or multiple myeloma or for treatment of bleeding such as patients with cervical or endobronchial malignancies. Some disease conditions, such as low-grade lymphoma, are long-standing and incurable. These conditions also fall into the palliative category because one is generally willing to sacrifice some long-term tumor control to avoid the development of treatment-related complications.

IV. Basis for prescription of irradiation

1. Evaluation of tumor extent (staging), including radiographic, radioisotope, and other studies.
2. Knowledge of the pathologic characteristics of the disease.
3. Definition of goal of therapy (cure vs. palliation).
4. Selection of appropriate treatment modalities (irradiation alone or combined with surgery, chemotherapy, or both).
5. Determination of the optimal dose of irradiation and the volume to be treated, according to the anatomic location, histologic type, stage, potential regional nodal involvement, and other characteristics of the tumor, and the normal structures present in the region.
6. Evaluation of the patient's general condition, periodic assessment of tolerance to treatment, tumor response, and status of the normal tissues treated.

In addition to coordinating the patient's care with the surgical and medical oncology teams, the radiation oncologist must work closely with the physics, treatment planning, and dosimetry staffs within the radiotherapy facility to ensure the greatest possible accuracy, practicality, and cost benefit in the design of treatment plans. The ultimate responsibility for treatment decisions and the technical execution of the therapy will always rest with the physician.

V. Radiobiologic principles

A. Probability of tumor control

It is axiomatic in radiation therapy that higher doses of irradiation produce better tumor control, and numerous dose–response curves for a variety of tumors have been published. For every increment of radiation dose, a certain fraction of cells will be killed; therefore the total number of surviving cells will be proportional to the initial number present and the fraction killed with each dose (Fletcher GH. *Textbook of radiotherapy.* Philadelphia: Lea & Febiger, 1980). Thus various levels of irradiation will yield different probabilities of tumor control, depending on the extent of the lesion (number of clonogenic cells present). **Subclinical disease** has been referred to as deposits of tumor cells that are too small to be detected clinically and even microscopically but, if left untreated, may subsequently evolve to clinically apparent tumor. For subclinical disease in squamous cell carcinoma of the upper respiratory tract or for adenocarcinoma of the breast, doses of 45 to 50 Gy will result in disease control in more than 90% of patients. **Microscopic tumor,** such as at the surgical margin, should not be regarded as subclinical disease; cell aggregates 10^6/cc or greater are required for the pathologist to detect them. Therefore these volumes must receive higher doses of irradiation, in the range of 60 to 65 Gy in 6 to 7 weeks for epithelial tumors.

For **clinically palpable tumors,** doses of 60 (for T1) to 75 to 80 Gy or higher (for T4 tumors) are required (2 Gy/day, five fractions weekly). This dose range and probability of tumor control (TCP) has been documented for squamous cell carcinoma and adenocarcinoma (Fletcher GH. *Textbook of radiotherapy.* Philadelphia: Lea & Febiger, 1980). Ideally, the radiation oncologist would have the ability to deliver doses in this range. However, these doses are often beyond the tolerance of normal tissues. Exceeding normal tissue tolerance may result in debilitating or life-threatening complications.

The term **boost volume** is used to describe the residual tumor volume receiving the highest dose of irradiation. Baclesse (*Acta Union Int Contra Cancrum* 1959;15:1023–1026) introduced the concept of a boost to describe the additional dose given to the residual tumor after the initial subclinical dose has been delivered. The boost is designed to obtain the same probability of control as for subclinical aggregates (Fletcher GH. *Textbook of radiotherapy.* Philadelphia: Lea & Febiger, 1980.) For example, the initial large volume will often receive 45 to 50 Gy followed by a boost dose of 10 to 30 Gy through small portals.

One consequence of these concepts is use of portals that are progressively reduced in size (“shrinking field” technique) to administer higher doses of irradiation to the central portion of the tumor where more clonogenic cells (presumably hypoxic) are present, in comparison with lesser doses required to eradicate the disease in the periphery, where a lower number and better-oxygenated tumor cells are assumed to be present.

B. Effects of radiation on normal tissue

A variety of changes in normal tissues are induced by ionizing radiation, depending on the total dose, fractionation schedule (daily dose and time), and volume treated; these factors are closely interrelated (Fig. 3.2). For many normal tissues, the necessary dose to produce a particular sequela increases as the irradiated fraction of volume of the organ decreases (Table 3.1).

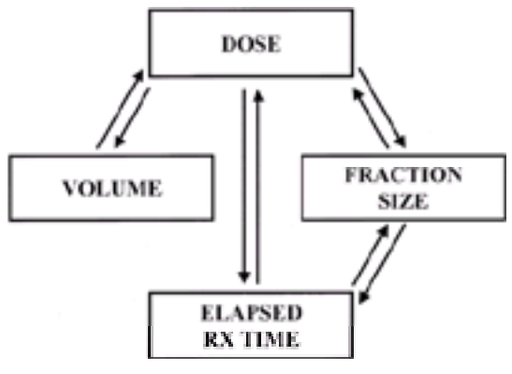

FIG. 3.2. Basic dosimetric parameters determining normal tissue effects in radiation therapy. (From Perez CA, Brady LW, Roti Roti JL. Overview. In: Perez CA, Brady LW, eds. *shape Principles and practice of radiation oncology.* 3rd ed. Philadelphia: Lippincott-Raven, 1998:1–17, with permission.)

TABLE 3.1. POSSIBLE SPECIFIC SEQUELAE OF THERAPY DISCUSSED IN INFORMED CONSENT

As the total dose to a particular tumor and surrounding normal tissues increases, both TCP and normal tissue complication probability (NTCP) increase. Both TCP and NTCP are sigmoidal in shape. The farther these two curves diverge, the more favorable the **therapeutic ratio** (Fig. 3.3). When the curves are close together, increases in irradiation dose will lead to exponential increases in NTCP. The TCP and NTCP curves can be separated by use of biologic modifiers, radioprotectors, three-dimensional conformal irradiation, or intensity-modulated radiation therapy. When separated, higher doses of radiation therapy can be delivered more safely. Chemotherapy also modifies the TCP and NTCP curves, often by shifting both curves to the left. Thus with chemoradiation, lower doses of radiotherapy are required to produce a given TCP/NTCP.

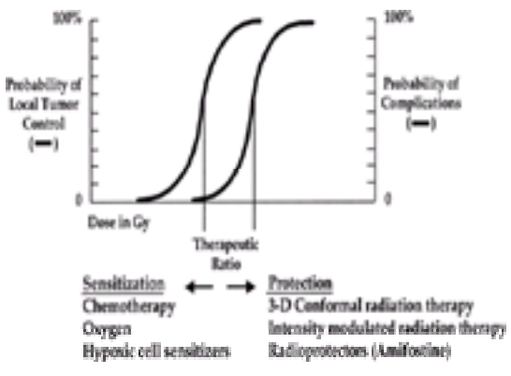

FIG. 3.3. The therapeutic ratio represents the relationship between two sigmoidal curves; the tumor control probability (TCP) and the normal tissue complication probability (NTCP) curves. The further the two curves are separated, the higher the TCP and the lower the NTCP.

Higher-tolerance doses have been observed than initially reported for a variety of organs, which stresses the importance of updating this information in the light of more precise treatment planning and delivery of irradiation and more accurate evaluation and recording of sequelae (*Int J Radiat Oncol Biol Phys* 1991;21:109–122). Burman et al. (*Int J Radiat Oncol Biol Phys* 1991;21:123–135) used these estimates to develop a series of tolerance curves for multiple organs.

Radiation causes cell death by direct cell kill via DNA double-strand breaks or by causing sublethal and potentially lethal damage. Sublethal damage repair (SLDR) is defined by the increase in cell survival that occurs when a single dose of x-rays is divided into two equal fractions. Potentially lethal damage repair (PLDR) is defined by the increase in cell survival that occurs by modifying growth conditions (i.e., oxygenation) during a single dose of x-rays. Both SLDR and PLDR are important concepts in considering normal tissue repair. Normal tissues have a substantial capacity to recover from sublethal or potentially lethal damage induced by radiation (at tolerable dose levels). Injury to normal tissues may be caused by the radiation effect on the microvasculature or the support tissues (stromal or parenchymal cells).

The minimal tolerance dose is defined as $TD_{5/5}$, which represents the dose of radiation that could cause no more than a 5% severe complication rate within 5 years after treatment. An acceptable complication rate for severe injury is 5% to 10% in most curative clinical situations. Moderate sequelae are noted in varying proportions (10% to 25% of patients), depending on the dose of irradiation given and the organs at risk. The $TD_{5/5}$ for various organs is listed in Table 3.2. These parameters continue to be adjusted as clinical data are obtained from conformal planning systems.

TABLE 3.2. NORMAL TISSUE TOLERANCE TO THERAPEUTIC IRRADIATION

Chronologically, the effects of irradiation have been subdivided as **acute** (first 6 months), **subacute** (second 6 months), or **late,** depending on the time they are observed. The gross manifestations depend on the kinetic properties of the cells (slow or rapid renewal) and the dose of irradiation given.

No correlation has been established between the incidence and severity of acute reactions and the same parameters for late effects (Karcher KH, ed. *Progress in radio-oncology II.* New York: Raven Press, 1982:287–296). This may be due to the difference in the slopes of cell-survival curves for acute or late effects (Steel GE, Adams GE, Peckham MT, eds. *Biological basis of radiotherapy.* Amsterdam: Elsevier Science, 1983:181–194).

Combining irradiation with surgery or cytotoxic agents frequently modifies the tolerance of normal tissues and/or tumor response to a given dose of irradiation, which may necessitate adjustments in treatment planning and dose prescription. For example, in curative radiation therapy for cancer of the esophagus, concurrent chemotherapy consisting of 5-fluorouracil (5-FU) and cisplatin and radiation therapy to 50 Gy result in improved local tumor control and similar esophagitis rates when compared with irradiation alone to doses of 64 Gy.

C. **Dose–time factors**

Dose–time considerations constitute a complex function that expresses the interdependence of total dose, time, and number of fractions in the production of

a biologic effect within a given tissue volume (Fig. 3.2).

In general, fractionation of irradiation will spare acute reactions because of compensatory proliferation in the epithelium of the skin or the mucosa, which accelerates at 2 or 3 weeks after initiation of therapy (*Br J Radiol* 1973;54:29–35). However, a prolonged course of therapy with small daily fractions will decrease early acute reactions but will not protect from serious late damage to normal tissue, may allow the growth of rapidly proliferating tumors, and may be inconvenient for the patient and uneconomic.

Short overall times are required for tumors with rapid proliferation. For median potential doubling times of 5 days and intermediate radiosensitivity, overall times of 2.5 to 4 weeks would be optimal. More slowly proliferating tumors should be treated with longer overall times. With regard to fractionation, Fowler (Steel GE, Adams GE, Peckham MT, eds. *Biological basis of radiotherapy.* Amsterdam: Elsevier Science, 1983:181–194) stated that five fractions per week are preferable to three fractions, because there is less log cell killing with the latter schedule (about 1 log for all, except 1 or 2 weeks overall time).

Radiation treatments may be delivered by conventional fractionation, hypofractionation, hyperfractionation, or accelerated fractionation schedules. In the United States, **conventional fractionation** is defined as 30 to 40 fractions delivered once daily over a period of 7 to 8 weeks. Total doses for conventional fractionation are typically in the range of 60 to 75 Gy and are delivered in fraction sizes of 1.8 to 2.0 Gy. The other fractionation schedules are defined by overall treatment duration and total dose of radiation compared with conventional fractionation. **Hypofractionation** refers to a shorter overall treatment duration and a lower total dose designed to achieve the same TCP. For example, in the Manchester system, radical treatments are delivered in 16 fractions over a 3-week period. The fraction sizes are larger than conventional fractionation and are delivered once daily. Common examples of hypofractionation in the United States are palliative therapy regimens of 30 Gy in 10 fractions over a 2-week period or 10 Gy in a single fraction. The difficulty with hypofractionation is the effect of the larger dose per fraction on normal tissues. Delivering larger fractions of irradiation negates the normal tissue-sparing effects of fractionation by decreasing SLDR.

The basic rationale of **hyperfractionation** is that the use of small dose fractions of 1.1 to 1.2 Gy allows higher total doses to be delivered over the same treatment duration (as conventional fractionation) within the tolerance of late-responding tissues. Late-responding tissues such as bowel, spinal cord, kidney, lung, and bladder have the same probability of complications with hyperfractionation. However, the patient will experience more acute reactions as a result of the larger total dose. The typical period between daily fractions is 6 hours to allow late tissue repair. An example of hyperfractionation is 69.6 Gy total dose delivered over a 6-week period in twice-daily fractions of 1.2 Gy for head and neck or lung cancer. The basic rationale for **accelerated fractionation** is that a reduction in overall treatment time decreases the opportunity for tumor cell regeneration during treatment and therefore increases the probability of tumor control for a given total dose. Thus the fraction size is decreased, and the treatment duration is decreased compared with conventional fractionation. Examples of accelerated fractionation include continuous hyperfractionated accelerated radiation therapy (CHART) delivering 54 Gy in 36 fractions over 12 days for non–small cell lung cancer or delivering 45 Gy in 30 fractions over a 3-week period in small cell lung cancer.

D. Prolongation of overall treatment time, tumor control, and morbidity

Treatment interruptions result in a lower TCP for the same total dose received. The total dose of irradiation to produce a given probability of tumor control must be increased when fractionation is prolonged beyond 4 weeks because of repopulation of surviving cells, which may result in improved nutrition of those cells after early shrinkage of the tumor due to the initial irradiation fractions. Withers et al. (*Acta Oncol* 1988;27:131–146) estimated that the dose of irradiation is to be increased by 0.6 Gy for every day of interruption of the treatment. Taylor et al. (*Radiother Oncol* 1990;17: 95–102), in 473 patients with squamous cell carcinoma of the head and neck treated with irradiation, estimated an increment in isoeffect dose per day to be larger than 1 Gy (a dose consistent with the Withers estimate of 0.6 Gy).

There is the potential impact of modifying the overall time by *split course* when the daily fractions of irradiation administered are higher than conventional (administration of 2.5- to 3-Gy tumor dose for 10 fractions, 2 or 3 weeks' rest, and administration of a second course similar to the first one for a total of 50 or 60 Gy). The Radiation Therapy Oncology Group (RTOG) reported no therapeutic advantage with this technique in a variety of studies of head and neck tumors or carcinoma of the uterine cervix, lung, or urinary bladder. Tumor control and survival were comparable to those obtained with conventional fractionation. If anything, the late effects have been slightly greater in the split-course groups.

Conversely, reports published by the University of Florida of patients with carcinoma of the head and neck, uterine cervix, and prostate treated with definitive doses of radiation therapy with conventional fractionation but with a rest period halfway through the course of therapy showed that some groups of patients in the split-course regimen had lower tumor control and survival, probably as a result of the repopulation of clonogenic surviving cells in the tumor during the rest period (*Int J Radiat Oncol Biol Phys* 1980;6:1645–1652; *Int J Radiat Oncol Biol Phys* 1980;6:175–181). The split-course technique has been largely abandoned in the United States.

E. Linear–quadratic equation (a/b ratio)

Recently formulations based on dose–survival models have been proposed to evaluate the biologic equivalence of various doses and fractionation schedules. These assumptions are based on a linear–quadratic survival curve represented by the equation:

$$\text{Log}_e S = aD + bD^2$$

in which a represents the linear (i.e., first-order dose dependent) component of cell killing, and b represents the quadratic (i.e., second-order dose dependent) of cell-killing component. Thus a represents the more reparable (over a few hours) component of cell damage. Figure 3.4 represents a cell-survival curve showing both immediate and late responses to a single fraction of irradiation. At dose A, the a (linear) component of cell killing predominates. At dose B, the b (quadratic) component of cell killing predominates. The dose at which the two components of cell killing are equal constitutes the a/b ratio. Note that neutrons produce a constant rate of cell kill opposed to x-rays, because of the negligible contribution of sublethal damage to cell death.

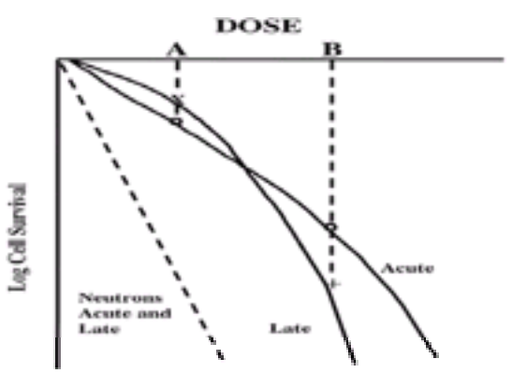

FIG. 3.4. Hypothetical survival curves for the target cells for early and late effects in normal tissues exposed to x-rays or neutrons. The a/b ratio is lower for late effects than for early effects in x-irradiated tissues, resulting in a greater change in effect in late-responding tissues with change in dose. At dose A, survival of target cells is higher in late-effects than in early-effects tissues; at dose B, the reverse is true. Increasing the dose per fraction from A to B results in a relatively greater increase in late than acute injury. For neutrons, the a/b ratio is high, with no detectable influence of the quadratic function (bd^2) over the first two decades of reduction in cell survival, implying that accumulation of sublethal injury plays a negligible role in cell killing by doses of neutrons of clinical interest. (From Withers HR, Thames HD, Peters LJ. Biological basis for high RBE values for late effects of neutron irradiation. *Int J Radiat Oncol Biol Phys* 1982;8:2071, with permission.)

The severity of late effects changes more rapidly with a variation in the size of dose per fraction when a total dose is selected to yield equivalent acute

effects. With a decreasing size of dose per fraction, the total dose required to achieve a certain isoeffect increases more for late-responding tissues than for immediately responding tissues. Thus in hyperfractionated regimens, the tolerable dose would be increased more for late effects than for early effects. Conversely, if large doses per fraction are used, the total dose required to achieve isoeffects in late-responding tissues would be reduced more for late effects than for early effects. In general, immediately reacting tissues have a high a/b ratio (between 8 and 15 Gy), whereas tissues involved in late effects have a low a/b ratio (1 to 5 Gy). A biologically equivalent dose (BED) can be obtained by using this formula:

BED = – S/a
BED = nd[1 + d/(a/b)]

To compare two treatment regimens, with some reservations, the following formula can be used.

Dr/Dx = a/b + dx/(a/b)

in which Dr is the known total dose (reference dose), Dx is the new total dose (with different fractionation schedule), dr is the known fractionation (reference), and dx is the new fractionation schedule.

Following is an example of use of this formula (with some reservations!): Suppose 50 Gy in 25 fractions is delivered to yield a given biologic effect. If one assumes that the subcutaneous tissue is the limiting parameter (late reaction), it is desirable to know what the total dose to be administered will be, by using 4-Gy fractions. Assume a/b = 5 Gy.

Using this formula

Dx = Dr
a/b + dr
a/b + dx

Thus

Dx = 50 Gy(5 + 2/5 + 4) = 39 Gy

Answer: A dose of 50 Gy in 25 fractions provides the same biologic equivalent dose as 39 Gy in 4-Gy fractions.

VI. Radiation treatment planning

A. Introduction to treatment planning

International Commission on Radiation Units and Measurements (ICRU) No. 50 (*ICRU and 50. Prescribing, Recording, Reporting, Photon Beam Therapy*. International Commission on Radiation Units and Measurements, Washington, DC, 1994) has defined the volumes of interest in treatment planning. The delineation of tumor and target volumes is a crucial step in radiation therapy planning. Gross tumor volume (GTV) is all known gross disease including abnormally enlarged regional lymph nodes. When GTV is determined, it is important to use the appropriate computed tomography (CT) window and level settings that give the maximal dimension of what is considered potential gross disease. Other diagnostic imaging studies in addition to CT, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), are valuable tools used by the radiation oncologist to define GTV. Clinical target volume (CTV) encompasses the GTV plus regions considered to harbor potential microscopic disease. Planning target volume (PTV) provides a margin around the CTV to allow variation in treatment setup and other anatomic motion during treatment such as respiration. The PTV does not account for treatment machine beam characteristics. Treatment portals must adequately cover all treatment volumes in addition to a margin to compensate for geometric inaccuracies during irradiation exposure.

Simulation has been used in most instances to identify the tumor volume and sensitive structures accurately and to document the configuration of the portals and target volume to be irradiated. Two types of simulation units are used in most clinics. A conventional simulator consists of a table and gantry with 360 degrees of rotation as well as fluoroscopy and diagnostic x-ray capability. Many centers also have a CT-simulator, in which patients are positioned for treatment with various immobilization devices; a CT scan is obtained of the area of interest, and contours are delineated (GTV, CTV, and PTV) from the CT images at a computer workstation.

Treatment aids, such as shielding blocks, molds, masks, immobilization devices, and compensators, are extremely important in treatment planning and delivery of optimal dose distribution. Simpler treatment-delivery techniques that yield an acceptable dose distribution should be preferred over more costly and complex ones, in which a greater margin of error on a day-to-day treatment basis may be present. Repositioning and immobilization devices are critical because the only effective irradiation is that which strikes the clonogenic tumor cells.

Quality assurance is a vital part of every radiotherapy clinic. Localization (portal) films are the primary tools for quality assurance in radiation delivery. The portal film is exposed during treatment delivery and is compared with the corresponding simulator film (reference image). Treatment-delivery verification also may be accomplished with on-line imaging (electronic portal imaging) devices (*Int J Radiat Oncol Biol Phys* 1993;27:707–716). Errors detected by portal imaging can be caused by alterations in patient positioning, errors in field size and orientation, or placement and shaping of the beam apertures. Portal films are obtained during the initial treatment setup and weekly thereafter, as recommended by the AAPM Task Group on Comprehensive Clinical Quality Assurance. The frequency of portal imaging may be increased by considering factors such as treatment site, patient weight, and the patient's ability to maintain a fixed position.

Various steps can be taken to decrease toxicity in normal tissues, including precise treatment-planning and irradiation techniques, selective decreased volume receiving higher doses dictated by estimated cell burden, and maneuvers to exclude sensitive organs from the irradiated volume. With the emphasis on organ preservation (which is being applied to patients with tumors in the head and neck, breast, and rectosigmoid, and soft tissue sarcomas), treatment planning is critical to achieve maximal tumor-control probability and satisfactory cosmetic results.

B. Three-dimensional treatment planning

The CT simulator allows more accurate definition of tumor volume and anatomy of critical normal structures, three-dimensional (3-D) treatment planning to optimize dose distribution, and radiographic verification of volume treated, as is done with conventional simulators (*Int J Radiat Oncol Biol Phys* 1994;30:887–897). Advances in computer technology have augmented accurate and timely computation, display of 3-D radiation dose distributions, and dose–volume histograms (DVHs) (*Semin Radiat Oncol* 1992;2:246–256). These developments have stimulated sophisticated 3-D treatment-planning systems, which yield relevant information in evaluation of tumor extent, definition of target volume, delineation of normal tissues, virtual simulation of therapy, generation of digitally reconstructed radiographs, design of treatment portals and aids (e.g., compensators, blocks), calculation of 3-D dose distributions and dose optimization, and critical evaluation of the treatment plan.

In addition, DVHs are extremely useful as a means of dose display, particularly in assessing several treatment-plan dose distributions. They provide a complete summary of the entire 3-D dose matrix, showing the amount of target volume or critical structure receiving more than a specified dose level. Because they do not provide spatial dose information, they cannot replace the other methods of dose display such as room-view displays, but can only complement them. For example, the DVH may show the percentage PTV receiving the prescribed dose, but cannot locate the portion of the PTV receiving less than the prescribed dose. Treatment verification is another area in which 3-D treatment-planning systems play an important role. Digitally reconstructed radiographs of sequential CT slice data are used to generate a simulation film that can be used to aid in portal localization and comparison with the treatment portal film for verifying treatment geometry.

The increased sophistication in treatment planning requires parallel precision in patient repositioning and immobilization and portal-verification techniques (*Int J Radiat Oncol Biol Phys* 1988;14:777–786). Portal films, used for geometric/topographic verification, are generally of fair quality, making accurate identification of internal landmarks difficult. Several real-time on-line verification systems allow monitoring of the position of the area to be treated during

radiation exposure.

Computer-aided integration of the data generated by 3-D radiation-treatment planning with parameters used on the treatment machine, including gantry and couch position, may decrease localization errors and enhance the precision and efficiency with which irradiation is administered.

Conformal radiation therapy, including 3-D (3D CRT) and intensity-modulated radiation therapy (IMRT), represent important advances in the precise delivery of radiation therapy. 3D CRT–planning software is widely available through commercial vendors and, in our opinion, represents the standard of care for definitive radiation therapy. 3D CRT–planning systems provide the radiation oncologist the tools to encompass the entire tumor target, avoid marginal misses, and account for normal tissue dose–volume relations (*Int J Radiat Oncol Biol Phys* 1995;33:979–983; *Int J Radiat Oncol Biol Phys* 2000;46:3–6).

C. **Intensity-modulated radiation therapy**

This new approach to 3-D treatment planning and conformal therapy optimizes the delivery of irradiation to irregularly shaped volumes through a process of complex inverse treatment planning and dynamic delivery of irradiation that results in modulated fluence (intensity) of photon beams. By varying the fluence across multiple treatment fields, the irradiation dose can be modulated to conform to irregular shapes (i.e., concave) and to design a heterogeneous dose distribution.

A few IMRT hardware and software packages are commercially available including rotational slice-by-slice, dynamic multileaf, and static (or step and shoot) multileaf methods. Central to intensity modulation is the development of multileaf collimators (MLCs) and the concept of inverse treatment planning. MLCs are a set of shielding vanes measuring 1 cm wide that are located in the head of the linear accelerator and shape the radiation portal. Each vane is controlled independently and can remain static (static MLC) or move across the treatment field during “beam on” time (dynamic MLC). To understand inverse treatment planning, one must first understand traditional forward treatment planning. Under forward treatment planning, the radiation oncologist draws the radiation portals, considers the dose distribution generated by those portals, and adjusts the portals according to the desired dose distribution. Forward planning is cumbersome. Inverse planning reverses that order. The radiation oncologist contours the desired target volumes and critical structures to be avoided and prescribes an ideal dose distribution. Inverse planning starts with the ideal dose distribution and finds through trial and error (simulated annealing) the beam characteristics (fluence profiles) that produce the best approximation of the ideal dose. A back-projection technique conforms the irradiation dose to the shape of the tumor through careful choice of filters, beam placement, and shaping of the portals, minimizing dose to critical adjacent structures (*Med Phys* 1993;38:291–304; *Radiother Oncol* 1988;12:129–140; *Med Phys* 1994;21:913). First-generation IMRT technology is now in clinical use and is under investigation at various academic centers. We are certain to see more advanced second- and third-generation IMRT technology in use within the next few years.

The first IMRT technique, rotational slice-by slice IMRT, was described by Carol et al. (*Int J Radiat Oncol Biol Phys* 1992;24(suppl 1):158) with modulated photon beams that could be delivered with dynamic MLCs designed to deliver specific doses to irregularly shaped volumes. Scanning fields are subdivided into subfields of uniform intensity. The rotational intensity-modulated technique (NOMOS Peacock, Sewickley, PA) narrows the radiation beams, each 2 to 4 cm wide, which are further divided into four small beams that can each be turned on or off by the MLC of the linear accelerator as the exposure proceeds. One rotation treats two slices. After one gantry rotation, an indexing apparatus attached to the table moves the table precisely to the next position in preparation for the next rotational treatment. The photon fluence is modified throughout each gantry rotation by a computer-driven collimating system that varies the position of the collimating vanes (*Int J Radiat Oncol Biol Phys* 1994;29:213–214).

The collimator consists of 40 divergent tungsten vanes, each 8 cm thick, which functionally narrow the beam coming from the accelerator. Each beam projects to 8.5 by 10 mm at 100-cm distance from the target, and all beams are divergent. As the gantry rotates around the patient, each of these 40 small beams can be turned on or off by movement of its vane for a variable period, thus creating the intensity modulation required in the inverse solution. Because a rotation about the patient treats only the equivalent of two slices throughout the patient (e.g., 17 mm in length), the treatment couch must be successively indexed between rotations when longer targets are treated. A region of adjacent field mismatch between two successive rotations is created for each index of the treatment couch. This is accomplished with a special couch-indexing device with a 0.1-mm resolution digital readout, which clamps to the rail supports on the side of the treatment couch. The overall field size is determined by collimator width (20 cm) and the number of cylindrical slices treated.

Because there is successive field matching with the NOMOS Peacock technique, immobilization is vitally important to avoid overdosing or underdosing successive fields. The initial use of this technique was for intracranial or head and neck patients. A removable invasive stereotactic fixation device was designed that attached to the patient's skull. Later, the system supported the use of standard noninvasive immobilization devices such as a thermoplastic mask.

VII. **Combination of therapeutic modalities**

A. **Irradiation and surgery**

The rationale for *preoperative radiation therapy* relates to its potential ability to eradicate subclinical or microscopic disease beyond the margins of the surgical resection, to diminish tumor implantation by decreasing the number of viable cells within the operative field, to sterilize lymph node metastases outside the operative field, to decrease the potential for dissemination of clonogenic tumor cells that might produce distant metastases, and to increase the possibility of resectability. The main disadvantage of preoperative irradiation is that it may interfere with normal healing of the tissues affected by the radiation. Such interference, however, is minimal when radiation doses are less than 45 to 50 Gy in 5 weeks.

The rationale for *postoperative irradiation* is based on the fact that it is possible to eliminate any residual tumor in the operative field by destroying subclinical or microscopic foci of tumor cells after the surgical procedure by eradicating adjacent subclinical foci of cancer (including lymph node metastases) and by delivering higher doses than can be achieved with preoperative irradiation, the greater dose being directed to the volume of high-risk or known residual disease.

The potential disadvantages of postoperative irradiation are related to the delay in initiation of radiation therapy until wound healing is completed. Theoretic and experimental evidence suggests that the radiation effect may be impaired by vascular changes produced in the tumor bed by surgery.

B. **Irradiation and chemotherapy**

Chemotherapy and radiation therapy are combined to obtain an additive or supraadditive effect (Phillips. *Radiation oncology: technology and biology.* Philadelphia: WB Saunders, 1994:113–151). Enhancement describes any increase in effect greater than that observed with either chemotherapy or irradiation alone on the tumor or normal tissues. Calculation of the presence of additivity, supraadditivity, or subadditivity is simple when dose–response curves for irradiation and chemotherapy are linear. When chemotherapeutic agents are used, (as described by Goldie John MJ, Flam MS, et al., eds. *Chemoradiation: an integrated approach to cancer treatment.* Philadelphia: Lea & Febiger, 1993), the agents should not be cross resistant, and each agent should be quantitatively equivalent to the other.

Chemotherapy alone or combined with irradiation may be used in several settings. **Primary chemotherapy** is used as part of the primary lesion treatment (even if later followed by other local therapy) and when the primary tumor response to the initial treatment is the key identifier of systemic effects. **Adjuvant chemotherapy** is used as an adjunct to other local modalities as part of the initial curative treatment. Frei (*J Natl Cancer Inst* 1989;80:1088–1089,) proposed the term **neoadjuvant chemotherapy** when this modality is used in the initial treatment of patients with localized tumors, before surgery or irradiation.

Administration of chemotherapy **before** irradiation produces some cell killing and reduces the number of cells to be eliminated by the irradiation. Use of chemotherapy **during** radiation therapy has a strong rationale because it could interact with the local treatment (additive and even supraadditive action) and also could affect subclinical disease early in treatment. Nevertheless, the combination of modalities may enhance normal tissue toxicity.

C. **Integrated multimodality cancer management**

Combinations of two or all three of the classic modalities are frequently used to improve tumor control and patient survival. Steel and Peckham (Steel GG, Adams GE, Peckham MJ, eds. *The biological basis of radiotherapy*. The Netherlands: Elsevier Science, 1983:239–248) postulated the biologic basis of cancer therapy as spatial cooperation, in which an agent is active against tumor cells spatially missed by another agent, addition of antitumor effects by two

or more agents; and nonoverlapping toxicity and protection of normal tissues. Figure 3.4 illustrates the selective use of a given therapeutic modality to achieve tumor control in each compartment. Large primary tumors or metastatic lymph nodes must be removed surgically or treated with definitive radiation therapy. Regional microextensions are eliminated effectively by irradiation without the anatomic and at times physiologic deficit produced by equivalent medical surgery. Chemotherapy is applied mainly to control disseminated subclinical disease, although it also has an effect on some larger tumors.

Organ preservation is being vigorously promoted, as it enhances the quality of life and psychoemotional feelings of our patients with excellent tumor control and survival, as has been demonstrated in many tumors.

VIII. Follow-up

Continued support of the patient during therapy is mandatory, with at least one weekly evaluation by the radiation oncologist to assess the effects of treatment on the tumor and the side effects of therapy. Psychological and emotional reinforcement, medications, dietetic counseling, oral cavity care, and skin-care instructions are integral parts of the management of these patients and should result in better therapeutic outcome.

IX. Quality assurance

A comprehensive quality-assurance program is critical in any radiation oncology center to ensure the best possible treatment for the individual patient and to establish and document all operating policies and procedures.

Quality-assurance procedures in radiation therapy will vary, depending on whether standard treatment or a clinical trial is carried out at single or multiple institutions. Particularly in multiinstitutional studies, clear instructions and standardized parameters are needed in dosimetry procedures, treatment techniques, and treatment planning to be carried out by all participants. Many reports of the Patterns of Care Study demonstrate a definite correlation between the quality of the radiation therapy delivered at various types of institutions and the outcome of therapy.

A. Quality-assurance committee

The director of the department appoints the committee, which meets regularly to review: results of review and audit process, physics quality-assurance program report, outcome studies, mortality and morbidity conference, any case of “mis-administration” or error in delivery of more than 10% of the intended dose, and any chart in which an incident report is filed. Additional details can be obtained from the American College of Radiology.

CHAPTER 4. PRINCIPLES OF SURGICAL ONCOLOGY

Rebecca L. Aft

Role of the surgical oncologist
Diagnostic procedures: acquisition of material for diagnosis
Fine-needle aspiration cytology
Core needle biopsy
Cutaneous punch biopsy
Open biopsy
Staging: determining the extent of disease and resectability
Mediastinoscopy
Laparotomy
Laparoscopy
Lymphadenectomy
Sentinel lymph node biopsy
Surgical treatment
Primary resection
Operative principles
Extent of resection
Laparoscopic and laparoscopy-assisted surgeries
Metastases and recurrent disease
Distant metastasis
Resection for recurrent locoregional disease
Palliative surgery
Reconstruction: functional and cosmetic
Newer treatment modalities
Cryotherapy
Radiofrequency ablation
Surgery for complications of treatment
Surgical complications: obstruction, stricture
Medical complications
Vascular access
Central venous catheterization
Arterial catheters: hepatic artery infusion catheters
Enteral feeding tubes
Gastrostomy tubes
Jejunostomy tubes
Suggested Readings

I. Role of the surgical oncologist

Early cancer therapy centered on surgical excision as the primary treatment modality for solid tumors. It was theorized that cancer spread occurred sequentially from the primary site to the regional lymph nodes and then on to distant sites. Therefore it was hypothesized that complete local excision of all cancerous cells would lead to effective disease control. In patients with untreated cancer, median survival was frequently measured in months. Early *en bloc* resection of tumors with contiguous normal surrounding tissue and lymph nodes led to improved overall survival. As a consequence, increasingly aggressive and extensive resections of malignant tumors were performed. As the initial improvement in survival began to plateau, it became apparent that successively larger resections to obtain locoregional control of larger tumors did not necessarily translate into further survival benefit. This led to the testing and development of screening strategies and adjuvant therapies. The current role for the surgeon in the management of patients with cancers involves a broad spectrum of surgical procedures for diagnosis, local control, cure, and palliation.

II. Diagnostic procedures: acquisition of material for diagnosis

Once a lesion has been identified, it is usually the surgeon's role to provide adequate material for definitive diagnosis. The method of biopsy requires consideration of the differential diagnosis, amount of tissue needed for definitive diagnosis, location of the lesion, and potential forms of treatment. It is preferable to perform biopsies of lesions at the periphery where viable tumor is located, because the cores of solid tumors may be necrotic. This also allows the pathologist to evaluate the invasion of normal tissue because some tumors (thyroid) have low mitotic rates and bland cytologic features, which are insufficient for determining malignancy. General principles for biopsy include sampling representative tissue, obtaining adequate tissue for diagnosis, procuring viable tissue, minimizing contamination of adjacent uninvolved tissues, orienting the tissue for margin analysis, and providing tissue to the pathologist in the appropriate conditions (fresh or fixed).

A. Fine-needle aspiration cytology

Fine-needle aspiration (FNA) yields a smear of single cells and aggregates for cytologic analysis. The biopsy is performed by using a 22- to 25-gauge needle, which can be percutaneously guided to most anatomic sites. Although the track of the needle is theoretically contaminated with malignant cells, in practice, FNA-track metastases are rarely a clinical problem. Cells are collected in the hub of the needle and subsequently expelled onto slides. The slides are air dried or sprayed with cytofixative for staining. The most common stains used for analysis are Papanicolaou for nuclear morphology and Diff-Quick for cytoplasmic features. Diagnosis is based on the cytologic features of the cells including cohesiveness, nuclear and cytoplasmic morphology, and number. An advantage of FNA is that a wide area of the tumor can be sampled. Limitations include small sample size; lack of information on histologic architecture which cannot distinguish between *in situ* and invasive tumors (breast, thyroid); inability to obtain grade of tumors; and interpretation of certain immunohistochemical stains. FNA can be useful for diagnosing recurrent lymphoma; however, for a primary diagnosis of lymphoma, more tissue may be required.

B. Core needle biopsy

Core needle biopsies yield fragments of tissue, which allows the evaluation of tumor architecture. The biopsy is performed by using 14- to 16-gauge needles specifically designed for this purpose (Tru-Cut, Bioptry). The procedure is performed by anesthetizing the skin overlying the lesion, puncturing the skin with an 11 blade, inserting the biopsy needle into the tumor, and deploying the biopsy device. Core needle biopsies can be combined with imaging such as mammography (stereotactic core biopsy), computed tomography (CT), or ultrasonography. A false-negative biopsy may result if the needle misses or skives (pares) the malignant tumor, which may occur with very sclerotic cancers such as breast. The most common complication of core needle biopsies is bleeding, and the procedure should be cautiously performed in patients with coagulopathies. In addition, masses near large vascular structures, hollow organs, or in the central nervous system (CNS) are not amenable to this procedure.

C. Cutaneous punch biopsy

Punch biopsies are used to obtain tissue from cutaneous lesions by using 2- to 6-mm round surgical blades. A full-thickness skin specimen including subcutaneous fat is obtained. The procedure is performed by anesthetizing the skin and advancing the punch blade into the lesion. The core of tissue is removed from the wound with a forceps, and the tissue base is divided with scissors. The wound can be closed with a single absorbable suture. The procedure is simple to perform with few complications and is useful for obtaining tissue for pathologic diagnosis from suggestive skin lesions (melanoma, basal cell, or squamous cell carcinoma) that may subsequently require definitive surgical resection.

D. Open biopsy

1. **Incisional biopsy**

   Occasionally neoplasms are not amenable to percutaneous needle biopsy because of anatomic location, requirements for large amounts of tissue for diagnosis (sarcomas), or concern regarding sampling errors in diffuse lesions. An incisional biopsy is the most expedient method for obtaining tissue for definitive diagnosis. These procedures are usually performed in an outpatient surgical setting. Incisional biopsies are performed by placing an incision directly over the lesion after anesthetizing the skin. A wedge of tissue large enough for accurate diagnosis is removed from the periphery of the lesion. Excellent hemostasis must be obtained to avoid hematogenous seeding. The biopsy incision should be planned such that it can be included in tissue to be removed by subsequent definitive surgery (longitudinal for limb sarcomas) because some tumors have a propensity for seeding the biopsy incision. A biopsy site that is far removed from the potential operative incision can severely jeopardize later attempts for surgical control of the tumor or potential limb-sparing procedures and can result in a compromised operation.

2. **Excisional biopsy**

   Excisional biopsies remove the entire lesion and are best suited for small lesions. This may be curative for small cancers (melanoma, breast cancer, sarcoma, basal cell carcinomas). Depending on the size of the lesion and the closure required, excisional biopsies can be performed as an office-based procedure or in the operating room. All specimens should be oriented for accurate margin assessment. This allows the surgeon to resect additional tissue for inadequate or close margins.

III. **Staging: determining the extent of disease and resectability**

When distant disease is suspected, most cancers can be staged with CT, positron emission tomography (PET), magnetic resonance imaging (MRI), or bone radionuclide scans. However, surgical staging procedures for melanoma, breast cancer, a subset of abdominal, and thoracic malignancies are more sensitive than currently available radiographic modalities and alter patient management in a large percentage of cases.

A. **Mediastinoscopy**

   Mediastinoscopy is used for the preoperative staging of bronchogenic carcinoma and evaluation of mediastinal adenopathy. In the case of bronchogenic carcinoma, the presence of nodal disease abrogates the need for surgical resection. The procedure is performed under general anesthesia. A transverse surgical incision is made above the sternal notch, and a mediastinoscope is inserted along the trachea. Lymph nodes biopsies are performed in the tracheal, anterior subcarinal, and tracheobronchial angles and examined for metastatic disease. The procedure is highly sensitive (100%) and specific (90%) in staging of bronchogenic carcinoma and has low morbidity and mortality.

B. **Laparotomy**

   Radiographic staging and laparoscopy have largely replaced laparotomy. Laparotomy is used selectively for staging ovarian and nonseminomatous testicular cancers. The procedure is performed under general anesthesia through a midline incision. The procedure has low morbidity and short recovery. Complications include infection, bleeding, wound dehiscence, and rare events related to exploration of the intraabdominal contents and general anesthesia.

C. **Laparoscopy**

   Laparoscopy is now considered an effective tool for diagnosis and staging of intraabdominal malignancies (liver, pancreas, stomach, and medullary thyroid carcinoma). Laparoscopy has been shown to decrease the incidence of unnecessary laparotomies for unresectable disease in up to 70% of patients with abdominal malignancies. Diagnostic laparoscopy for staging is usually performed at the time of a planned laparotomy. If distant or unresectable disease is found, then an unnecessary laparotomy is avoided. The procedure is performed under general anesthesia. A laparoscope is introduced through an infraumbilical port after the abdomen is insufflated with carbon dioxide. Placement of accessory ports aids in dissection and retraction, which allow most intraabdominal organs to be viewed. Biopsies can be obtained of solid organs, lymph nodes, and suggestive lesions. When laparoscopy is combined with intraoperative ultrasonography, lesions deep in the parenchyma of an organ can be identified, as well as tumor invasion into adjacent structures, such as major blood vessels. This is especially useful in evaluation of the liver and pancreatic malignancies and may be the most sensitive imaging technique for the detection of liver metastases. The procedure has few complications and may be performed on an outpatient basis. Port-site metastasis and intraabdominal spread by the pneumoperitoneum, although of theoretical concern, are rare (less than 1.0% of cases).

D. **Lymphadenectomy**

   The location, type of cancer, and clinical evidence of nodal involvement are the major considerations in performing lymphadenectomy. Presence and extent of nodal involvement is the most accurate risk indicator of distant disease development for many cancers. In general, regional lymph nodes should be removed when the likelihood of metastases is high or if lymph nodes are involved by clinical examination. If possible, regional lymph nodes should be removed at the time of the primary surgery. If a lymph node is found to exceed 3 cm in size, the tumor is likely has extranodal extension and involves the perinodal fat. These lymph nodes should be resected with surrounding fat and, if of low morbidity, the adjacent nerves (intercostal brachial sensory nerve of the axilla). Studies are ongoing to determine the survival benefit of lymphadenectomies in cancer resections (stomach, pancreas, breast). The major morbidity of regional lymphadenectomy is limb lymphedema and injury to adjacent nerves.

E. **Sentinel lymph node biopsy**

   Sentinel lymph node biopsy (SLNB) is based on data demonstrating hierarchical lymphatic drainage occurring from the primary tumor to the first draining lymph node (sentinel lymph node, SLN) to the remaining nodes in the regional lymphatic basin. Numerous studies have demonstrated that localized malignancies metastasize to the SLN before involving other nodes in the basin. Therefore the presence or absence of metastatic disease in the SLN predicts the status of the entire regional lymphatic basin. SLNB is currently used for staging the axilla in breast cancer and regional nodal basins in melanoma. Two techniques are used for lymphatic mapping, which may used independently or in combination. The first technique involves the injection of a radiolabeled colloid around the lesion, which is followed radiographically and/or intraoperatively by using the gamma probe. The second technique uses isosulfan blue, which is injected intraoperatively around the tumor and allowed to percolate through the lymphatics. In both techniques, an incision is made at the edge of the nodal basin, and the SLN is identified by tracing blue or radioactive lymphatic channels to the first blue or radioactive node. If more than one nodal basin is potentially involved, then preoperative lymphoscintigraphy may be performed to identify the draining nodal basins. In experienced hands, the procedure has very high specificity and sensitivity. The advantages of SLNB are selective lymph node dissections in those patients who would benefit most, avoiding the morbidity associated with lymph node clearance in those patients with low risk of disease, and the ability to perform immunohistochemical stains or polymerase chain reaction (PCR) to detect micrometastatic disease. Disadvantages of SLNB are related to skill of the operator, which may result in a significant false-negative rate.

IV. **Surgical treatment**

Surgical planning involves consideration of the tumor stage and location, the general health of the patient, expected morbidity and mortality of the procedure, probability of successful treatment, and the availability and effectiveness of other treatment modalities. Surgical resection of solid tumors provides excellent local control and is currently the only curative option for most solid tumors.

A. **Primary resection**

1. **Principles of surgical resection**

   The primary goal of cancer surgery is the complete extirpation of local and regional disease for local control and for decreasing the risk of local recurrence. This involves removing the primary lesion with adequate margins of normal surrounding tissue to minimize the risk of local recurrence. The stage, mechanisms of local spread, morbidity, and mortality of the procedure must be taken into consideration before any surgical procedure is undertaken. In patients with metastatic disease, long-term control may not be as important as it is in patients who have localized disease, which may be surgically curable. Knowledge of the most common avenues of spread for the various histologic types of cancers is essential for successful local control. Depending on the cell of origin, cancers may spread mucosally, submucosally, along fascial planes, or along nerves (Table 4.1). With advances in anesthesia, postoperative care, and reconstructive procedures, large surgical procedures can be performed safely in elderly patients and patients with

multiple comorbid conditions. Intraoperatively, successful resection requires good exposure, excision of previous biopsy sites, maintaining a bloodless surgical field to visualize the extent of tumor spread, and *en bloc* resection of the tumor and surrounding normal tissue. Local recurrence or wound seeding can be theoretically be minimized by minimal manipulation of the tumor, confining dissection to normal tissue, and early ligation of major feeding vessels at their origin. Complete removal of the tumors has many favorable effects including minimizing residual disease and eliminating hypoxic, poorly vascularized cells, which are drug and radiation resistant.

Tissue	Margin	Rationale
Melanoma		
Thin (<0.75 mm)	1 cm	Localized
Thick (>1.0 mm)	2 cm	Increased risk of local recurrence
Sarcoma	Excise entire muscle group or 1 cm	
Breast, invasive	1 cm	Must be combined with radiation therapy because of multi-locality
Colon	2–5 cm	
Esophagus	10 cm	Potential for extensive submucosal spread
Squamous cell CA of head/neck	1 cm	May be limited by adjacent structures
Lung	Excise lobe or lung	
Pancreas	1 mm–1 cm	Margins may be limited by surrounding vessels
Liver	1 cm	
Basal cell carcinoma	2 mm	Very localized malignant area
Stomach	6 cm	Intramural spread

TABLE 4.1. ADEQUATE TISSUE MARGINS FOR PRIMARY MALIGNANCY TREATED WITH SURGERY ALONE

2. **Premalignant lesions and prophylactic surgery**

Surgery is indicated for premalignant lesions and noninvasive cancers of the skin, mouth, cervix, colon, breast, and thyroid, although only a proportion of such lesions may progress to malignancy (Table 4.2). Several inherited disorders associated with increased cancer risk have been described. Surgery can significantly reduce cancer occurrence (Table 4.3).

Organ	Pathology	Detection Method
Cervical	Atypia	Papanicolaou test
Mouth leukoplakia	Dysplasia	Oral examination
Gastroesophageal	Dysplasia (Barrett)	Endoscopy
Breast	In situ	Mammogram/physical exam

TABLE 4.2. SURGERY FOR *IN SITU* AND ATYPIA

Disorder	Cancer Risk	Surgery
Familial polyposis coli	100% risk	Colectomy
Ulcerative colitis	With dysplasia, >50% risk	Colectomy
MEN/FVTC	100% medullary thyroid cancer (genetic screening)	Thyroidectomy
BRCA1/2	>60% breast cancer	Mastectomy

FVTC, familial medullary thyroid cancer carrier; MEN, multiple endocrine neoplasia.

TABLE 4.3. PROPHYLACTIC SURGERY

B. **Operative principles**

1. **Anatomy**

The anatomic location of cancers is an important consideration in surgical planning. Some tumors cannot be adequately treated by surgical resection alone because of anatomic constraints, which may result in incomplete excision (nasopharynx). Residual microscopic disease after surgical resection can sometimes be treated effectively with adjuvant radiation therapy to decrease local recurrence. Those patients whose lesions are intimately involved with major blood vessels (lung/aorta), or bilaterally involve an essential organ (liver), or with a limited life expectancy due to the natural history of the disease may not benefit from surgical resection.

2. **Neoadjuvant therapy before resection**

If a lesion is resectable and localized at the time of diagnosis, then surgery should be performed. Large lesions or lesions invading into surrounding structures that are not initially resectable may be amenable to volume reduction with initial (neoadjuvant) chemotherapy or radiation therapy. This strategy has allowed successful but more limited, less morbid resections, or function-preserving resections of many cancers (colorectal, breast, larynx, pancreatic cancers). In addition, the response to neoadjuvant therapy is useful for monitoring response to various treatment regimens. If a pathologic complete response is possible, the surgical site should be marked with metallic clips at the time of biopsy for future identification at the time of surgery. Disadvantages of neoadjuvant therapy are possible delays in undergoing standard curative therapy.

Preoperative radiation therapy may be used alone or in combination with chemotherapy to reduce tumor size before resection. Advantages of preoperative radiation therapy are potentially smaller treatment fields and reduced potential seeding of the tumor during surgery. Disadvantages of preoperative radiotherapy include the resulting fibrosis, which may obscure resection margins and increase the difficulty and morbility of the operation. Preoperative radiation therapy renders the wound edges functionally ischemic, which may affect the type of reconstruction performed and tissue resected or result in increased wound complications. Overall, preoperative radiation or chemotherapy limits the ability to plan radiation or chemotherapy based on the initial anatomic extent of disease. Finally, although neoadjuvant therapy may decrease the size of the lesion, there is generally little benefit in overall survival.

C. **Extent of resection**

Extent of resection depends on the organ involved and method of local spread. Adequate margins range from 1 mm to 5 cm for cutaneous and hollow organ tumors (Table 4.1). Resections for solid organ tumors are usually guided by the blood supply, and usually a lobe (liver, lung), the entire organ (kidney), or a partial resection (pancreas) is performed. The most efficacious method for local control and prevention of local recurrence is wide excision. This may require encompassing any biopsy incision or needle tract into the *en bloc* excision. If the malignancy is adherent to a contiguous organ, then a partial resection of

the latter organ may be performed to obtain negative margins. Most solid tumors have a propensity for dissemination via local lymphatics to regional lymph nodes. If a lymph node in the draining area exceeds 3 cm in size, the tumor is likely extranodal and involves the perinodal fat. Local excision is then inadequate and *en bloc* resection of the organ, regional lymph nodes, and adjacent involved regions should be performed. To prevent seeding of tumor, the no-touch technique can be used, which includes minimal palpation of the tumor and early ligation of the blood supply to limit dislodgment of the tumor cells into the venous circulation. Although the ability of these techniques to reduce local recurrence is controversial, their theoretic value has led to widespread acceptance. If a second area of the body requires operation at the time of tumor excision, gloves, gowns, sheets, and instruments must be changed. This further prevents transplantation of tumor to a distant site.

If margins are positive after resection, options include further operation, adjuvant therapy, or careful follow-up. If microscopic tumor is found at the resection margin, adjuvant postoperative radiation may be given. However, this may be associated with a higher risk of tumor recurrence, poorer cosmetic results, and more radiation complications due to the higher radiation doses required (breast, sarcoma, head/neck cancers). These patients may benefit from reexcision of the tumor bed to achieve microscopically clear margins if this is technically feasible. In these cases, the potential morbidity and mortality of reoperation should be assessed.

D. **Laparoscopic and laparoscopy-assisted surgeries**

Laparoscopic resections or laparoscopy-assisted tumor resections are under development and increasingly performed. The most common laparoscopic cancer operation performed is colectomy. Laparoscopy-assisted distal pancreatectomies, gastrectomies, and esophagectomies have been reported. In general, laparoscopic procedures result in shorter hospital stay, less intraoperative blood loss, decreased requirement for analgesics, and earlier return to normal activities. Concerns have been raised regarding margin width and *en bloc* resection of draining nodal basins; however, early studies examining these issues for colectomy have reported no significant difference.

V. Metastases and recurrent disease

A. Distant metastasis

With many types of cancer, death is often a result of metastatic disease. It is often assumed that the patient with disseminated disease is not a candidate for surgical procedures. However, subsets of patients with isolated metastases are amenable to a complete surgical resection (hepatic and pulmonary) with resulting increased survival. Excisions of symptomatic metastases that cannot be treated by other means are appropriate for resection to improve quality of life (melanoma, breast, thyroid, and other endocrine cancers). This includes patients with subcutaneous metastases that present cosmetic problems and bowel metastases that cause obstruction or bleeding. Patients with multiple metastases to the lung or liver should be considered for resection if the metastases are present in only one organ system, if there is adequate normal parenchyma remaining after resection, and if the operative risk is minimal. The longer the time interval between initial diagnosis and the appearance of metastatic disease, the more likely surgery will be beneficial and result in increased overall survival. Resection of a small number of pulmonary metastases from sarcoma or localized lung and liver metastases from colorectal cancers will result in increased survival for approximately 25% of patients.

B. Resection for recurrent locoregional disease

Local recurrence of cancer can result from incomplete excision at the initial operation, the presence of residual cancer cells distant from the primary lesion, or second primary tumors that develop in residual normal tissue. Intensive follow-up is used to detect recurrent or persistent tumors before distant dissemination occurs. With some cancers, the presence of local recurrence may signal the presence of distant disease in a proportion of patients (approximately 50% for breast cancer). Similar surgical principles apply to resection of recurrent disease.

C. Palliative surgery

Significant improvement in quality of life and alleviation of symptoms can be achieved with palliative surgery, which allows patients to resume as many of their normal daily activities as possible (Table 4.4). This includes resection for obstruction, pain, bleeding, or perforation of a hollow viscus or for hormonal effects of endocrine tumors (insulinomas, gastrinomas, medullary thyroid cancers).

Presentation	Surgical Procedure
Malignant pleural effusion	Thoracostomy tube, sclerosis
Biliary obstruction	Stent or choledochojejunostomy
Bowel obstruction, large	Colostomy with mucous fistula
Bowel obstruction, small	Resection, bypass, gastrostomy tube
Bowel obstruction, duodenal	Gastrojejunostomy
Esophageal obstruction	Stent, gastrostomy tube
Locally advanced breast cancer	Salvage mastectomy

TABLE 4.4. PALLIATIVE SURGICAL PROCEDURES

VI. Reconstruction: functional and cosmetic

Advances in the understanding of the tissue blood supply have allowed improvements in the coverage of surgical defects after cancer resections. Rarely are disfiguring primary closures or skin grafts the only option. Two advances have led to major changes in plastic reconstructions of cancer resections. The first was the anatomic elucidation of muscular blood supply, which allowed tissue associated with a defined vascular network to be moved to a defect within reach of its pedicle. The second advance was in the field of microsurgery, which allowed muscle flaps with the overlying subcutaneous fat and skin to be detached from their original blood supply and reanastomosed to vessels in a different anatomic area. These advances meant that multiple-stage reconstructions were no longer required to bring well-vascularized tissue into a surgical defect. This decreases the risk of postoperative wound complications and avoids delays in commencing adjuvant therapy. Currently, immediate reconstruction is frequently performed under the same anesthesia as an oncologic resection. With these new techniques, large amounts of tissues can be reliability transplanted to fill dead spaces, pad and cover susceptible organs or structures, and provide restoration of form, function, and contour. Free and pedicled tissue transfers are used to for reconstruction after surgery for the breast, mandibular area, and perineum. Commonly used donor myocutaneous flaps include the latissimus dorsi, rectus abdominis, and gracilis muscles. If bone is required, fibula-based flaps are commonly used. Flap success rate is 95%, and multiple studies have demonstrated improved quality of life with reconstruction procedures and no decrement in the ability to detect recurrence. Disadvantages of reconstruction are secondary problems at the donor site and increased operative time.

VII. Newer treatment modalities

A. Cryotherapy

Intraoperative cryoablation is regarded as an effective form of palliative therapy and may cure some patients with small tumors. Intraoperative ultrasound is used to monitor hepatic cryosurgery for nonresectable disease. Hepatic cryotherapy involves the freezing and thawing of liver tumors by means of a cryoprobe inserted into the tumors. During freeze/thaw cycles, intracellular and extracellular ice forms, leading to tumor destruction. Tumors are then left *in situ* to be absorbed. Cryosurgery can treat multiple lesions and allows salvage of more uninvolved liver parenchyma than does surgical resection. Postoperative complications include hemorrhage, biliary fistula, myoglobinuria, and acute renal failure. Overall morbidity rates range from 6% to 50%. Mortality rates range from 0 to 8%. Hepatic cryosurgery is an option for patients with isolated colorectal cancer liver metastases that are not surgically resectable but are limited enough to allow cryoablation of all lesions. It is unclear whether cryoablation will lead to survival equivalent to that after surgical resection.

B. Radiofrequency ablation

This technique involves percutaneous or intraoperative insertion of a radiofrequency (RF) probe into the center of a hepatic tumor under ultrasound or CT guidance. RF energy is then emitted from the electrode and absorbed by the surrounding tissue. This process generates heat, leading to coagulation necrosis of the treated tissue. The initial limitation of this therapy was the small (1.5 cm) diameter of necrosis achievable with a single RF probe. Newer probes allow treatment of larger volumes. The primary advantage of RF ablation over cryosurgery lies in the low incidence of complications and the ease of performance under CT or ultrasound guidance. RF ablation can be performed percutaneously, thus avoiding laparotomy or laparoscopy.

VIII. Surgery for complications of treatment

A. Surgical complications: obstruction, stricture

Adhesions from prior surgery, radiation enteritis, and recurrent cancer are the most common causes of intestinal obstruction in patients with a history of malignancy presenting with nausea, vomiting, abdominal distention, and obstipation. The approach to diagnosis and treatment of obstruction in patients with cancer should be similar to that for patients with benign disease. A colonic obstruction should be excluded by a diatrizoate (Hypaque) enema. CT scans of the abdomen and pelvis can be helpful for determining the presence of a transition point, bowel-wall thickening, or the presence of recurrent disease. For patients with a small bowel obstruction and no signs of compromised bowel viability (tenderness, leukocytosis, fever, persistent tachycardia), a trial of nasogastric decompression and intravenous hydration is warranted. One fourth of patients will resolve their obstruction with conservative measures. Those patients who do not demonstrate resolution after a finite period should undergo laparotomy. Cancer patients with benign obstructions from adhesions or internal herniation benefit from operation. If malignant obstruction is present, resection or bypass of the obstructed segment may be performed; however, only 35% of patients will have durable relief of symptoms after surgical treatment. These patients should be strongly considered for gastrostomy tube placement at the time of surgery, which provides significant palliation by relieving emesis and the need for nasogastric suction. Radiation-induced enteritis may be clinically indistinguishable from adhesive small bowel obstruction. In such patients, intraoperative inspection of the bowel is the means for diagnosis. In cases of radiation enteritis, short segments of narrowed bowel may be resected; however, long segments should be treated with bypass.

B. Medical complications

Gastrointestinal (GI) lymphomas may occasionally respond so rapidly to chemotherapy that perforation of the bowel wall or hemorrhage may occur, requiring urgent or emergency surgery. Neutropenic enterocolitis (typhlitis), characterized by fever, diarrhea, and right lower quadrant pain, may occur in the patient who is severely neutropenic from chemotherapy. Most episodes resolve with conservative management of bowel rest, nasogastric decompression, and broad-spectrum antibiotics. Serial abdominal examinations and abdominal films should be performed. Surgical intervention is indicated for perforation and sepsis. Right hemicolectomy with ileostomy and mucous fistula is the operation of choice and may be reversed after several months. Small and large bowel ileus is common in cancer patients. Treatment involves bowel rest and cessation of narcotics, which results in improvement in most patients.

IX. Vascular access

A. Central venous catheterization

Many cancer patients require frequent venous catheterization for phlebotomy, chemotherapy, or infusions. Peripheral venous sites for catheterization can become quickly exhausted because of the venotoxic effects of the cytotoxic agents, the trauma of repeated use, and the undesirability of performing access procedures in limbs with proximal lymphadenectomies. Central venous catheters are designed for repeated venous access. Although they are generally easily placed, complications include pneumothorax, hemothorax, air embolism, cardiac arrhythmia, and arterial injury. Over the long term, these catheters can cause central vein thrombosis, embolism, infection, and scarring. Relative contraindications to placement include uncorrected thrombocytopenia or coagulopathy and prior irradiation to the head or neck, which can result in scarring. For these latter patients, an ultrasound before the procedure maybe useful to establish the patency of their veins. Patients who are hypercoagulable from their cancers may benefit from low-dose warfarin (1 to 2 mg per day) to prevent central venous thrombosis.

1. Hickman catheters/Broviac catheters

Tunneled externalized central venous catheters of the Hickman or Broviac type are available in single- to triple-lumen varieties and have wide internal diameters, which allows blood sampling and results in higher patency rates. A Dacron cuff in the extravascular subcutaneous portion of the catheter develops fibrous ingrowth, serves as a mechanical barrier to infection, and prevents accidental dislodgement. Catheters are placed percutaneously by using the Seldinger technique into the subclavian or internal jugular vein or by venous cutdown into the cephalic or external jugular veins. The catheter is inserted under fluoroscopic guidance to ensure proper placement at the superior vena cava–atrial junction. Patency can be maintained by flushing with heparinized saline (100 U/mL) every month and after each use. If catheter thrombosis occurs, patency can be reestablished by infusing streptokinase. The catheter exit site should be cleaned and dressed every 24 to 72 hours by using sterile technique. Infection may involve the device, the catheter tunnel, or the exit site. Signs of catheter-tunnel or exit-site infection include erythema, induration, and suppuration, and require immediate catheter removal. Sepsis from catheter infection should be documented by blood cultures drawn from both the catheter and peripheral sites. Coagulase-negative staphylococci are the most common pathogens isolated. The majority of catheter-based infections can be treated effectively with a 10- to 14-day course of intravenous antibiotics. However, persistence of positive cultures necessitates catheter removal. If untreated, catheter infections may lead to septic thrombophlebitis of the catheterized vessel, endocarditis, or a distant focus of suppuration such as osteomyelitis, septic arthritis, or disseminated abscesses. Hickman catheter–related infections are 5 times more common than infections in implanted ports. Disadvantages of Hickman catheters are limitations of patient activity, frequent maintenance, and malfunction due to thrombotic occlusions. Advantages are easy access with standard needles and bedside removal.

2. Implantable catheters: Portacath, Infusaport

Completely implantable subcutaneous catheters comprise a reservoir with a silicone septum, which is available in single and double lumens attached to a silicone catheter. Port access is performed with a Hueber needle that punctures but does not tear the silicone septum. The integrity of the septum is maintained for 1,500 to 2,000 cannulations. The port is placed in a subcutaneous pocket, and the attached catheter is threaded into the subclavian, internal jugular, or in special circumstances, into the femoral vein by using fluoroscopic guidance to ensure correct positioning. Ports should be flushed monthly with heparinized saline to maintain patency. Infections may involve the port pocket, the port reservoir, or the catheter. Port-pocket infections require removal of the catheter. The main advantages of the implantable catheters are cosmesis, few restrictions on activities such as bathing, low maintenance (monthly flushing to maintain patency), and low incidence of infection, which make it ideal for intermittent long-term therapy. The main disadvantages are access, which requires trained personnel and a Hueber needle, and higher cost compared with peripheral access.

B. Arterial catheters: hepatic artery infusion catheters

Hepatic artery infusion (HAI) catheters are currently in clinical trials to treat hepatic metastases and have been for about 15 years. HAI chemotherapy targets liver metastases, which derive most of their blood supply from the hepatic arterial circulation, in contrast to normal liver, which derives most of its blood supply from the portal circulation. In addition, higher levels of local therapy can be achieved without concomitant systemic toxicity due to the clearance of many chemotherapeutic agents from first pass through the liver. HAI chemotherapy is generally reserved for patients without evidence of extrahepatic disease. These catheters are placed at laparotomy. Before placement, patients undergo an angiogram to define regional arterial anatomy because of the highly variant arterial anatomy in this area. The infusion port or continuous infusion pump is placed in the abdominal subcutaneous tissues over the rectus muscle fascia, and the catheter is tunneled into the abdomen. The tip of catheter is placed in the gastroduodenal artery at its junction with the common hepatic artery. Cholecystectomy is required to prevent chemotherapy-induced chemical cholecystitis, and complete separation of the hepatic arterial circulation from the gastroduodenal blood supply must be achieved to prevent gastrointestinal toxicity. Postoperatively, radiolabeled microaggregated albumin is injected into the infusion pump, and a scintillation scan is obtained to verify hepatic infusion and exclusion of extrahepatic perfusion. Chemotherapeutic agents are injected into the port reservoir, which is designed to ensure a continuous infusion of a constant amount of agent. Studies have demonstrated higher response rates with HAI than with systemic chemotherapy; however, no survival advantage has been observed. Current strategies combine liver resection, residual tumor ablation, and HAI pump placement.

X. Enteral feeding tubes

Malnutrition is common in the cancer patient and may be related to inadequate voluntary intake, altered metabolism, or the effects of therapy. Enteral alimentation can be useful before or after surgery or during therapy. Early concerns that hyperalimentation would lead to rapid tumor growth have not been borne out by experience, and in severely malnourished patients (less than 80% standard weight for height), there is a measurable improvement in operative morbidity if nutritional supplementation is provided 7 to 10 days before operation. Postoperatively, enteral or parenteral alimentation can support the cancer patient who is unable to eat because of a healing anastomosis or a postoperative ileus. During chemotherapy or radiation therapy, inflammation, infection, or

strictures may lead to inadequate oral intake requiring enteral alimentation. The route of administration of nutritional support is selected based on length of anticipated need, intestinal tract function, degree of malnutrition, access for administration, and potential complications. In patients with adequate gastrointestinal function, enteral alimentation is preferred over the parenteral route. Enteral alimentation is less expensive, leads to fewer metabolic imbalances, preserves the gastrointestinal architecture, and is thought to prevent bacterial translocation. The most common morbidities associated with enteral alimentation are abdominal distention, nausea, or diarrhea, which can occur in 10% to 20% of patients. These symptoms usually abate with a decreased rate of infusion or strength of the formula.

A. **Gastrostomy tubes**

Gastrostomy tubes (G-tubes) may be placed percutaneous or intraoperatively. They can serve the dual functions of conduits for feeding or intestional decompression. Other advantages of a G-tube are bolus feeding with high-osmolar formulas because of the reservoir capacity of the stomach, and the ability to replace dislodged tubes easily through the gastrocutaneous fistula. Disadvantages include risk of aspiration in patients with lower esophageal sphincter dysfunction or without an intact gag reflex. Enteral feeds can be administered by bolus (200 to 400 mL over a 5- to 10-minute period) and is the preferred feeding method in ambulatory patients because it is less confining.

B. **Jejunostomy tubes**

Jejunostomy tubes are small-caliber feeding tubes placed distal to the ligament of Treitz by laparotomy or laparoscopy. Generally the tubes are placed through a surgical Witzel tunnel to prevent obstruction proximal to the site of insertion and to reduce the risk of leak. The advantages of J-tubes are minimal risk of aspiration and the ability to feed distal to the obstruction or fistula. Because there is no reservoir capacity, enteral feeds are administered continuously over 12- to 24-hour periods, and there is limited tolerance to high osmolar loads. Once dislodged, these tubes are not easily replaced. In addition, because of the small caliber, these tubes may become clogged with inspissated material and require vigorous flushing to reestablish patency.

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CHAPTER 5. PRINCIPLES OF HIGH-DOSE CHEMOTHERAPY AND STEM CELL TRANSPLANTATION

Peter Westervelt, Ravi Vij, and John DiPersio

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I. Introduction

The process of bone marrow or peripheral blood–derived hematopoietic stem cell transplantation (HSCT) involves the administration of dose-intensive chemotherapy and/or radiation, followed by rescue with either autologous or human leukocyte antigen (HLA)-matched allogeneic sibling or unrelated donor–derived hematopoietic stem cells, and, in the case of nonautologous transplant, posttransplant immunosuppression to prevent and/or treat graft-versus-host disease. This chapter briefly summarizes the underlying principles and practical aspects of both autologous and allogeneic HSCT, including the indications for the use of these modalities, and common complications and their management.

II. History

It has been known for almost 50 years that transplanted syngeneic bone marrow or spleen cells are capable of rescuing lethally irradiated animals that would otherwise die of marrow aplasia. Similar experiments conducted by using hematopoietic cells from allogeneic donors, however, universally resulted in the death of the recipients, despite hematopoietic engraftment, because of a subacute wasting syndrome involving the skin, gut, and liver, the consequence of a donor-derived immune-mediated process termed graft-versus-host disease (GVHD). The first allogeneic bone marrow transplants in humans were performed in the 1950s after the administration of lethal irradiation to patients with terminal malignancies. These attempts were largely unsuccessful because of lethal acute GVHD (with the exception of transplants performed by using identical twin donor/recipient pairs) and disease relapse. In the 1970s, advances in HLA typing, improved conditioning regimens, better prevention and treatment of GVHD, and improvements in supportive care led to the first success in allogeneic bone marrow transplantation. Since then, several important advances have taken place, including the establishment of large registries of potential bone marrow donors to facilitate the identification of suitable unrelated donors for patients lacking matched sibling donors; the use of autologous bone marrow or stem cells to facilitate the delivery of dose-intensive chemotherapy and radiotherapy regimens; the development of methods for collecting mobilized HSCs from peripheral blood as an alternative to bone marrow; and recognition and exploitation of the important antitumor effect mediated by the immune cells in an allogeneic graft. It is now estimated that more than 17,000 allogeneic and 30,000 autologous HSCTs are performed worldwide on an annual basis (source: International Bone Marrow Transplantation Registry [IBMTR]/American Bone Marrow Transplantation Registry [ABMTR]; http://www.abmtr.org/index.html). The major indications for SCT are listed in Table 5.1.

Malignant Diseases	Nonmalignant Disease
Hematopoietic neoplasms	Congenital/Acquired marrow-failure syndromes
Acute myeloid leukemia	Aplastic anemia
Acute lymphoblastic leukemia	Paroxysmal nocturnal hemoglobinuria
Chronic myeloid leukemia	Fanconi anemia
Chronic lymphocytic leukemia	Others
Myelodysplastic syndrome	
Multiple myeloma	Hemoglobinopathies
Non-Hodgkin lymphoma	Thalassemia
Hodgkin disease	Sickle cell disease
Solid tumors	Immunodeficiency syndromes
Testicular cancer	Inborn errors of metabolism
Neuroblastoma	Autoimmune diseases
Renal cell carcinoma	
Ovarian cancer?	
Breast cancer?	

TABLE 5.1. INDICATIONS FOR STEM CELL TRANSPLANTATION

III. Pretransplant evaluation of candidates for hematopoietic stem cell transplantation

The evaluation of patients considered for HSCT is designed primarily to identify significant comorbid conditions that might negatively affect a patient's ability to withstand the toxicity of HSCT. It is recommended that the pretransplant evaluation, summarized in Table 5.2, be undertaken within 4 to 6 weeks of the planned procedure. In general, the pretransplant evaluation is similar for both allogeneic and autologous HSCT, except as noted in Table 5.2. Although many centers are reluctant to offer allogeneic HSCT to patients older than 55 years, and autologous HSCT to those older than 65 to 70 years, age alone should not be considered an absolute contraindication, but rather one of many factors affecting the overall suitability of a patient for HSCT.

Test	Comment
History and physical examination	Assess performance status, ↑ active infection, ↓ significant organ system dysfunction
Review of tissue samples	Confirmation of diagnosis
Review of initial staging and restaging tests	Assess responsiveness to therapy and current disease status
Bone marrow biopsy/aspirate	
Confirmatory donor and recipient HLA and ABO/Rh blood typing (allogeneic HSCT candidates)	
Serum chemistry panel (electrolytes, creatinine, bilirubin, AST, ALT, alkaline phosphatase, LDH)	Creatinine ↓ (it may result in altered metabolism of drugs commonly used in HSCT [certain antibiotics, methotrexate]); AST, ALT, bilirubin ↓ 2 times normal increases the risk of veno-occlusive disease
Radioventriculogram (RVG) or echocardiogram	LVEF ↓ 40–45% desirable
Electrocardiogram	↑ Evidence of life-threatening arrhythmia
Chest radiograph	↑ Evidence of active infection
Pulmonary function tests (DLCO)	FEV1, FVC, DLCO ↓ 50% predicted
Viral serologies (CMV, HSV, HIV, HTLV-I, hepatitis A, hepatitis B core antigen and surface antibody, hepatitis C)	HSV seropositivity requires antiviral prophylaxis; hepatitis seropositivity without evidence of active disease increases the risk of veno-occlusive disease, but is not a contraindication to HSCT
Radiation oncology evaluation	TBI conditioning regimen candidates
Nutrition evaluation	
Pregnancy test (gonadotropin, serum)	
Sperm/oocyte banking	

ECG, electrocardiogram; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CMV, cytomegalovirus; HSV, herpes simplex virus; HIV, human immunodeficiency virus; HTLV-I, human T-cell lymphotropic virus; LVEF, left ventricular ejection fraction; PFT, pulmonary function; DLCO, carbon monoxide diffusion in the lung; TBI, total body irradiation.

TABLE 5.2. PRETRANSPLANT EVALUATION

IV. **Procurement of stem cells**

A. **Bone marrow.** Marrow is collected from the posterior iliac crest in the operating room, under general or spinal anesthesia. The donor is asked not to eat or drink anything after midnight on the day of the planned stem cell harvest. Preoperative testing includes a complete blood count, coagulation, and chemistry profile. Marrow is collected by using wide-bore needles and syringes rinsed with a harvest solution prepared by mixing tissue-culture media and 10,000 to 15,000 IU heparin. The marrow is transferred into a collection bag with graded filters containing 50 mL of the harvest solution. Usually 100 to 300 aspirations are necessary, with approximately 5 to 10 mL of bone marrow (and peripheral blood) being collected with each aspiration. A target collection of 2 to 4 × 10^8 nucleated cells/kg of recipient weight averages about 1 L in volume. Marrow is sent to the processing laboratory in standard blood-transfer bags. Unrelated donor marrow must be transported from the collection center to the transplant institution in an insulated container at room temperature or on wet ice within 24 hours.

During the harvest, the patient should be given an adequate volume of intravenous fluids for volume resuscitation. Most donors are hospitalized overnight after bone marrow harvest. The incidence of anemia after marrow donation depends on the preoperative hemoglobin and blood loss. Policies regarding transfusion vary among individual centers. Banked autologous units are usually used for normal donors. Fatigue, pain at the harvest site, nausea, and vomiting are the most common side effects observed. Hypotension, syncope, and severe postspinal headache are occasionally seen. Rare cases of major complications related to anesthesia, infection, hemorrhage, mechanical injury, or transfusion have been reported. Most patients need a mild narcotic analgesic for a few days. Iron supplementation for a period of 1 month is usually prescribed at discharge.

B. **Peripheral blood.** Stem cells also can be harvested from the peripheral blood of patients or normal donors by using a process called apheresis. Peripheral blood stem cell (PBSC) collection by apheresis is usually performed as an outpatient procedure. Subcutaneous granulocyte–colony-stimulating factor (G-CSF; 10 to 16 µg/kg/donor body weight) is the cytokine most commonly used for stem cell mobilization. G-CSF is administered for 4 or 5 days before the date of stem cell collection. In the case of autologous stem cell harvest, chemotherapy (e.g., high-dose cyclophosphamide [Cytoxan]) in addition to growth factors may be used to increase the stem cell yield. This increases the number of stem cells circulating in the peripheral blood by both expansion of stem cells in the marrow and inducing the egress or “mobilization” of these stem cells from the bone marrow to the peripheral blood. Apheresis in such cases is usually started 16 days after initiation of chemotherapy or when the absolute neutrophil count recovers to 1,000 to 5,000/µL. Donors may experience some myalgia, bone pain, headache, nausea, and fever with these high doses of G-CSF. White blood cell (WBC) counts may reach 70 to 80 × 10^9/L by day 5. Although leukostasis has not been reported, most centers reduce the dose if these levels are attained earlier or if the WBC count exceeds 75,000/µL. PBSCs are collected by apheresis through the antecubital veins in normal donors and via an apheresis catheter in autologous collections. During a single 3- to 6-hour procedure, 9 to 20 L of blood volume is processed. The mononuclear–platelet fraction is retained, whereas the remainder is reinfused. Donors frequently require calcium supplementation during the apheresis procedure for perioral numbness, parasthesias, and carpopedal spasm due to hypocalcemia induced by the anticoagulation with acid-citrate-dextrose solution used during apheresis. After apheresis, transient thrombocytopenia is common.

C. **Stem cell goal.** A unique antigen “CD34” is expressed on the surface of HSCs. Purified human stem cells expressing CD34 not only grow in vitro in response to hematopoietic growth factors but also can be used to reconstitute the entire lymphohematopoietic system of a lethally irradiated human. This antigen has been used to identify and quantitate the number of stem cells in bone marrow or peripheral blood products. There is an excellent correlation between the number of CD34 cells infused per kilogram recipient weight and the pace of both neutrophil and platelet recovery after stem cell infusion. Target CD34 cell collections vary according to institutional policies. Most centers collect a minimum of 2.5 × 10^6 $CD34^+$/kg recipient weight. A goal of 5 × 10^6 CD34/kg increases the probability of early platelet recovery. A large majority of normal donors achieve this goal with 1 to 2 days of apheresis. Patients undergoing autologous PBSC harvest may require several days of apheresis depending on the extent of prior therapy.

V. **Processing of stem cells**

In the case of allogeneic transplantation with major ABO incompatibility, the PBSC/bone marrow product must be red cell depleted. In the case of minor ABO incompatibility, the product is plasma depleted. The product also may be plasma depleted when volume reduction is desired.

To allow time for treatment with the preparative regimen, autologous stem cells (and in some instances, allogeneic stem cells) must be cryopreserved. Dimethyl sulfoxide (DMSO) is the most common cryoprotective agent. Cells are cryopreserved in 10% DMSO with albumin or human AB serum in small vials or in freezing bags with a capacity of 100 to 200 cc. The products are stored in the vapor or liquid phase of liquid nitrogen at –156°C to –196°C. Most centers use a controlled-rate freezer for freezing the product.

Several institutions have protocols for ex vivo manipulation of the stem cell product. Protocols for expansion of stem cells use a variety of cytokine cocktails. Most of these affect the more committed precursors, resulting in a reduced duration of neutropenia after stem cell infusion of these ex vivo expanded products. Some investigators use positive (CD34+ progenitors) or negative selection techniques (use of chemotherapeutic agents [e.g., 4-HC, mafosfamide, etoposide or antibodies]) to deplete the stem cell product of tumor cells in the autologous transplant setting. There is as yet no evidence from randomized studies to suggest that this affects patient outcome. In the allogeneic transplant setting, several investigators are studying the effect of depletion of T cells and various subsets by using a variety of pharmacologic, immunologic, and elutriation techniques. T-cell depletion is increasingly being used in the case of HLA-mismatched transplants and in protocols that involve donor leukocyte infusions after myeloablative and nonmyeloablative transplantation. These techniques can produce a 2- to 4-log depletion of T cells. Although this does reduce the incidence of GVHD, it results in a higher incidence of graft failure, posttransplant lymphoproliferative disorders, and opportunistic infections due to severe immunodeficiency.

VI. **Conditioning regimens**

The goals of the conditioning regimen, although overlapping, differ somewhat for autologous and allogeneic HSCT. With autologous HSCT for malignant diseases, the purpose of the conditioning regimen is to deliver chemotherapy and/or radiation at near-myeloablative dose intensity to maximize tumor cell kill, while avoiding nonhematopoietic dose-limiting toxicity. With allogeneic HSCT, there is an important additional requirement for sufficient host lymphoablation to permit donor cell engraftment.

A large number of dose-intensive conditioning regimens for allogeneic and autologous HSCT have been developed over the past 30 years. Whereas the earliest conditioning regimens used in allogeneic HSCT for acute leukemias relied primarily on total body irradiation (TBI) in combination with chemotherapy, regimens combining multiple chemotherapy agents have been developed more recently for use in autologous HSCT. The design of specific conditioning regimens has been largely empiric, however, and there are few objective data on which to recommend the use of any given regimen over another. The choice of conditioning regimen is therefore more often based on factors such as patient age and comorbidity, prior exposure to specific agents or radiation, and known activity of specific agents against the patient's underlying disease. A representative list of conditioning regimens in common use in 2000 is compiled in Table 5.3.

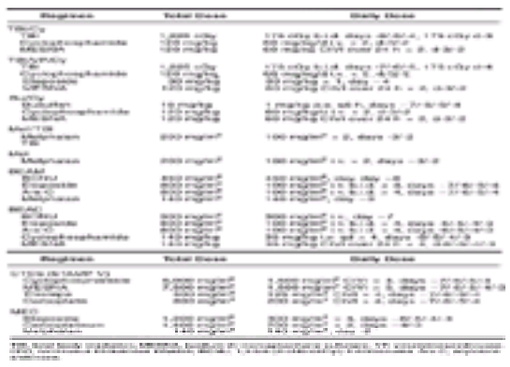


TABLE 5.3. COMMONLY USED CONDITIONING REGIMENS IN HSCT

The dosing of chemotherapy drugs for dose-intensive conditioning regimens is usually based on ideal body weight (IBW), to avoid excessive nonhematopoietic toxicities in obese patients. A formula used at our center for calculation of ideal body weight in adults is

IBW (kg) = [(2.3) × (height in excess of 60 inches)] + 50 (men)

IBW (kg) = [(2.3) × (height in excess of 60 inches)] + 45.5 women)

An adjusted ideal body weight formula is often used for dosing calculations:

Adjusted IBW = [0.2 × (actual weight – IBW)] + IBW

To calculate the dose of chemotherapy:
If actual is greater than ideal, use actual.
If actual is 100% to 120% of ideal, use ideal.
If actual is more than 120% of ideal, use adjusted.

A. **Nonmyeloablative conditioning regimens**

In the past few years, a number of nonmyeloablative conditioning approaches (“minitransplant” regimens) have been developed to reduce regimen-related toxicities, but nevertheless exploit allogeneic graft-versus-tumor effects, or to render suitable the application of allogeneic HSCT for nonmalignant indications. The primary goal of these regimens is to provide sufficient lymphoablation to allow durable donor engraftment, while avoiding the toxicities associated with the maximally cytotoxic doses of radiation and/or chemotherapy required for high-order tumor cell killing. Nonmyeloablative conditioning regimens may result initially in a mixed donor/recipient chimerism state, which can often be converted to full donor chimerism on reduction in immune suppression, and/or the reinfusion of additional donor lymphoid cells. Potential disadvantages of nonmyeloablative conditioning regimens include the risk of nonengraftment or graft rejection, lack of efficacy in treating high-tumor-burden states like relapsed/resistant acute leukemia, and the continued problem of GVHD. A representative listing of nonmyeloablative conditioning regimens is compiled in Table 5.4

Regimen	Total Dose	Daily Dose
Cy/FDA		
Cyclophosphamide	120 mg/kg	60 mg/kg/day × 2, days −7/-6
Fludarabine	125 mg/m^2	25 mg/m^2 × 5, days −5/-4/-3/-2/-1
MESNA	120 mg/kg	60 mg/kg CIVI over 24 h × 2, -6/-3
Cy/ATG/Thymic RT		
Cyclophosphamide	200 mg/kg	50 mg/kg/day × 4, days −6/-5/-4/-3
Thymic RT	700 cGy	day −1
Antithymocyte globulin	45–90 mg/kg	15–30 mg/kg × 3, days −2/-1/+1
MESNA	200 mg/kg	50 mg/kg CIVI over 24 h × 4, days −6/-5/-4/-3
Bu/FDA/ATG		
Busulfan (oral)	8 mg/kg	4 mg/kg/day × 2, days −6/-5
Fludarabine	150 mg/m^2	30 mg/m^2/day × 5, days −10/-9/-8/-7/-6-5
Antithymocyte globulin	40 mg/kg	10 mg/kg/day × 4, days −4/-3/-2/-1

ATG, antithymocyte globulin.

TABLE 5.4. NONMYELOABLATIVE CONDITIONING REGIMENS

B. **Specific agents used in hematopoietic stem cell transplantation conditioning regimens**

TBI-containing conditioning regimens are most commonly used in HSCT for acute leukemias, chronic myelogenous leukemia (CML), lymphomas, multiple myeloma, and aplastic anemia. Fractionated TBI with a total dose greater than 1,000 cGy is sufficiently lymphoablative to the host to be incorporated in allogeneic HSCT regimens to facilitate donor engraftment. Other advantages of TBI include its activity against a variety of malignancies, even in the face of relative resistance to chemotherapy, and its ability to penetrate sanctuary sites (e.g., central nervous system [CNS] and testicles). Relative contraindications to TBI include extensive prior radiation, impaired pulmonary function, and older age. The nonhematologic toxicities associated with TBI include pneumonitis, mucositis, cataracts, infertility, impaired growth and development (in pediatric patients), and second malignancies. The toxicities of TBI are correlated with total dose, dose intensity (single dose vs. fractionated dosing), and dose rate.

Busulfan (Bu)-containing regimens (most commonly Bu/cyclophosphamide [Cy]) are often substituted for TBI conditioning regimens for HSCT when there are contraindications to TBI. Busulfan is active against a variety of hematologic malignancies (acute myelogenous leukemia [AML], acute lymphocytic leukemia [ALL], CML). It is metabolized primarily in the liver and through tissue alkylation. Urinary excretion of busulfan is minimal. The erratic oral absorption of busulfan can be problematic and may result in inadvertent under- or overdosing. Aggressive antiemetic prophylaxis is recommended before oral busulfan administration. The busulfan dose should be repeated in patients who vomit within 30 minutes of oral administration or in those who vomit pill fragments. Intravenous busulfan is now available and can be substituted for oral busulfan at an intravenous-to-oral dose ratio of 0.8:1. Busulfan also can decrease seizure threshold. Phenytoin should be started as seizure prophylaxis 24 hours before starting busulfan, and therapeutic serum phenytoin levels should be maintained until 48 hours after the last busulfan dose. An increased incidence of venoocclusive disease has been noted in patients in whom high plasma busulfan levels were observed, although busulfan levels are not monitored in routine practice.

Cyclophosphamide is a non–cell-cycle-specific alkylating agent that is highly immunosuppressive (but nonmyeloablative) at doses used in HSCT. It has significant activity against a wide variety of hematologic malignancies and solid tumor types. Cyclophosphamide is a prodrug that undergoes activation through the hepatic cytochrome P450 system. Its nonhematologic dose-limiting toxicity is hemorrhagic myocarditis, which may occur as pleuritic chest pain with electrocardiogram (ECG) changes characteristic of pericarditis within the first several days of exposure, and can progress to fatal congestive heart failure in extreme cases. Factors predictive of severe cardiac toxicity include higher doses (greater than 150 mg/kg total), increased age, prior mediastinal radiotherapy, and a history of congestive heart failure. The other notable toxicity associated with cyclophosphamide is hemorrhagic cystitis, which results from urinary excretion of a metabolite (acrolein), and may occur over several days after exposure. Hemorrhagic cystitis may be prevented with aggressive alkaline hydration (D5W with 2 ampules of bicarbonate infused at 200 to 250 mL/hour, beginning 6 to 12 hours before cyclophosphamide and continuing for 24 hours after), and/or concurrent sodium 2-mercaptoethane sulfonate (MESNA) administration (total dose equivalent to daily cyclophosphamide milligram dose, administered either by continuous intravenous infusion (CIVI) over 24 hours beginning 2 hours before cyclophosphamide, or split into two equal doses, administered 30 minutes before and 4 hours after each cyclophosphamide dose).

BCNU (1,3-bis-[2-chloroethyl]-1-nitrosourea) is an alkylating agent active against a variety of solid tumor types. It is lipophilic and penetrates the blood–brain barrier. BCNU undergoes spontaneous hydrolysis, as well as hepatic microsomal metabolism, which may be induced by agents such as phenobarbital. The dose-limiting toxicities are pneumonitis and hepatic damage. Pneumonitis may be acute or may occur subacutely over several weeks after exposure, with pulmonary infiltrates, fibrosis, hyaline membrane formation, and decreased exercise tolerance. Pulmonary-function testing may reveal reduced forced vital capacity (FVC) and carbon dioxide diffusion in the lung (DLCO). Treatment with corticosteroids (prednisone, 2 mg/kg/day, tapered slowly over 3 months) may result in resolution of pulmonary toxicity if initiated early. High-dose BCNU also has been associated with thrombotic thrombocytopenia purpura (TTP). The outcome of patients with BCNU-induced TTP is poor despite aggressive therapy.

Melphalan is a nitrogen mustard analogue alkylating agent. It has significant activity against multiple myeloma, breast carcinoma, and neuroblastoma. It is highly protein bound and rapidly metabolized to inactive hydroxylated forms, with extensive and unpredictable pharmacokinetic variability between individual patients. Although 5% to 15% of the drug is excreted unchanged in the urine, no significant differences in melphalan pharmacokinetics have been demonstrated in patients with impaired renal function (creatinine clearance [CrCl] less than 40 mL/minute) undergoing HSCT. Mucositis and hepatic venoocclusive disease (VOD) are the nonhematologic dose-limiting toxicities of melphalan.

Etoposide is a podophyllotoxin derivative that acts a topoisomerase II inhibitor. It has activity against a variety of hematologic malignancies and solid tumors. It is metabolized primarily through glucuronidation in the liver. However, 30% to 40% is excreted unchanged in the urine, and so high-dose etoposide should be avoided in the face of renal impairment. The nonhematologic dose-limiting toxicities of etoposide are mucositis and hepatic injury.

Thiotepa is a nitrogen mustard analogue alkylating agent. It has activity against solid tumors, including breast and ovarian carcinoma. Thiotepa is lipid soluble and highly protein bound in plasma. It undergoes extensive hepatic oxidative metabolism through the cytochrome P450 system and also undergoes tissue alkylation. There is minimal urinary excretion. The nonhematologic dose-limiting toxicities of thiotepa include CNS toxicity (somnolence, confusion, coma) and mucositis.

Carboplatin is a carboxylated cisplatin analogue that crosslinks DNA. It is active against solid tumors, including breast, ovarian, and testicular carcinomas. The excretion of carboplatin is almost exclusively urinary and correlates with CrCl. The nonhematologic dose-limiting toxicities include mucositis, peripheral neuropathy, and hepatotoxicity.

VII. Thawing and infusion of stem cells

A bicarbonate infusion is started a few hours before the scheduled infusion of cryopreserved stem cells to minimize renal damage, as the DMSO used for cryopreservation can cause significant hemolysis of contaminating red cells. Similar precautions are required in the case of ABO-incompatible allogeneic transplants. Once the urine is alkaline (pH 7.0), the patient is premedicated with acetaminophen, diphenhydramine and/or hydrocortisone, and antiemetics. Emergency medication and equipment should be available at the bedside to carry out resuscitation in the event of hemodynamic collapse.

Cryopreserved stem cell products are thawed in a temperature-controlled water bath at 37°C to 40°C. Each 100-mL bag is infused over a 15-minute period. Longer infusion times subject the stem cells to DMSO toxicity. Side effects associated with the DMSO in stem cell products include flushing, unpleasant taste, nausea and vomiting, and allergic reactions. Granulocytes and plasma proteins in the product may produce fever, tachycardia, and hypo- or hypertension. Rare, potentially fatal anaphylactic reactions, occurring within minutes of HSC infusion have been reported, and likely represent allergic reactions to DMSO. In the event of a potential anaphylactic reaction, the infusion should be halted immediately, and treatment of anaphylaxis initiated with epinephrine and, if necessary, cardiovascular resuscitation. After stabilization of the patient, and the administration of corticosteroids (methylprednisolone, 1 mg/kg i.v.) and antihistamines (diphenhydramine, 50 mg i.v., ranitidine, 150 mg i.v.), the HSC infusion should be cautiously resumed at a slow infusion rate under close observation with continuous cardiac monitoring. Steroids and antihistamines should be continued for 48 hours. DMSO infusion also can cause hypotension due to mast cell–mediated histamine release, for which diphenhydramine premedication and intravenous fluid support is usually sufficient. Bradycardia, second-degree heart block, and complete heart block have been observed, usually within 1 to 3 hours of cryopreserved HSC infusion. Cardiac complications of cryopreserved HSC infusion can often be avoided or minimized by slowing the rate of infusion, and spreading the infusion of large products (more than five bags) over a 2-day period. DMSO-induced hemolysis in rare cases may be severe enough to result in renal dysfunction.

Allogeneic stem cells are generally infused fresh. The infusion should be started slowly and the patient monitored for any hypersensitivity reactions. Large-volume bone-marrow products should ideally be infused over a period of 3 to 4 hours, and the patient should be monitored closely for fluid overload.

VIII. Supportive care

A. **Antiemetics.** The conditioning regimens typically used in HSCT are highly emetogenic, and it is essential that aggressive antiemetic regimens be used on both a prophylactic and an as-needed basis. A serotonin-receptor antagonist (ondansetron, 32 mg i.v., granisetron, 10 µg/kg i.v., or anzemer 100 mg i.v.) should be given daily during the conditioning regimen in combination with either dexamethasone (10 mg i.v.), lorazepam (1 mg i.v.), or prochlorperazine (10 mg i.v.), 30 minutes before chemotherapy or radiation. Because nausea, vomiting, and anorexia may persist for several days after the conditioning regimen is completed, antiemetics should remain available on an as-needed basis, in addition to intravenous hydration sufficient for maintenance requirements (see nutritional support). In addition to the agents listed, scopolamine, metoclopramide, and droperidol (with diphenhydramine) may be effective in this setting. A more comprehensive discussion of antiemetics is found in Chapter 30.

B. **Nutritional support**

Patients undergoing allogeneic or autologous HSCT often present significant challenges to the maintenance of proper nutritional balance. Patients weighing less than 95% of IBW at the time of HSCT experience significantly increased nonrelapse mortality. Unfortunately, some patients have preexisting nutritional compromise before HSCT, because of underlying disease processes and/or prior treatment. Decreased intake or absorption of nutrients commonly results from anorexia, nausea and vomiting, mucositis, and enteritis. Increased metabolic requirements result from chemotherapy and/or radiation-induced tissue breakdown, fever, infection, corticosteroid administration, and GVHD. It is recommended that all patients undergo a baseline nutritional assessment before HSCT to identify those with significant deficiencies, determine nutritional requirements, and develop a nutritional treatment plan.

Aggressive intravenous hydration (normal saline, 200 to 250 mL/hour) is often initiated before to the conditioning regimen to decrease regimen-related toxicities, and should be continued at maintenance levels (half-normal saline, approximately 1,500 mL/m ^{2}/day) thereafter until oral intake is capable of meeting daily requirements. Patients may be candidates for total parenteral nutrition (TPN) when significant nutritional deficiencies are identified or if there is prolonged (more than 5 to 7 days) impairment of oral intake or intestinal absorption secondary to mucositis. Objective parameters for initiation of TPN include weight, less than 95% of IBW; albumin, less than 2.5; and caloric intake, less than 1,000 cal/day or less than 60% of estimated needs. Prolonged TPN administration may result in cholestasis, liver steatosis, and liver enzyme elevations, which are generally reversible on its discontinuation. The ongoing requirement for TPN should be reassessed at regular intervals and enteral alternatives (tube feeding) considered when appropriate. Recommended nutritional monitoring in all patients during the peritransplant period includes daily weights, electrolytes, creatinine, and biweekly albumin and liver enzyme determinations. Although it is recommended that raw eggs, undercooked meats, and fresh fruits and vegetables be avoided during the neutropenic period to reduce the risk of infection, there are no data to support the routine use of food sterilization.

C. **Growth factors.** Hematopoietic growth factors, primarily G-CSF, granulocyte–macrophage (GM)-CSF, and, to a lesser extent, erythropoietin, are widely used in the HSCT setting and are discussed individually. The use of other recombinant cytokines, such as interleukin 3 (IL-3), stem cell factor, flt3 ligand, and thrombopoietin, is investigational.

G-CSF (filgrastim) is a recombinant human cytokine that stimulates the proliferation and differentiation of granulocytic progenitor cells, whereas GM-CSF (sargramostim; Leukine) exerts similar effects on monocytic and mixed progenitor cells as well. Both are used clinically in the setting of HSCT to decrease the time to neutrophil recovery and may provide benefit in some cases of graft failure. G-CSF or GM-CSF administration after autologous and allogeneic HSCT has been shown to shorten the period of neutropenia (absolute neutrophil count [ANC], less than 500/µL) by 3 to 6 days in most studies, although other studies have demonstrated no significant benefit. A survival benefit has never been demonstrated with either G-CSF or GM-CSF in the allogeneic or autologous HSCT setting. Neither agent has been shown to affect erythroid or platelet recovery significantly. No increases in leukemic relapse or acute GVHD have been observed with either agent. G-CSF and GM-CSF are most commonly administered as a daily subcutaneous injection, but can given as an intravenous infusion. The dose of G-CSF is 5 µg/kg, and the dose of GM-CSF is 250 µg/m ^{2}/day. G-CSF or GM-CSF treatment after HSCT is often started on the day (d 0) or day after (d + 1) stem cell infusion, but may be delayed for up to 6 to 8 days without significant reduction in efficacy. Treatment is continued

until the ANC exceeds 1,000 to 1,500/µL for 2 to 3 days. Medullary bone pain is the primary toxicity of either G-CSF or GM-CSF and may be severe enough to require narcotics. Anaphylactic reactions also have been reported.

Erythropoietin (Epoetin) is a recombinant cytokine that stimulates the proliferation and differentiation of committed erythroid progenitors. The role of erythropoietin in HSCT is not well defined. Randomized studies in allogeneic HSCT have shown earlier erythroid engraftment after erythropoietin treatment, but translation into decreased red cell transfusion requirements has not been definitively demonstrated. No significant benefit has been shown in the autologous HSCT setting. Erythropoietin may be useful in decreasing the time to red cell transfusion independence in the setting of delayed erythroid engraftment after allogeneic HSCT (e.g., major ABO mismatch). Erythropoietin may be administered at a dose of 150 to 300 units/kg 3 times per week, or at 40,000 units per week. It is most commonly given as a subcutaneous injection, although it may be given as an i.v. bolus. An erythropoietin level should be checked before starting erythropoietin, because the likelihood of response is greater in the face of a low level than if a level appropriately elevated for the degree of anemia is observed. No significant toxicities are associated with the use of erythropoietin in HSCT.

D. **Transfusions.** Transfusions of erythrocytes and platelets are commonplace in HSCT. Automatic transfusion parameters are arbitrary and vary between institutions, although it is reasonable to maintain hemoglobin levels greater than 8 to 9 g/dL, and platelets greater than 10 to 20,000/µL. To reduce the risk of transfusion-associated GVHD in immunocompromised HSCT patients, all cellular blood products (**except stem cell products!**) should be irradiated with 2,500 cGy before administration. Allogeneic HSCT patients who are cytomegalovirus (CMV) seronegative should receive CMV-negative products preferentially, to reduce the risk of CMV transmission and disease. Leukofiltration with third-generation blood filters may be an acceptable alternative if CMV-negative products are unavailable. There is no evidence that autologous HSCT patients derive significant benefit from CMV-negative blood products, regardless of serologic status. A possible exception may be recipients of T cell–depleted autologous HSC products, in whom prolonged delays in T-cell recovery and a corresponding increased risk of opportunistic infections after transplant are expected (including CMV disease). Transfusions of granulocytes have been used in the setting of HSCT as an adjunct to antibiotic treatment of serious infections (e.g., fungal infections) in neutropenic patients, as well as prophylaxis against infection during neutropenia. Earlier studies conducted nearly two decades ago, before the availability of growth factors, demonstrated only marginal benefit with granulocyte transfusion. The use of growth factors for granulocyte mobilization has allowed the collection of much larger numbers of granulocytes. This could potentially make the granulocyte transfusion more effective in reducing infectious complications during prolonged neutropenia or immune suppression. There has been no evidence, however, that granulocyte transfusion in any setting to date has had a significant impact on survival. Furthermore, there is a potential risk of CMV transmission from donor to recipient, which may be associated with significant morbidity and mortality in allogeneic HSCT recipients.

E. **Infection prophylaxis.** Infection susceptibility in HSCT patients is increased because of neutropenia, impaired skin and mucosal barriers, indwelling foreign bodies (catheters), and, in the case of allogeneic and unrelated donor HSCT recipients, impaired T-cell function due to immunosuppressive agents and/or T-cell depletion. The infectious organisms that are clinically significant to HSCT include both endogenous flora and environmental pathogens. Measures to prevent infection during the peritransplant period vary considerably between institutions, and although grounded in common sense, are largely empiric. At our institution, measures used to reduce the risk of infection in the HSCT unit include stringent mouth care, masks for patient use outside of their rooms, strict handwashing of healthcare providers and visitors on entering and leaving patient rooms, positive-pressure air circulation within the patient room, and high-efficiency particulate air (HEPA) filtration for the entire bone marrow transplant (BMT) unit. Patients are encouraged to ambulate in the halls of the BMT unit, provided a mask is worn outside their room. The ingestion of fresh fruits and vegetables or undercooked meat should be avoided. More rigorous measures of infection control, including *routine* “gloving and gowning” before patient room entry or the use of gut-sterilizing antibiotic prophylaxis regimens, remain in use at certain centers, but are without clear evidence of benefit.

Some centers routinely use antimicrobial prophylaxis regimens (e.g., ciprofloxacin, 250 to 500 mg p.o. b.i.d.; or trimethoprim/sulfamethoxazole DS, 1 tablet p.o. b.i.d.; or rifampin, 300 mg p.o. b.i.d.). These provide selective decontamination of the gastrointestinal (GI) tract while preserving anaerobic colonization. Prophylaxis is generally begun on entering the hospital and continued until neutrophil recovery or the initiation of intravenous antibiotics. There are few data to support the use of routine bacterial surveillance cultures in the management of patients undergoing HSCT, with the possible exception of weekly stool cultures to detect the emergence of antibiotic-resistant organisms (vancomycin-resistant enterococcus).

Acyclovir prophylaxis (400 mg p.o. t.i.d., or 250 mg/m^2 i.v. q12 hours) should be initiated on day 0 in all patients seropositive for herpes simplex virus (HSV) and continued until resolution of neutropenia (ANC more than 500/µL) in autologous HSCT patients, and until discontinuation of immunosuppression in allogeneic HSCT patients. The use of prophylactic ganciclovir and fluconazole reduces the incidence of CMV and *Candida* species infections, respectively, but neither approach has improved overall survival in allogeneic HSCT patients. Therefore most centers use a preemptive approach to prevent life-threatening CMV disease, by diagnosing asymptomatic CMV reactivation. CMV reactivation can be detected by shell vial viremia or by polymerase chain reaction (PCR) detection of CMV DNA. The incidence of life-threatening CMV disease can be significantly reduced by preemptive treatment of asymptomatic CMV viremia with ganciclovir (5 mg/kg b.i.d. for 21 days, or 5 mg/kg b.i.d. for 10 to 14 days, and then 5 mg/kg/day 3 to 5 times per week until day 100). Acyclovir HSV prophylaxis should be held during preemptive ganciclovir treatment and restarted on its completion.

Trimethoprim–sulfamethoxazole (Bactrim DS, 1 tablet p.o., biweekly) prophylaxis against *Pneumocystis carinii* pneumonia (PCP) should be initiated after myeloid engraftment after allogeneic HSCT and continued for at least 1 year after transplant or until immunosuppression is discontinued. Alternative PCP prophylaxis regimens include monthly inhaled pentamidine monthly or oral dapsone (100 mg p.o. b.i.d.).

F. **Pain management**

Pain is a common problem after HSCT. Whereas acetaminophen may be sufficient for mild pain, narcotics are frequently required. Narcotics should be administered initially by nursing staff on an as-needed basis, with dosage titrated to effect. When dosing exceeds 4 to 6 times over an 8-hour period, it is appropriate to move to a patient-controlled analgesia (PCA) device. It is essential that both analgesia and sedation be monitored and recorded on a frequent and regular basis in patients receiving narcotics via PCA, and the requirement for continuation assessed daily. In addition to sedation and respiratory depression, attention should be paid to other opioid toxicities, including nausea, constipation, urinary retention, and mental-status changes. The concurrent use of other sedating medications (e.g., benzodiazepines) should be limited in patients receiving opioids, because of additive sedative effects. Nonsteroidal antiinflammatory agents (NSAIDs) have limited utility in the HSCT setting because of their undesirable platelet, renal, and GI effects.

G. **Central venous access.** All patients undergoing HSCT should have an external central venous catheter placed before admission, with a minimum of two to three access ports to facilitate the delivery of intravenous fluids, antibiotics, blood products, parenteral nutrition, and other medications during the peritransplant period. In patients undergoing autologous HSCT, large-bore pheresis catheters placed for HSC collection before admission may be retained for this purpose. A number of issues are related to the routine care and use of central venous catheters.
   1. **Catheter occlusion.** Catheter lumens may become occluded, either partially (inability to withdraw blood despite ability to infuse fluids) or completely (inability to withdraw or infuse). In the event of catheter occlusion, attempts should initially be made episodically to infuse and withdraw 10 to 15 mL of saline. If this is unsuccessful, a chest radiograph should be obtained to rule out migration of the tip from the superior vena cava, in which case, catheter repositioning or replacement may be needed. If correct positioning is confirmed, tissue plasminogen activator (t-PA; 2 mg in 1 mL) may be injected into the occluded port and left for 30 to 60 minutes before reaccessing is attempted. t-PA treatment can be safely repeated up to 2 to 3 times with a high degree of success.
   2. **Infection.** Catheter-related infections are commonplace in the setting of HSCT. Exit-site infections, which are distal to the catheter cuff, are typically associated with localized redness, tenderness, and/or purulent drainage at the site of catheter extrusion from the skin. Fever and other systemic signs of infection may be absent. Conservative management with local wound care and oral or intravenous antibiotics is usually sufficient, unless the cuff has become externalized, in which case, the catheter must be removed and replaced. More serious tunnel infections are characterized by redness and tenderness tracking along the subcutaneous path of the catheter and are frequently associated with fever and expressible purulent drainage. Prompt initiation of intravenous antibiotics, catheter removal, and often surgical debridement of the site are required to prevent the development of a more extensive infection. Catheter-related sepsis results from microbial colonization of the intravascular portion of the catheter tip and is usually associated with systemic signs and symptoms, including fever, rigors, and occasionally cardiovascular instability. Localized signs of infection at the catheter site are often absent. Intravenous antibiotics are usually sufficient to treat catheter-related bacteremia, with catheter removal required only in the event of persistent fever or bacteremia, or in the case of documented fungemia or vancomycin-resistant enterococcus (VRE) bacteremia. Skin-colonizing organisms, such as *Staphylococcus epidermidis, Staphylococcus aureus,* and *Streptococcus viridans,* are the most common organisms isolated in suspected catheter-related infections. Vancomycin should be considered first-line empiric therapy for suspected catheter-related infections, pending microorganism identification and sensitivity. Clindamycin may be used as an alternative in patients intolerant of or allergic to vancomycin. An oral agent with good gram-positive coverage (e.g., dicloxacillin, 250 mg p.o. q.i.d.) may be acceptable for treating limited exit-site infections in nonneutropenic patients. Long-term use of catheters results in infection with resistant organisms like *Enterococcus faecium*. Infection with enterococcus requires removal

of the venous access device in addition to antibiotic therapy. Chloramphenicol has been the agent of choice for enterococci. However, new agents like linezolid and quinupristin/dalfopristin (Synercid) have significant activity against this organism.

3. **Catheter-related deep venous thrombosis.** Catheter-related deep venous thrombosis (DVT) is common in the HSCT setting, especially in association with large-diameter apheresis catheters. The presence of thrombocytopenia does not preclude the development of DVT. Signs and symptoms include unilateral upper extremity swelling and/or pain. In some cases, clot extension may result in superior vena cava (SVC) occlusion, with resultant cyanosis and swelling of the head, neck, and arms (SVC syndrome). The occurrence of pulmonary thromboembolism in this setting, although less common than with lower-extremity DVT, has been well documented. Diagnosis can usually be made with Doppler ultrasonography, although occasionally venographic contrast studies may be required. Treatment with intravenous heparin and subsequent coumadin is usually sufficient, and removal of the catheter is rarely required.

H. **Bone loss prophylaxis**

Accelerated loss of mineralized bone is a significant problem that predisposes to the spontaneous development of debilitating fractures of weight-bearing bones (primarily hip and spinal vertebral body). This is more common after allogeneic transplant, with potential causes of bone loss including hypogonadism, corticosteroid use, cyclosporine/FK-506 use, nutritional deficiencies of calcium and vitamin D, and decreased weight-bearing activity. The incidence of spontaneous fractures after allogeneic HSCT has not been extensively documented, but may be as high as 10% to 20% during the first year. Reasonable (but unproven) strategies to reduce bone loss in this setting include estrogen replacement in menopausal women, as well as empiric calcium (calcium carbonate, 1,000 to 1,500 mg/day) and vitamin D (400 IU/day) supplementation. Prophylactic bisphosphonate administration has been shown to be effective in preventing bone loss among nontransplant patients receiving long-term corticosteroids, but has not been formally evaluated after allogeneic HSCT. Bisphosphonates should be considered for patients with high pretransplant fracture risk (severe osteopenia [T-score between –1.0 and –2.5] or osteoporosis [T score less than –2.5], a history of spontaneous fractures, prolonged prior corticosteroid use), for patients receiving high-dose steroids (1 to 2 mg/kg/day) for prolonged periods after transplant, and for patients in whom severe osteopenia, osteoporosis, or spontaneous fractures develop after transplant.

IX. Complications of stem cell transplantation and their management

A. Graft-versus-host disease

Acute GVHD after allogeneic transplantation is a result of T cells in the donor graft recognizing host antigens as foreign. The major determinants of the incidence and severity of GVHD are the degree of genetic disparity at the major and minor histocompatibility loci, source of stem cells, age of the recipient and donor, donor sex, the regimen used for GVHD prophylaxis, and number of donor T cells infused.

The first clinical manifestation of acute GVHD is usually a mildly pruritic maculopapular rash occurring near the time of WBC engraftment. In the early stages, it is confined to the hairline and palms or soles. As it progresses, it may spread to involve the entire skin surface, and bullous lesions may develop. The liver also is a commonly involved organ. Liver involvement commonly is seen with conjugated hyperbilirubinemia, an elevation of the alkaline phosphatase, or less commonly, an elevation in transaminases. GI involvement also is common and is characterized by abdominal cramping and diarrhea. The stool output may reach several liters per day, resulting in fluid/electrolyte imbalance. The loss of the mucosal barrier results in the patient being predisposed to infections. Abrupt cessation of the diarrhea often heralds the onset of ileus and signifies a grim prognosis. There are two commonly used systems for grading acute GVHD, the Glucksberg Grading (Table 5.5) and the International Bone Marrow Transplant Registry (IBMTR) Severity Index (Table 5.6).

Clinical Grading of Acute Graft-Versus-Host Disease

Stage	Skin	Liver	Gut	Functional Impairment
0	0	0	0	0
I	1+–2+	0	0	0
II	1+–3+	1+	1+	1+
III	2+–3+	2+–3+	2+	2+
IV	2+–4+	2+–4+	3+	3+

Clinical Staging of Acute Graft-Versus-Host Disease

Stage	Skin	Liver	Gut
1+	Maculopapular rash <25% body surface	Bilirubin 2–3 mg/dL	Diarrhea 500–1,000 mL/d; persistent nausea
2+	Maculopapular rash 25–50% body surface	Bilirubin 3–6 mg/dL	Diarrhea 1,000–1,500 mL/d
3+	Generalized erythroderma	Bilirubin 3–6 mg/dL	Diarrhea >1,500 mL/d
4+	Desquamation and	Bilirubin >15 mg/dL	Pain + ileus

TABLE 5.5. GLUCKSBERG GRADING

	Skin		Liver		Gut (Diarrhea)	
Index	Stage	Rash Extent	Stage	Bili (mg/dL)	Stage	Vol (mL)
A	1	<25%	0	<2	0	<500
B	2	25–50% or	1–2	2–6 or	1–2	500–1,500
C	3	>50% or	3	6–15 or	3	>1,500
D	4	Bullae or	4	>15 or	4	Pain and ileus

IBMTR, International Bone Marrow Transplant Registry.

TABLE 5.6. IBMTR SEVERITY INDEX

Glucocorticoids constitute the first line of therapy for acute GVHD. Oral prednisone or i.v. methylprednisolone are administered at a dose of 1 to 2 mg/kg/day. Steroids are tapered slowly if improvement occurs. Some centers institute high-dose steroids at a dose of 1.0 g/m ^{2} for patients who fail to derive any therapeutic benefit with conventional doses. Patients with steroid-resistant disease have a poor prognosis. Options for therapy include the use of equine antithymocyte globulin or investigational protocols with immunosuppressant drugs and monoclonal antibodies directed against a variety of T-cell antigens. Some reports suggest that PUVA therapy for skin-only GVHD and extracorporeal photopheresis for systemic GVHD may provide therapeutic benefit. High-potency antimotility agents like belladonna and opium combinations and antisecretory drugs like octreotide (Sandostatin) may provide symptomatic relief to patients with large-volume diarrhea.

Chronic GVHD is conventionally defined as GVHD occurring more than 100 days after BMT. The greatest risk factor is a history of acute GVHD. Chronic GVHD is graded as limited or extensive (Table 5.7). The most common site of involvement is the skin, where lichenoid or sclerodermatous changes may result. Lichenoid changes and ulceration also may involve the buccal mucosa, resulting in dryness and pain, especially with spicy food. Ocular involvement results in an entity similar to keratoconjunctivitis sicca. Hepatic involvement results in a cholestatic picture. Dysphagia and weight loss are other common GI manifestations. Involvement of small bronchioles results in bronchiolitis obliterans, manifest by dyspnea and cough. The development of autoantibodies may result in clinical syndromes mimicking a wide variety of autoimmune diseases. A platelet count less than 10,000/μL is a poor prognostic factor for survival in patients with extensive-stage disease. Treatment with low-dose steroids and cyclosporine alone or in combination is the most common initial regimen. Alternatives include use of azathioprine, thalidomide, PUVA therapy, and photopheresis.

Limited chronic GVHD Either or both 1. Localized skin involvement 2. Hepatic dysfunction due to chronic GVHD
Extensive chronic GvHD Either 1. Generalized skin involvement or 2. Localized skin involvement and/or hepatic dysfunction due to chronic GVHD Plus 3a. Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis 3b. Involvement of eye (Schirmer's test with <5 mm wetting), or 3c. Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, or 3d. Involvement of any other target organ

TABLE 5.7. CLINICOPATHOLOGIC CLASSIFICATION OF CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD)

B. **Hepatic venoocclusive disease**

VOD is a potentially life-threatening complication of HSCT. Its etiology is incompletely understood, but VOD is believed to arise from damage to the hepatic endothelium, secondary to high-dose chemotherapy and/or radiation. VOD has been reported in 10% to 60% of HSCT series. Risk factors include a history of hepatic injury (e.g., hepatitis, ethanol abuse) with pretransplant transaminase elevation, a history of busulfan exposure, second transplants, mismatched or unrelated donor HSCT, and the use of methotrexate for GVHD prophylaxis. Clinically, VOD is characterized by a progressive increase in bilirubin with associated weight gain and/or ascites, usually within the first 30 days after transplant. The most common physical finding is tender hepatomegaly. Transaminase and alkaline phosphatase levels typically remain normal or minimally elevated. Histologic findings range from subendothelial swelling of the terminal hepatic venules in mild cases, to endothelial destruction with sinusoidal dilatation and engorgement with fibrinous clot, and hepatocyte necrosis. The diagnosis of VOD is most often made on clinical grounds, and liver biopsy is seldom indicated. The differential diagnosis includes acute GVHD, sepsis syndrome, and extrahepatic cholestasis. Spontaneous resolution of VOD is observed in up to 70% of cases. Supportive care measures are the mainstay of treatment for VOD, with careful attention to sodium and fluid management. No specific intervention has been demonstrated conclusively to alter the natural history of severe VOD. There have been anecdotal reports of improvement in cases of severe VOD after therapy with thrombolytic agents and heparin (t-PA, 20 mg i.v., over 4 hours for 4 consecutive days, and heparin, 150 units/kg/day). The risk of significant bleeding complications limits such an approach to only those patients with severe, life-threatening disease. Other treatment strategies of unproven benefit have included the use of prostaglandin E_1 (PGE_1), antithrombin III, heparin, and activated protein C. We have used high-dose steroids (methylprednisolone, 500 mg/m^2 i.v. q12 hours for six doses) in the setting of VOD, with minimal toxicity and frequent temporal correlation with clinical improvement. In the absence of randomized studies, however, it should be emphasized that improvement of VOD after such interventions cannot be distinguished from cases in which spontaneous resolution is observed without intervention.

Low-dose intravenous heparin (150 units/kg/day) as VOD prophylaxis has been shown to reduce nonfatal VOD, with minimal hemorrhagic complications, but lacked sufficient power to demonstrate efficacy in preventing severe VOD. It may be reasonable, nevertheless, to use low-dose heparin prophylaxis in patients prospectively identified to be at increased risk for VOD.

C. **Infection**

1. **Allogeneic transplantation**
   a. **Early.** Bacterial infections are common during the period of neutropenia and mucositis. Blood cultures should be drawn after the first temperature spike and a broad-spectrum agent with activity against *Pseudomonas aeruginosa* (based on pathogen-susceptibility data at individual institutions) should be initiated. Some institutions initiate an aminoglycoside for double gram-negative coverage concurrently. At Washington University, we reserve aminoglycosides for sick and hypotensive patients to minimize toxicity. A short empiric trial of vancomycin may be justified. However, it should be discontinued after 48 to 72 hours if blood cultures reveal no evidence of gram-positive infection. Studies have shown that in patients with neutropenic fevers who are hemodynamically stable, the addition of vancomycin does not improve the outcome. Most institutions also perform a chest radiograph with the first temperature spike. If bacteremia persists despite appropriate antibiotic coverage, the venous access device may need to be removed. Bacterial infections remain common even after neutrophil recovery, because of the long-term need for indwelling catheters.
   b. **Late.** Transplant recipients are predisposed to infections over the long-term because of prolonged immunosuppression. Although natural killer (NK) cell function may return to normal within weeks of transplantation, T- and B-cell function remain depressed for months to years after allogeneic transplantation. CMV poses the greatest risk for infections in this period. Patients are at a risk for CMV infection if either donor or recipient serology for CMV is positive before transplantation. Once neutrophil engraftment occurs, regular monitoring for CMV, viremia should be performed weekly for the first 100 days. Methods of screening for CMV viremia include shell vial, pp65 antigenemia test, and polymerase chain reaction (PCR). Some institutions give all at-risk patients prophylactic therapy with ganciclovir. However, because of the cytopenias associated with this drug, most institutions start preemptive therapy with ganciclovir if screening tests are positive. Despite regular monitoring, CMV pneumonitis, enteritis, and hepatitis occur in 5% to 10% of patients. Therapy for documented CMV disease consists of a combination of ganciclovir and intravenous immunoglobulin. Treatment of CMV disease consists of ganciclovir (5 mg/kg IV q12 hours for 21 days) and intravenous immunoglobulin (IVIG; 500 mg/kg i.v. every other day for 10 doses). Ganciclovir may cause significant and prolonged bone marrow suppression and should be withheld in the face of an ANC less than 500 cells/µL. Foscarnet (50 mg/kg q8 hours) may be substituted for ganciclovir for the treatment of CMV disease. BK virus and adenovirus may cause hemorrhagic cystitis during this period. No specific therapy exists. *Aspergillus* infection usually involves the lungs and sinuses. Therapy consists of regular amphotericin-B or one of the liposomal formulations. Opportunistic fungal infections like mucormycosis, and other endemic mycoses also may be seen. *Nocardia* and *Toxoplasma* species are potential pathogens in this immunocompromised population.
   c. **Delayed.** An increased susceptibility to infections with encapsulated bacteria (e.g., *Pneumococcus* and *Haemophilus* species) may been seen for several years after transplantation, particularly among patients with chronic GVHD.
2. **Autologous transplantation**

The spectrum and management of bacterial infections immediately after autologous transplantation is similar to that after allogeneic transplantation. Candidemia occurs in a small percentage of patients. Other opportunistic pathogens rarely cause infection after autologous transplantation. Reactivation of latent herpes simplex virus is rare, provided adequate prophylactic therapy is given. In the occasional patient, persistent culture-negative fever may develop after recovery of neutrophil counts. CT should be performed to exclude hepatosplenic candidiasis in these patients. If the scan is normal, most patients respond to removal of central venous access devices. In the absence of any evidence for localized infection, drug fever should be excluded.

D. **Gastrointestinal**

1. **Allogeneic transplantation**

Nausea and vomiting are commonly observed during conditioning. The management of these complications was discussed in the section on supportive care. Oral mucositis can be severe with regimens using fractionated dose radiation and etoposide. Oral rinses with saline, bicarbonate, or chlorhexidine, and candida prophylaxis with clotrimazole or nystatin is recommended. Topical anesthetic agents and analgesics also may be used to help with pain control. Severe cases require the intravenous administration of potent opiate drugs. Reactivation of latent herpes simplex infection is rarely a cause for mucositis if acyclovir prophylaxis is administered to seropositive patients. Diarrhea secondary to chemotherapy-induced mucosal injury responds to antimotility agents like diphenoxylate and loperamide. *Clostridium difficile* colitis is another common cause of diarrhea. Treatment with metronidazole or oral vancomycin is usually successful and should be instituted if the stool is positive for *C. difficile* toxin. Hyperbilirubinemia and elevation of hepatic enzymes may result from regimen- and medication-related toxicity, VOD, and parenteral nutrition solutions. Acute GVHD is an additional cause for upper and lower GI tract symptoms and hepatotoxicity in this patient population. The use of methotrexate for the prophylaxis of GVHD increases the incidence and severity of mucositis and hepatotoxicity in this patient population.

2. **Autologous transplantation**

Other than the lack of GVHD, the regimen-related toxicity profile is similar to that seen after allogeneic transplantation. Whereas hepatic VOD is observed almost exclusively in allogeneic or unrelated-donor HSCT, it may occasionally be seen in the setting of autologous HSCT. Its etiology, presentation, and management (discussed earlier) are similar in both settings.

E. **Cardiovascular**

1. **Allogeneic transplantation**

   Cyclophosphamide at high doses (120 mg/kg) exerts direct toxic effects on the myocardium, which may result in arrhythmias (e.g., atrial fibrillation/flutter, paroxysmal supraventricular tachycardia), pancarditis, and congestive heart failure in severe cases. Risk factors for cyclophosphamide-induced cardiac toxicity are believed to include prior extensive anthracycline treatment, mediastinal radiation, higher cyclophosphamide doses (more than 150 mg/kg), and lower baseline left ventricular ejection fraction (although not predictive of severe cardiac toxicity in a prospective study). Depletion of myocardial thiol-reducing agents has been suggested as the etiology of cyclophosphamide-induced cardiac toxicity. Cardiac toxicity usually develops within 5 to 7 days of cyclophosphamide infusion and may occur as substernal chest pain and dyspnea. Electrocardiography may demonstrate low QRS voltage and/or diffuse ST-segment elevation and T-wave inversions suggestive of pericarditis, and chest radiographs may demonstrate an enlarged cardiac silhouette and/or pulmonary edema in severe cases. Signs of right heart failure and cardiac tamponade (tachycardia, hypotension, peripheral edema, elevated jugular venous pulse) may be observed secondary to rapid accumulation of serosanguinous pericardial fluid and may require two-dimensional (2-D) echocardiography and emergency pericardiocentesis in rare circumstances. Therapy is supportive, with management of arrhythmias and fluid balance. Corticosteroids may be beneficial in the amelioration of pericarditis symptoms (pain), but have not been demonstrated to alter the natural history of severe of cyclophosphamide-induced cardiac toxicity. In mild cases, spontaneous resolution with rapid and complete recovery is usually observed.

2. **Autologous transplantation**

   Cyclophosphamide-related cardiotoxicity, as discussed earlier for allogeneic HSCT, also can be observed in the setting of allogeneic HSCT. Its etiology, presentation, and management are the same in both cases. Cardiac toxicities observed during the infusion of cryopreserved HSCs were discussed in the section on thawing and infusion of stem cells.

F. **Renal and genitourinary**
   1. **Allogeneic transplantation**

      Hemorrhagic cystitis typically is seen with lower abdominal pain, urinary urgency and frequency, and gross hematuria. As a regimen-related toxicity, it is most commonly observed in association with high-dose cyclophosphamide, but also may be seen after etoposide, busulfan, and/or radiation, most often within days of exposure, although the onset may be delayed for up to several weeks. Viral etiologies of hemorrhagic cystitis in immunocompromised allogeneic HSCT recipients include BK virus, adenovirus, JC virus, and cytomegalovirus. The presumptive diagnosis of a viral etiology is made with the detection of virus in urine together with a clinical presentation consistent with hemorrhagic cystitis, although the prevalence of asymptomatic viral shedding exceeds the incidence of clinically significant disease. Furthermore, JC and BK viral DNA detection by PCR in healthy, asymptomatic allogeneic transplant recipients is commonplace. The treatment of hemorrhagic cystitis is primarily supportive and includes aggressive hydration and diuresis to maintain urine flow, continuous bladder irrigation to prevent the formation of intraluminal clots, transfusional support to minimize thrombocytopenia and coagulopathy, and analgesia (narcotics are frequently required). In cases of intractable bladder hemorrhage, cystoscopy and formalin instillation may be indicated, although it is associated with significant morbidity (pain, scarring, impaired bladder function).

      Acute renal failure is a common complication of allogeneic HSCT, and in most cases is multifactorial, especially during the peritransplant period (first 30 days). Nephrotoxic medications frequently contribute to the development of acute renal failure (ARF). Nephrotoxic agents commonly used in the peri- and posttransplant settings include cyclosporine or FK506, aminoglycoside antibiotics, amphotericin, and intravenous contrast. Sepsis and renal hypoperfusion also may contribute to ARF, and occasionally postrenal etiologies, such as clot-related bladder-outlet obstruction or bladder atony (e.g., narcotics), may be implicated. The diagnosis of TTP should be considered, especially in patients receiving cyclosporine or FK-506. The workup of patients with unexplained ARF should include measurement of a postvoid residual volume and, if normal (less than 150 mL), a renal ultrasound should be obtained to exclude postrenal etiologies. A peripheral blood smear should be examined to exclude the presence of schistocytes. Urine electrolytes should be obtained for calculation of the fractional sodium excretion (FENa) to assess volume status. Conservative management measures include the maintenance of adequate hydration and avoidance of unnecessary additional exposure to nephrotoxic agents. Dosing of other medications should be adjusted as appropriate to reflect the degree of renal insufficiency. Nephrology consultation for hemodialysis should be considered, as appropriate, in the face of worsening renal function with oliguria, azotemia, and/or uncorrectable acidosis or electrolyte disturbances. In a clinical setting consistent with TTP (schistocytosis [more than three to five per high-power field; HPF], elevated lactate dehydrogenase [LDH], headache, and/or mental status changes) cyclosporine/FK506 should be discontinued, and consideration should be given to a trial of plasmapheresis, although outcomes with plasmapheresis in this setting are often disappointing.

   2. **Autologous transplantation**

      Hemorrhagic cystitis occurs in the setting of autologous HSCT, although viral etiologies are uncommon in this setting because of the absence of prolonged immunosuppression. The management is similar to that detailed earlier for allogeneic HSCT. The differential diagnosis and management of ARF in autologous HSCT is similar to those of allogeneic HSCT, as discussed earlier, with the exception that potential etiologies do not include cyclosporine and FK-506 treatment.

G. **Pulmonary**
   1. **Allogeneic transplantation**
      a. **Infections.** Pulmonary infections are a frequent complication of allogeneic HSCT. The frequency with which specific infectious agents are implicated varies over time throughout the posttransplant period. During the first 30 days after transplant, bacterial (both gram-positive and gram-negative) and fungal (*Candida* species, *Aspergillus*) pneumonias are common. Allogeneic transplant patients remain at risk for PCP while receiving immunosuppressive therapy, although the risk of PCP may be substantially reduced with the institution of prophylactic antibiotics on myeloid engraftment as discussed earlier. CMV pneumonitis occurs most frequently between days 30 and 100, although it can occur as late as 1 to 2 years after transplant and in the absence of detectable viremia. Risk factors for CMV pneumonitis include CMV seropositivity, age, acute GVHD, and CMV viremia.

         Other viral pneumonitis etiologies include respiratory syncytial virus (RSV), parainfluenza viruses, influenza viruses (type A and B), and rhinovirus. These infections may occur throughout the peri- and posttransplant period and have been associated with high mortality in immunocompromised patients. The incidence of these infections is clustered in the winter months and parallels the period of highest prevalence in the general population. Aerosolized ribavirin has been used to treat RSV pneumonitis in uncontrolled series with improved outcomes compared with historical controls, but was effective only if initiated early in the course of infection (before intubation). The role of RSV immunoglobulin remains unclear.

         Late pulmonary infectious etiologies (more than 100 days after transplant) among immunosuppressed allogeneic HSCT patients include encapsulated bacterial organisms, fungal organisms (*Aspergillus* and *Candida* species; occasionally blastomycosis, histoplasmosis, and others), *Nocardia,* and viral etiologies, as discussed earlier.

      b. **Diffuse alveolar hemorrhage.** This occurs most commonly during the first 30 days after allogeneic HSCT (often around the time of engraftment). It typically arises in the histologic setting of diffuse alveolar damage and concomitant thrombocytopenia. It is characterized clinically by focal or diffuse radiographic infiltrates, fever, and hypoxia, and is associated with high mortality (80% to 100%). Bronchoalveolar lavage (BAL) results in progressively increased bloody fluid return with successive lavages and negative cultures. Platelets should be transfused to maintain platelet counts above 50,000/µL, any coagulopathy should be corrected with fresh frozen plasma and empiric vitamin K, and empiric broad-spectrum antibiotics should be administered. Treatment with high-dose steroids (methylprednisolone, 500 mg q12 hours for 3 days, then tapered 50% every 3 days) has been shown to improve survival.
      c. **Idiopathic pneumonitis.** This is a noninfectious process that is thought to result from the toxic effects of radiation and dose-intensive chemotherapy (e.g., BCNU, cyclophosphamide, busulfan). The onset of symptoms typically occurs throughout the first approximately 100 days after HSCT and may be insidious. Clinical characteristics include patchy, multilobar pulmonary infiltrates, cough, fever, and dyspnea. Pulmonary-function testing frequently demonstrates evidence of a new restrictive process and/or impaired diffusion capacity. Management involves bronchoscopic evaluation and exclusion of treatable infectious processes, supportive care with oxygen, and if necessary, mechanical ventilation. Corticosteroids (prednisone, 1 to 2 mg/kg/day, tapered gradually over several weeks once clinical improvement is noted) have been shown to improve the outcome of pneumonitis associated with BCNU.
      d. **Bronchiolitis obliterans organizing pneumonia (BOOP).** This is a chronic, progressive inflammatory process that develops in the setting of chronic GVHD, resulting in airflow obstruction, susceptibility to recurrent respiratory infections, and to spontaneous pneumothorax. There are no clear etiologic links between infectious processes and the development of BOOP in allogeneic HSCT patients. Clinical symptoms include the insidious

onset of nonproductive cough and dyspnea on exertion, often in the absence of fever or radiographic abnormalities. Pulmonary-function testing characteristically demonstrates the development of obstructive physiology. Supportive measures include aggressive treatment of infections with antibiotics and the use of bronchodilators. Infection prophylaxis with oral antibiotics and IVIG (in patients with documented hypogammaglobulinemia) can be considered. Treatment with corticosteroids, especially in the setting of concomitant chronic GVHD, may be beneficial in stabilizing or slowing the progression of bronchiolitis obliterans.

2. **Autologous transplantation**

Pulmonary complications in the autologous HSCT setting are limited, in most cases, to the neutropenic peritransplant period, because of the rapid recovery of immune function on neutrophil reengraftment. Bacterial (gram-positive and gram-negative), fungal (most commonly *Candida*), and viral infections are common during the neutropenic period. CMV pneumonitis is uncommon in the autologous HSCT setting, but has been reported especially in patients receiving CD34+ selected transplants. Likewise, *P. carinii* is uncommon after autologous HSCT, with the exception of patients heavily pretreated with corticosteroids (e.g., ALL patients), or those receiving T cell–depleted or CD34+-purified autologous stem cell transplants. Chemotherapy (especially BCNU) or radiation-induced idiopathic pneumonitis may occur approximately 2 to 10 weeks after autologous HSCT. Its presentation and management are similar to those of idiopathic pneumonitis arising in the allogeneic HSCT setting, as discussed earlier.

H. **Central nervous system**

1. **Allogeneic transplantation**

Regimen-related CNS toxicity is rare. Busulfan is known to lower the seizure threshold. However, the use of prophylactic phenytoin (Dilantin) has reduced the incidence of this problem. High-dose cytosine arabinoside is known to cause cerebellar toxicity. Metabolic encephalopathies may be observed in patients in whom renal or hepatic dysfunction develops. Occasionally, intracranial hemorrhage may occur during the period of thrombocytopenia. Learning difficulties may be late sequelae of transplant and pretransplant therapy.

The use of cyclosporine and FK-506 after allogeneic transplantation is responsible for a wide array of neurologic symptoms. The side-effect profile of these drugs includes tremors, headaches, loss of vision, encephalopathy, seizures and a TTP-like syndrome due to a microangiopathic insult caused by cyclosporine and FK-506. Magnetic resonance imaging (MRI), specifically T_2-weighted images, after administration of gadolinium, reveals a hyperintense signal at the grey–white-matter junction, especially in the region of the occipital cortex. Therapy consists of discontinuation of the drug. Plasma exchange for cyclosporine-induced TTP is variably effective. Opportunistic infections (e.g., *Aspergillus, Nocardia,* and *Toxoplasma* sp.) are frequently seen in this patient population.

Posttransplant lymphoproliferative disorders may occur, especially after T cell–depleted transplants. These may have both peripheral adenopathy and CNS lesions. Rarely, progressive multifocal leukoencephalopathy may develop, especially in recipients of T cell–depleted allogeneic transplants because of severe immunodeficiency.

2. **Autologous transplantation**

Regimen-related toxicity and metabolic encephalopathy may occur, as after allogeneic transplantation. Opportunistic infections affecting the CNS are rare after autologous transplantation.

I. **Hematologic**

1. **Allogeneic transplantation**

Graft failure is a dreaded complication of allogeneic transplantation. Graft failure may be primary (defined as failure of the absolute neutrophil count to reach 2×10^6/dL by day 28 after transplant) or secondary (transient donor hematopoiesis). Graft failure occurs because of rejection of the donor hematopoietic cells by the immune system of the recipient. This is confirmed by variable number of tandem repeats (VNTR)/restriction fragment length polymorphism (RFLP) analysis or in the case of sex-mismatched transplantation by sex chromosomal analysis. The causes for graft failure include HLA disparity at major and minor loci, inadequate conditioning of the host, inadequate number of donor stem cells, T-cell depletion of the donor graft, inadequate immunosuppression, and allosensitization to donor antigens by transfusion from the donor before transplantation. In addition, there is a greater incidence of cytopenias after allogeneic transplants than after autologous transplantation because of an increased susceptibility to infections (e.g., CMV) and greater use of myelosuppressive drugs (e.g., ganciclovir, co-trimoxazole [Bactrim]). An immediate or delayed Coomb-positive hemolytic anemia may occur after ABO-mismatched allogeneic transplantation. In the case of major ABO incompatibility (recipient has antibody to donor red blood cells [RBCs]), some centers advocate that the recipient undergo a prophylactic plasma exchange if the recipient has high isohemagglutinin titers. Usually, simple RBC depletion of the donor graft is sufficient to avoid major hemolytic transfusion reactions. Once a hemolytic reaction occurs, therapy consists of administration of recipient-type RBCs or plasma-depleted group O RBCs. If plasma or platelet transfusion is required, they should be donor blood type. In case of minor ABO incompatibility (donor has antibody to recipient cells), prophylactic RBC exchange with group O RBCs may be considered. Once hemolysis occurs, group O RBCs and recipient-type plasma and platelet transfusions should be used.

2. **Autologous transplantation**

With autologous transplantation, although immunologic rejection of the graft is not possible, poor engraftment may result from insufficient/damaged stem cells, damaged marrow microenvironment, medication, or infection. DMSO-induced hemolysis in rare cases may be severe enough to result in renal dysfunction.

CHAPTER 6. AIDS-ASSOCIATED MALIGNANCIES

Benjamin Tan and Lee Ratner

Approach to Malignancy in the Acquired Immunodeficiency Syndrome Patient
General
Kaposi Sarcoma
The presentation of Kaposi sarcoma is dependent on the site
Pertinent history
A thorough physical examination
Diagnosis, workup, and staging
Pathology
Radiology and endoscopic procedures
Laboratory tests
Staging
Therapy
Antiretroviral therapy
Specific therapy for Kaposi sarcoma
Complications
Complications of acquired immunodeficiency syndrome–Kaposi sarcoma
Complications of therapy
Follow-up
Background
The role of Kaposi sarcoma herpes virus (KSHV)
Current focus of research
Acquired Immunodeficiency Syndrome–Associated Non-Hodgkin Lymphoma
Clinical presentation
B-symptoms
Lymph node enlargement
GI involvement
CNS or meningeal involvement
Pleural or pericardial effusions
The physical examination
Diagnosis, workup, and staging
Pathology
Radiology/Procedures
Laboratory tests
The Ann Arbor Staging
Therapy
Chemotherapy without HAART
Chemotherapy with HAART
Relapsed or refractory AIDS-NHL
CNS prophylaxis
Radiotherapy
Complications
Complications of the disease
Complications of therapy
Follow-up
Background
Current focus of research
Acquired Immunodeficiency Syndrome–Associated Primary Central Nervous System Lymphoma
Clinical presentation
Diagnosis, workup, and staging: pathology
Radiology/Procedures
Laboratory tests
Therapy
Cranial irradiation
Steroids
Combined chemotherapy with radiation
High-dose methotrexate
HAART
Complications of disease
Ocular lymphoma
Leptomeningeal lymphoma
Spinal cord involvement
Background
Other Acquired Immunodeficiency Syndrome–Associated Malignancies
AIDS-related Hodgkin disease (AIDS-HD)
Epithelioid cancers of the cervix and anus
Other cancers
Suggested Readings

APPROACH TO MALIGNANCY IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME PATIENT

I. **General.** In approximately 40% of patients infected with the human immunodeficiency virus (HIV), a malignancy develops during their lifetime. **Highly active antiretroviral therapy (HAART),** better prophylaxis, and effective treatment of opportunistic infections contribute to the improved survival of patients with acquired immunodeficiency syndrome (AIDS). With HIV infection, cancer risk increases gradually, and with prolonged survival of AIDS patients, more neoplasms are expected to develop in this population. Epidemic Kaposi sarcoma (KS), AIDS-related non-Hodgkin lymphoma (NHL), and cervical cancer are designated as AIDS-defining illnesses by the Centers for Disease Control and Prevention (CDC). The incidence of epithelioid anal cancer, Hodgkin disease (HD), multiple myeloma, testicular tumors, and childhood sarcomas also are increased in HIV-infected persons.

KAPOSI SARCOMA

I. **The presentation of Kaposi sarcoma is dependent on the site** and degree of KS involvement. KS can involve any part of the human anatomy, and its manifestations are highly variable, ranging from asymptomatic innocuous cutaneous macules to life-threatening visceral lesions.
   A. **Pertinent history** should include description of all areas of initial KS involvement; lesion duration and rates of progression; gastrointestinal (GI), pulmonary, and KS-specific symptoms as well as the duration of HIV infection; AIDS-defining illnesses; other sexually transmitted diseases; opportunistic infections; and current antiretroviral treatment.
   B. **A thorough physical examination** includes performance status, complete evaluation of the skin, oral cavity, and lymph nodes, with chest, abdomen, and neurologic assessments, and a rectal examination. **Baseline measurements** of at least five indicator lesions and determination of the number of lesions per

area (i.e., left leg, torso, head and neck) are necessary for later assessment of rate of progression and response to therapy. Photographs or drawings of sites of KS involvement are often helpful for follow-up evaluations.

1. **Cutaneous manifestations.** Early stages of KS may manifest only as innocuous light pink to brown macules or papules grossly indistinguishable from other skin lesions (e.g., bacillary angiomatosis). More advanced lesions develop the characteristic red to deep purple plaques, which may coalesce and involve a significant part of the patient's trunk or extremities. These lesions tend to be painless and nonpruritic, although bleeding and superficial infection or cellulitis may occur. Visceral KS can occur without skin manifestations.
   a. **Facial KS** typically involves the nasal and periorbital area. These may be cosmetically unappealing and cause anxiety and social stigmatization.
   b. **Oral cavity KS** occurs in 30% of patients and often involves the hard and soft palates and occasionally the gums, tongue, tonsils, and pharynx. Lesions may be macular, nodular, or exophytic, causing dysphagia, odynophagia, or speech difficulties.
   c. **Genital KS** forms irregular erythematous patches on the foreskin or shaft of the penis.
   d. **Lymphedema** may occur because of dermal and lymphatic involvement of KS, resulting in a marked nonpitting, sometimes wood-like edema of the lower extremities and genitals, sometimes disproportionally more severe to the degree of KS involvement. Skin breakdown may cause weeping, ulceration, and subsequent superimposed bacterial infections.
   e. **KS of the feet** may cause pain and ambulation difficulties.
2. **Nodal KS** may present with painless lymph node enlargement caused by focal or total replacement with KS. This should be differentiated from lymphoma and mycobacterial or HIV lymphadenitis.
3. **Visceral manifestations** most often affect the lungs and GI tract.
   a. **Pulmonary KS** affects 40% of patients and usually occurs with dyspnea without fever, cough, or hemoptysis. This may be progressive, debilitating, and rapidly fatal if left untreated.
   b. **Gastrointestinal KS** occurs anywhere in the GI tract in 40% of patients at diagnosis and is generally asymptomatic, although bleeding, obstruction, or enteropathy can occur.
   c. **Other visceral organs** such as the spleen, bone marrow, liver, heart, and pericardium may be involved with KS. However, central nervous system (CNS) involvement with KS is highly unusual.

II. **Diagnosis, workup, and staging**

A. **Pathology.** The diagnosis of KS is made by biopsy and histologic examination of cutaneous lesions, enlarged lymph nodes, or visceral tissues. Proliferation of abnormal mesenchymal, spindle-shaped endothelial cells with infiltration of extravasated erythrocytes, plasma cells, or lymphocytes is seen and is histologically similar to non–AIDS-related KS.

B. **Radiology and endoscopic procedures**
   1. A baseline **chest radiograph** is done for all patients with KS to exclude pulmonary KS and other cardiopulmonary disorders associated with HIV infection. Localized or diffuse interstitial reticulonodular infiltrates with mediastinal prominence may be seen in patients with pulmonary KS, and should be differentiated from *Pneumocystis carinii* pneumonia (PCP) and other atypical pneumonias.
   2. **Bronchoscopy** may reveal endobronchial erythematous KS-like lesions even with radiologically normal studies. Because transbronchial biopsies have poor histologic yield, a presumptive diagnosis of pulmonary KS can be made based on dyspnea without fever, chest radiograph, and bronchoscopic findings after the exclusion of other disease processes.
   3. **Thallium and technetium 99m scans** may help differentiate pulmonary KS, which is avid for these radiotracers, from lymphoma or infections.
   4. **Endoscopy** may be warranted in patients with bleeding, obstruction, or enteropathy and may reveal raised erythematous submucosal lesions.

C. **Laboratory tests** should include standard blood counts, electrolytes, and liver functions, but also an assessment of the status of the patient's immune status.
   1. **A baseline complete blood count (CBC) with differentials** may reveal leukopenia, anemia, and thrombocytopenia typical in patients with advanced HIV infection. **Macrocytosis** may be related not only to HIV, but also to antiretroviral therapy (e.g., zidovudine, AZT). Anemia should suggest a **stool occult guaiac test,** which may detect bleeding from GI KS.
   2. **Lymphopenia** may reflect the degree of the patient's immunodeficiency, although **quantitative CD4/CD8 counts** accurately determine the patient's risk for opportunistic infections.
   3. **The plasma HIV RNA or HIV viral load** is not only an important prognostic factor correlating active HIV replication to tempo of disease progression and mortality risk, but also a tool to assess the efficacy of antiretroviral therapy.
   4. **A comprehensive metabolic panel** may reveal underlying renal or hepatic dysfunction and electrolyte imbalances.

D. **Staging:** The AIDS Clinical Trials Group (ACTG) developed a staging system for KS, grouping patients into good-risk or poor-risk categories based on tumor extent (T), the patient's immune status based on CD4 count (I) and presence and severity of HIV-associated systemic illnesses (S) (Table 6.1).

	Good Risk (0) All of the Following	Poor Risk (1) Any of the Following
Tumor (T)	Confined to skin and/or lymph node and/or minimal oral disease	Tumor-associated edema or ulceration; extensive oral KS; visceral KS
Immune status (I)	CD4 count $\geq 150/mm^3$	CD4 count $<150/mm^3$
Systemic illness (S)	Karnofsky status $\geq 70\%$ No B symptoms No opportunistic infection or thrush	Karnofsky status $<70\%$ B symptoms History of opportunistic infection and other HIV-related illnesses

ACTG, AIDS Clinical Trial Group; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; KS, Kaposi sarcoma

TABLE 6.1. ACTG STAGING OF AIDS-ASSOCIATED KAPOSI SARCOMA

III. **Therapy**

A. **Antiretroviral therapy** should be given to all patients with AIDS-related KS. The clinical course of KS appears to be influenced by the state of HIV control. Maximal reduction of HIV viral load with HAART not only causes regression and disappearance of cutaneous and visceral KS, but also prolongs the duration of response of lesions to anti-KS therapy (Bower J. *AIDS Res Hum Retrovir* 1999;21:A24). Because KS is not considered curable, the **goal of therapy** is palliation of KS-related symptoms, prolongation of the patient's progression-free and overall survival, and improvement in quality of life and cosmetic appearance. **Treatment options** should be individualized, based on the extent of the disease and the severity of KS-related symptoms, taking into consideration the patient's wishes.

B. **Specific therapy for Kaposi sarcoma**
   1. **Localized mucocutaneous KS** producing no symptoms does not mandate immediate aggressive anti-KS therapy. Patients with indolent lesions may benefit from participating in the many investigational therapies for KS. In patients with cosmetically disfiguring lesions, local treatments with cryotherapy and laser therapy may produce good tumor control.
      a. **Intralesional chemotherapy with vinblastine** produces a response rate of 70% (Bourdeaux. *J Am Acad Dermatol* 1993;28:61). However, response durations are short.
      b. **Topical alitretinoin** (9-*cis*-retinoic acid or Panretin) 0.1% gel, approved by the Food and Drug Administration (FDA) in 1999, inhibits KS growth by binding to retinoic acid receptors on KS cells, inducing apoptosis. A randomized, double-blinded trial of 305 patients treated with three to four applications/day of alitretinoin or vehicle gel demonstrated a 35% complete and partial response rate with alitretinoin compared with 18% with vehicle gel (Walmsley. *JAIDS* 1999;22:235). Shorter time to tumor response and longer response duration in both previously treated or untreated KS patients also were reported with topical retinoid use. Adverse drug reactions are generally mild to moderate erythema, desquamation, and skin cracking, alleviated with topical vitamin E.
      c. **Local radiation** may palliate more extensive, symptomatic lesions not amenable to topical or intralesional therapy, producing an overall response rate of more than 90% in patients with oral or cutaneous KS (*Am J Clin Oncol* 1999;22:286; Kirova. *Radiother Oncol* 1998;46:19). Pain and radiation burns are the most common side effects.
   2. **Extensive cutaneous KS with no visceral involvement**
      a. **Interferon-a** may be used in patients with extensive cutaneous KS with no visceral involvement in patients with relatively modest immunosuppression (CD4 count, more than 200 cells/µL). Subcutaneous interferon at 1 million units or 10 million units daily, with the reverse transcriptase inhibitor didanosine, produced response rates of 40% and 55%, respectively, with equal duration of response (110 weeks). Drug tolerance was poor in patients with CD counts less than 200 cells/µL (*JAIDS* 2000;23:A22).
      b. **More aggressive cytotoxic chemotherapy** may be warranted in patients with rapidly growing lesions or visceral disease.
   3. **Visceral KS** usually mandates aggressive systemic KS therapy. Cytotoxic chemotherapy can provide effective palliation, especially in patients with pulmonary KS, bulky symptomatic lesions, or significant tumor-associated edema. Agents such as vinca alkaloids, etoposide, bleomycin, and doxorubicin

are active against KS but are associated with myelosuppression (Table 6.2)

Regimen	Dosages	Reference
Doxil	20 mg/m^2 i.v. q2 wk	Northfelt. *J Clin Oncol* 1998;16:2445
Daunoxome	40 mg/m^2 i.v. q2–4 wk	Gill. *J Clin Oncol* 1996;14:2353
Paclitaxel	100 mg/m^2 i.v. over 3 h q2 wk	Gill. *J Clin Oncol* 1999;17:1876
Vincristine	2 mg i.v. q wk	
Vinorelbine	20 mg/m^2 i.v. bolus q2 wk	Nasti. *J Clin Oncol* 2000;18:1550
BV	Bleomycin 10 mg/m^2 i.v. Vincristine 2 mg i.v. q2 wk	Stewart. *J Clin Oncol* 1998;16:683
ABV	Doxorubicin 20 mg/m^2 i.v. Bleomycin 10 mg/m^2 i.v. Vincristine 1 mg i.v. q2 wk	Northfelt. *J Clin Oncol* 1998;16:2445

AIDS, acquired immunodeficiency syndrome.

TABLE 6.2. SELECTED THERAPEUTIC REGIMENS FOR AIDS-RELATED KAPOSI SARCOMA

a. **Liposomal anthracyclines including pegylated liposomal doxorubicin (Doxil) and liposomal daunorubicin (Daunoxome)** represent the standard first-line treatment for AIDS-related KS. Doxil or use liposomal doxorubicin, at 20 mg/m ^{2} every 2 to 3 weeks, has better response rates and less toxicity than bleomycin plus vincristine (BV) or a doxorubicin (Adriamycin), bleomycin, vincristine (ABV) regimen in patients with advanced KS (Stewart. *J Clin Oncol* 1998;16:683; Northfelt. *J Clin Oncol* 1998;16:2445). Patients treated with single-agent liposomal doxorubicin have similar response rates (80%) compared with Doxil plus BV, with less toxicity and a trend toward improved survival. Likewise, response rates and survival are similar for patients treated with Daunoxome alone compared with ABV (Gill. *J Clin Oncol* 1996;14:2353). The major side effect of liposomal anthracyclines is myelosuppression. The incidence of extravasation injury, mucositis, nausea, alopecia, and cardiomyopathy with liposomal anthracyclines is lower than that with nonliposomal anthracyclines.
   b. **Paclitaxel** is approved as second-line treatment of KS. Initial studies using paclitaxel at 100 mg/m ^{2} every 2 weeks or 135 mg/m^2 every 3 weeks reported response rates of 59% to 71% with a long median duration of response (more than 10 months) even in anthracycline-pretreated patients (Saville. *Lancet* 1995;346:26; Welles. *J Clin Oncol* 1998;16: 1112; Gill. *J Clin Oncol* 1999;17:1876). Myelosuppression, alopecia, neuropathy, and hypersensitivity reactions are major toxicities.
   c. **Vinorelbine** has a 43% response rate in patients with one or more prior systemic therapies for KS (Nasti. *J Clin Oncol* 2000;18:1550) but is associated with myelosuppression.

IV. **Complications**
   A. **Complications of acquired immunodeficiency syndrome–Kaposi sarcoma.** Although visceral KS, especially GI and pulmonary KS, may prove fatal, AIDS-related immunosuppression and its consequent opportunistic infections remains the major cause of morbidity and mortality in patients with KS. Superimposed bacterial, fungal, and parasitic infections in ulcerated, weeping lesions are not uncommon. Severe debilitation from pulmonary KS and hemorrhage from GI involvement of KS also may be seen.
   B. **Complications of therapy.** The use of HAART with systemic anti-KS therapy, such as paclitaxel, may potentially cause profound toxicity in some patients with AIDS–KS. Because of enhanced myelosuppression, zidovudine is generally less tolerated than other reverse transcriptase inhibitors. The metabolism of both paclitaxel and anti-HIV protease inhibitors involve cytochrome P450. Chemotherapy may decrease CD4 counts and therefore increase the possibility of opportunistic infections. However, the actual effects of chemotherapy on HIV dynamics remain unclear, as no consistent trends in plasma HIV RNA levels were noted in KS patients treated with chemotherapy.

V. **Follow-up** of patients with AIDS-related KS should be done in collaboration with an infectious disease specialist. Changes in antiviral therapy, development and treatment of other AIDS-related opportunistic infections (e.g., *Candida* sp., cytomegalovirus [CMV], PCP, or *Mycobacterium avium intracellulare* [MAI]) or syndromes (e.g., cachexia, hypogonadism) may affect the patient's tolerance of anti-KS therapy; thus an updated accurate list of current medications is important. Serial plasma HIV RNA, CD4 counts, CBC, and chemistries should be monitored closely. **Indicator lesions** should be measured, and the number of KS lesions in indicator regions (extremities/torso/head) counted. Chest radiographs also should be done at timely intervals to assess development of KS or response to therapy.

VI. **Background. Epidemic KS** is the most common malignancy associated with AIDS. Among HIV-infected persons, the risk for KS is more than 70,000-fold compared with that in non–HIV-infected controls. KS can occur throughout the course of HIV infection. Since the widespread use of HAART to treat HIV infection, the overall incidence of KS in the United States decreased dramatically (Ledergerber. *Br J Med* 1999;319:23). However, in other parts of the world with limited access to HAART, KS incidence continues to increase. The high incidence of KS in homosexual men with AIDS (10% to 13%) compared with that in other HIV-risk groups such as intravenous (i.v.) drug abusers and hemophiliacs (1% to 2%), and the parallel decline of KS and sexually transmitted diseases (STDs) in homosexual men support the theory of a sexually transmitted pathogen involved in KS development.
   A. **The role of Kaposi sarcoma herpes virus (KSHV),** also known as human herpes virus 8 (HHV8) has recently been implicated in the pathogenesis of KS (Chang. *Science* 1994;266:1965). KSHV/HHV8 is present in virtually all cases of KS, whether HIV related or non–HIV related, such as endemic, Mediterranean, or transplant-related KS (Offerman. *JAIDS* 1999;21:S58). KSHV also is implicated in other disorders such as primary effusion lymphoma (PEL) and Castleman disease. However, KSHV infection alone is not sufficient to cause KS. In approximately one third of patients co-infected with KSHV and HIV, KS develops within 10 years after HIV seroconversion (Rezza. *J Natl Cancer Inst* 1999;91:1468).

      A current model for the pathogenesis of KS proposes the creation of an inflammatory–angiogenic environment induced by KSHV and the HIV tat protein through a cascade of cytokines such as interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), basic fibroblast growth factor and g-interferon (Mesri. *Blood* 1999;93:4031). KSHV proteins identified in KS are involved in proliferation (viral IL-6, viral macrophage inhibitory protein, and viral cyclin), resistance to apoptosis (viral bcl-2 and viral FLIP), inhibition of interferon antiviral activity (viral interferon regulatory factor), cellular activation (K1), and angiogenesis (viral G protein–coupled receptor).

VII. **Current focus of research.** Based on recent knowledge of the pathogenesis of KS, potential targeted therapies for KS are in various stages of development.
   A. Angiogenesis inhibitors such as the fumagillin analogue TNP-470, SU5416 (a VEGF-receptor inhibitor), aflavoperidol EMD 121974, and IL-12 have shown some activity in phase I and II trials. Thalidomide caused KS regression in 40% of patients at doses up to 1,000 mg/day for as long as 12 months (Little. *J Clin Oncol* 2000;18:2593). The matrix metalloproteinase inhibitor, COL-3, when administered orally, also showed encouraging responses (44% RR) (Cianfrocca. *J Clin Oncol* 2002;20:153). Nasal IM862, a synthetic antiangiogenic dipeptide, produced a 36% response rate with minimal side effects in KS (Tulpule. *J Clin Oncol* 2000;18:716).
   B. The cellular differentiating compound alitretinoin given orally, can produce responses in 37% to 46% of KS patients but may be associated with headache, skin cracking, erythema or desquamation, hypertriglyceridemia, and subclinical pancreatitis.
   C. Anti-KSHV therapy with cidofovir or foscarnet and inhibition of cytokines responsible for KS growth are being investigated. Time to KS progression was prolonged in patients treated with foscarnet compared with that in patients given ganciclovir (211 days vs. 22 days) in a retrospective study (Robles. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999;20:34).
   D. Preclinical data on FAS ligand gene therapy with an adenoviral vector, triggering apoptosis in KS cells, is intriguing because antiapoptotic proteins are expressed in advanced KS lesions (Simon. *JAIDS* 2000;23:A22; Sturzel. *J Natl Cancer Inst* 1999;91:1725).

ACQUIRED IMMUNODEFICIENCY SYNDROME–ASSOCIATED NON-HODGKIN LYMPHOMA

Generally, AIDS-associated NHL is more aggressive and occurs at more advanced stages with more frequent extranodal sites than does NHL in immunocompetent patients. AIDS-NHL displays marked clinicopathologic heterogeneity and may be grouped into three general categories: systemic lymphomas, PELs, and primary CNS lymphoma.

I. **Clinical presentation.** Pertinent **history** should also include performance status, duration of HIV infection, history and treatment of opportunistic infections, and current antiviral therapy.
   A. **B-symptoms,** such as fever, night sweats, and weight loss in excess of 10% of the normal body weight are very common and should be attributed to AIDS-associated NHL only after the exclusion of opportunistic infections. Extreme fatigue from anemia caused by bone marrow involvement may be seen.
   B. **Lymph node enlargement** may be asymptomatic or associated with pain or obstructive symptoms. This should be differentiated from persistent generalized lymphadenopathy (PGL) or other AIDS-related illnesses. More than two thirds of patients will have extranodal presentations.
   C. **GI involvement** causing anorexia, nausea, vomiting, GI bleeding, change in bowel habits, or obstruction occur in 10% to 25% of patients. Jaundice and abdominal discomfort may be due to lymphomatous liver involvement.

D. **CNS or meningeal involvement** resulting in seizures, altered mental status, and neurologic deficits occurs in 10% to 20%.
E. **Pleural or pericardial effusions** may cause dyspnea and chest discomfort, especially in patients with PEL.
F. **The physical examination** should include careful examination and measurements of enlarged lymph nodes, spleen, and liver. Pulmonary and cardiac examinations may reveal pleural or pericardial effusion. A thorough neurologic examination also should be done to determine the presence of meningismus or focal neurologic deficits.

II. **Diagnosis, workup, and staging**

A. **Pathology.** Definite diagnosis of AIDS-related NHL is made with positive identification of lymphoma in lymph node biopsies or other tissues (bone marrow, cerebrospinal fluid [CSF], pleural effusion, liver, etc.) with a positive HIV enzyme-linked immunosorbent assay (ELISA) test confirmed with Western blot analysis or plasma HIV RNA. More than 95% of AIDS-related NHLs have a B-cell phenotype and represent a heterogeneous group of aggressive and high-grade lymphomas. One to two thirds of patients with AIDS-NHL have diffuse large-cell lymphoma (AIDS-DLCL) or small noncleaved cell Burkitt lymphoma (AIDS-BL), although immunoblastic or anaplastic types can occur.

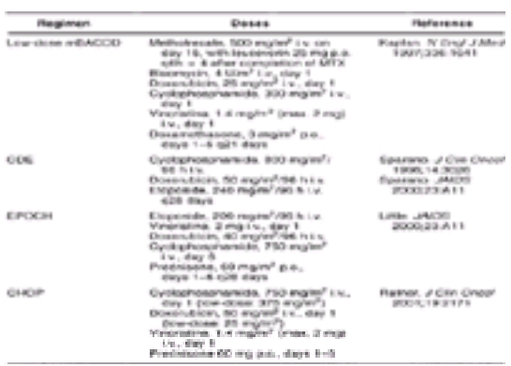
B. **Radiology/Procedures**

1. **Computed tomography (CT) scan** of the chest, abdomen and pelvis with CT or magnetic resonance imaging (MRI) scan of the brain is necessary for the staging of AIDS-related NHL. Special note should be given to the retroperitoneal and mesenteric adenopathy, sites not usually affected in PGL. Hepatic, splenic, and pulmonary lesions may be seen.
2. **Bone marrow aspiration and biopsies** reveal bone marrow involvement in approximately 20% of patients, associated with increased risk for CSF involvement of AIDS-NHL.
3. **A diagnostic lumbar puncture** should be performed and CSF sent for cytologic examination. Cell count and protein may be normal or elevated, whereas glucose may be low. Analysis of CSF for Epstein–Barr virus (EBV) DNA by polymerase chain reaction (PCR) may predict lymphomatous meningitis.
4. **Diagnostic thoracentesis or pericardiocentesis** may be required to diagnose patients with PEL because this diagnosis is usually not associated with any identifiable mass.
5. **Nuclear medicine scans.** Gallium scanning may be a useful means of differentiating lymphoma from reactive lymphadenopathy and can be used after therapy to detect persistent disease (gallium avid) or fibrosis (gallium negative). Positron emission tomography with fluorodeoxyglucose (FDG-PET) scan also may be used to detect residual disease after therapy.

C. **Laboratory tests.** CBCs may reveal anemia, leukopenia, or thrombocytopenia, even with no marrow involvement by AIDS-NHL. Serum chemistries may show abnormalities in liver-function tests, elevated lactate dehydrogenase (LDH) and calcium or uric acid. Electrolytes and creatinine also should be checked and monitored during therapy. Plasma HIV RNA and CD4 counts are done to assess the patient's immune status.

D. **The Ann Arbor Staging** for NHL also is used in AIDS-related NHL (see Chapter 15). Prognostic factors correlating with poor survival in patients with AIDS-related NHL include stage IV disease, Karnofsky performance status less than 70%, CD4 count of less than 100/mm ^{3}, elevated LDH, and history of opportunistic infections before lymphoma diagnosis.

III. **Therapy.** A large majority of patients with AIDS-related NHL will have widespread disease on presentation and should be treated aggressively even if dissemination is not confirmed initially. Combination chemotherapy in AIDS-associated NHL has yielded poor response rates and markedly inferior survival rates compared with those in non–AIDS-related NHL (Table 6.3).



Regimen	Doses	Reference
Low-dose mBACOD	Methotrexate, 500 mg/m² i.v. on day 15, with leucovorin 25 mg p.o. q6h × 6 after completion of MTX Bleomycin, 4 U/m² i.v., day 1 Doxorubicin, 25 mg/m² i.v., day 1 Cyclophosphamide, 300 mg/m² i.v., day 1 Vincristine, 1.4 mg/m² (max. 2 mg) i.v., day 1 Dexamethasone, 3 mg/m² p.o., days 1–5 q21 days	Kaplan. *N Engl J Med* 1997;336:1641
CDE	Cyclophosphamide, 800 mg/m²/96 h i.v. Doxorubicin, 50 mg/m²/96 h i.v. Etoposide, 240 mg/m²/96 h i.v. q28 days	Sparano. *J Clin Oncol* 1998;14:3020 Sparano. *JAIDS* 2000;23:A11
EPOCH	Etoposide, 200 mg/m²/96 h i.v. Vincristine, 2 mg i.v., day 1 Doxorubicin, 40 mg/m²/96 h i.v. Cyclophosphamide, 750 mg/m² i.v., day 5 Prednisone, 60 mg/m² p.o., days 1–5 q28 days	Little. *JAIDS* 2000;23:A11
CHOP	Cyclophosphamide, 750 mg/m² i.v., day 1 (low-dose: 375 mg/m²) Doxorubicin, 50 mg/m² i.v., day 1 (low-dose: 25 mg/m²) Vincristine, 1.4 mg/m² (max. 2 mg) i.v., day 1 Prednisone 60 mg p.o., days 1–5	Ratner. *J Clin Oncol* 2001;19:2171

TABLE 6.3. REGIMENS USED IN AIDS-NHL

A. **Chemotherapy without HAART.** Before the widespread use of HAART, standard-dose chemotherapy with combination chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) achieved complete response (CR) rates in 36% to 56% but median survival of only 4 to 7 months. Patients tolerated chemotherapy poorly, and an increased incidence of opportunistic infections was seen secondary to exacerbation of the patient's immunodeficient state. Thus lower-dose regimens were tested.

A randomized trial comparing low-dose and standard-dose **mBACOD** did not show any statistically significant difference in CR rates (41% vs. 52%), median survival (35 weeks vs. 31 weeks), 1- and 2-year survival rates (27%, 11% vs. 24%, 7%) (Kaplan. *N Engl J Med* 1997;336:1641). Long-term survival can be achieved in patients with no more than one of the following poor prognostic factors: age older than 35 years, intravenous drug user (IVDU), stage III to IV, and CD4 counts of less than 100/µL (Straus. *J Clin Oncol* 1998;16:3601). Currently this regimen is considered by many to be the standard initial treatment of AIDS-NHL.

B. **Chemotherapy with HAART.** The AIDS Malignancy Consortium Study administered six to eight cycles of low-dose or standard-dose **CHOP** in combination with HAART in patients with AIDS-NHL (Ratner. *J Clin Oncol* 2001;19:2171). Both regimens resulted in CR rates similar to those reported with CHOP without HAART (30% to 48%). The protracted schedule of **CDE** (cyclophosphamide, 200 mg/m^2/day; doxorubicin, 12.5 mg/m^2/day; and etoposide, 60 mg/m^2/day), given as a 96-hour infusion with HAART, produced a CR rate of 42% with an 18-month median survival and a 55% 1-year survival. Before routine antiviral use, CDE produced a median survival of only 8.2 months (Sparano. *JAIDS* 2000;23:A11). Patients treated with dose-adjusted **EPOCH** (etoposide, vincristine, doxorubicin, cyclophosphamide, and cytarabine) chemotherapy with suspension of antiviral treatment demonstrated a 77% CR rate with 80% progression-free and 73% overall survival after 29 months (Little. *JAIDS* 2000;23:A11).

C. **Relapsed or refractory AIDS-NHL** has an extremely poor outcome. For cytarabine (Ara-C) and platinum-based therapies, **ESHAP** (etoposide, methylprednisolone, cisplatin, and high dose cytarabine) had a higher overall and CR rate compared with DHAP (dexamethasone, cisplatin, and high dose cytarabine) (62% vs. 8% and 31% vs. 0%, respectively) with a 12-month median survival (Levine. *JAIDS* 2000;23:A24). A response rate of 26% was reported in patients with refractory/resistant NHL with etoposide, mitoxantrone, and prednimustine, but median survival was dismal at 2 months (Tirelli. *Cancer* 1996;77:2127). Mitoguazone, although well tolerated, produced only a 23% response rate.

D. **CNS prophylaxis** with 4 weekly treatments of either intrathecal cytarabine (50 mg) or methotrexate (10 to 12 mg) reduces the risk for CNS relapse. Lymphomatous meningitis should be treated with weekly intrathecal chemotherapy or via an Ommaya reservoir until the CSF is clear of malignant cells, and then on a more protracted schedule.

E. **Radiotherapy** may be given as palliation to bulky, rapidly enlarging, organ-compressing, or CNS lesions or as consolidation to patients with localized lymphoma after chemotherapy.

IV. **Complications**

A. **Complications of the disease.** Rapidly enlarging tumors may compromise airways and other vital organs. Significant hepatic dysfunction, hypercalcemia, and CNS relapse may occur. Opportunistic infections and other AIDS-related illnesses are causes for morbidity and mortality in patients with AIDS-NHL; thus PCP and mycobacterial prophylaxis should be continued during active lymphoma therapy if indicated.

B. **Complications of therapy**

1. Lymphocytotoxic chemotherapy may cause depletion of CD4 and total lymphocyte counts, increasing the risk of severe myelosuppression and infections. Potential interactions with chemotherapy and HAART may produce substantial and unexpected toxicities that may require dose delay or reduction, possibly compromising optimal antilymphoma therapy.
2. **Tumor lysis syndrome** may occur with chemotherapy. Aggressive hydration, allopurinol, and alkalinization of urine should be instituted during therapy, and electrolytes and renal functions monitored carefully.
3. Intrathecal therapy may be associated with arachnoiditis, intraventricular bleeding, or infection.
4. Severe hyperglycemia also can occur with protease inhibitors and prednisone.

V. **Follow-up.** The optimal care of a patient with AIDS-NHL should be done in collaboration with an infectious disease specialist. During active treatment, CBC, chemistries, plasma HIV RNA, CD4 counts, and tumor measurements are important. Restaging with radiologic scans and bone marrow biopsies should be done after completion of chemotherapy and periodically afterward. Patients with CSF positive for lymphoma should have CSF cytology, Gram stains and culture, and

cell counts done before each treatment to assess disappearance or persistence of CNS lymphoma and to modify frequency of treatments.

VI. **Background. NHL** is the second most common malignancy associated with AIDS. The risk for developing NHL in persons with HIV infection is 165- to 200-fold greater compared with that of the general population. Despite the advent of HAART, the incidence of AIDS-NHL continues to increase. Lymphomagenesis in an HIV-infected patient is complex and involves immunosuppression, HIV-related cytokine upregulation, B-cell hyperstimulation, and finally, expansion of the AIDS-NHL malignant clone. Approximately 40% of AIDS-DLCL, 90% of immunoblastic lymphomas, and 30% of AIDS-BL are associated with **EBV.** AIDS-BL also is associated with the protooncogene **c-*myc*** activation and tumor-suppressor gene **p53** disruption. Deregulation of **BCL-6,** essential for germinal center formation, occurs in 100% of AIDS-BL and in approximately 50% of AIDS-DLCL. **PEL** occurs in 5% of HIV-infected individuals, and all cases are associated with KSHV and, frequently, co-infection with EBV.

VII. **Current focus of research.** Monoclonal antibody therapy using the anti-CD20 rituximab in combination with chemotherapy (CHOP or CDE) is being studied in the treatment of AIDS-related NHL. High-dose chemotherapy with **stem cell transplantation** for AIDS-related NHL also has been reported and awaits further evaluation (Zaia. *JAIDS* 2000;23:A12; Krishnan. *JAIDS* 2000;23:A29). Approaches targeting EBV or herpesvirus infection by using adoptive T-cell immunotherapy and possibly vaccine therapy are actively being investigated.

ACQUIRED IMMUNODEFICIENCY SYNDROME–ASSOCIATED PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

I. **Clinical presentation** of AIDS–primary central nervous system lymphoma (PCNSL) is usually related to the site and extent of its CNS involvement. Seizures, paresis, slurred speech, or focal neurologic deficits as well as nonspecific symptoms such as headaches, memory loss, lethargy, malaise, confusion, or dementia must be differentiated from CNS toxoplasmosis, HIV encephalopathy, progressive multifocal leukoencephalopathy, and other viral, fungal, or mycobacterial etiologies.

II. **Diagnosis, workup, and staging: pathology.** Although a brain biopsy is the gold standard for diagnosis, tumor location and other factors may preclude this invasive procedure. CT-guided stereotactic brain biopsies can produce high diagnostic rates with acceptable morbidity comparable to traditional open-brain biopsy. Histology reveals a B-cell lymphoma, usually large-cell or immunoblastic subtypes.

   A. **Radiology/Procedures**
      1. **CT or MRI** scan of the head may reveal single or multiple ring- or contrast-enhancing lesions located in the cerebral hemispheres, cerebellum, basal ganglia, brainstem, or periventricular structures. However, it may be difficult to distinguish lymphoma from cerebral toxoplasmosis, the most common cause of discrete CNS lesions in an HIV patient.
      2. PET scans may differentiate the highly metabolic lymphoma lesions from the hypometabolic CNS toxoplasmosis (Pierce. *Ann Intern Med* 1995; 123:594).
      3. **Thallium-201 SPECT** combined with CSF PCR analysis for EBV DNA also has been shown to be highly sensitive and specific diagnostic tool for PCNSL (Antinori. *J Clin Oncol* 1999;17:554). These should be performed after identification of a CNS mass in an AIDS patient.
      4. **Fundoscopy with slit-lamp evaluation** may detect ocular involvement of lymphoma.
   B. **Laboratory tests.** CSF analysis may reveal elevated proteins, low glucose, and mononuclear pleocytosis, but cytology may be unrevealing (positive only in 20% to 25%). Plasma HIV RNA and CD4 counts are done to assess the level of viral activity and degree of immunosuppression.

III. **Therapy.** The clinical outcome for patients with HIV-associated CNS lymphomas depends on early diagnosis and institution of treatment. The choice of therapy depends on the patient's general condition.

   A. **Cranial irradiation** alone resulted in a 53% rate of tumor regression and slightly improved survival compared with those in untreated patients in a large retrospective study (Corn. *Int J Radiat Oncol Biol Phys* 1997;38:601). Because of the multifocal nature of AIDS-PCNSL, radiation should be directed to the whole brain and meningeal fields to the level of the second cervical vertebra without spinal irradiation.
   B. **Steroids** have been used to limit edema, but the impact on survival is unclear.
   C. **Combined chemotherapy with radiation** may benefit a subset of patients with AIDS-PCNSL with CD4 counts of at least 200/mm^3, good performance status, no significant comorbid medical condition, and lymphoma confined to the brain. Systemic and intrathecal methotrexate, thiotepa, and procarbazine followed by radiation resulted in six complete remissions in 10 patients, with some patients surviving for 1 year or more (Forsyth. *Neurology* 1994;22:1473).
   D. **High-dose methotrexate** at 3 g/m^2 every 14 days with leucovorin rescue and no radiation resulted in complete responses in seven of 15 patients with a median survival of 290 days and significant improvements in quality of life (Jacomet. *AIDS* 1997;11:1725).
   E. **HAART** therapy also has been reported to cause prolonged remissions in AIDS-PCNSL (McGowan. *AIDS* 1998;12:952). Zidovudine, ganciclovir, and IL-2 treatment resulted in complete responses in three of seven AIDS-PCNSL patients (Raez. *J AIDS* 1999;21:A31).

IV. **Complications of disease**

   A. **Ocular lymphoma** may involve the vitreous, uvea, or retina and is usually bilateral. Bilateral ocular irradiation or high-dose cytarabine or methotrexate, which penetrates the vitreous, may be given.
   B. **Leptomeningeal lymphoma** can be treated with intrathecal methotrexate or cytarabine via Ommaya reservoir.
   C. **Spinal cord involvement** is rare.

V. **Background**

AIDS-PCNSL occurs in 2% to 11% of HIV-infected patients, representing a 3,600-fold higher incidence of this disease as compared with that in the general population. It is associated with severe myelosuppression with CD4 counts often less than 50/mm^3 and a median survival of only 1 to 3 months. It is the most common noninfectious CNS lesions in patients with AIDS.

EBV is identified in 100% of AIDS-related PCNSL. Latently infected B cells proliferate and develop into malignant clones in the relatively immunoprivileged CNS secondary to decreased immunosurveillance resulting from HIV-related T-cell depletion. C- *myc* rearrangements and bcl-2 expression also have been found.

OTHER ACQUIRED IMMUNODEFICIENCY SYNDROME–ASSOCIATED MALIGNANCIES

I. **AIDS-related Hodgkin disease (AIDS-HD).** Although not considered an AIDS-defining illness, HD risk for HIV-infected individuals is increased to eightfold that of the general population. The **mixed cellularity** subtype is the most frequent pathology in AIDS-HD. Latent membrane protein (LMP-1) is expressed in virtually all cases of AIDS-HD suggest the etiologic role of EBV in the development of AIDS-HD. AIDS-related HD is clinically more aggressive and less responsive to therapy than non–AIDS-related HD. Similar to AIDS-NHL, AIDS-HD usually is seen with widespread extranodal disease causing B symptoms in 70% to 96% of patients.

Optimal therapy for AIDS-HD is not known. Anthracycline-based therapy such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) with granulocyte–colony-stimulating factor (G-CSF) resulted in a 43% CR rate and 18-month median survival (Levine. *AIDS* 1997;14:A12). EBVP (epirubicin, vinblastine, bleomycin, and prednisone) with concomitant G-CSF resulted in 74% CR rates, but 3-year survival was only 32% (Errante. *Ann Oncol* 1999;10:189). Treatment with the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone) and concomitant HAART appears feasible in AIDS-HD and awaits confirmatory results.

II. **Epithelioid cancers of the cervix and anus** also are increased in AIDS patients by virtue of the increased prevalence of the oncogenic human papilloma virus (HPV) infection among high-risk groups. HIV may alter the natural history of HPV-associated cancers, but treatment is similar to that for epithelioid cancers in non–HIV-infected patients.

III. **Other cancers.** Multiple myeloma risk also is elevated by 4.5-fold in HIV-positive patients. The risk for testicular cancer is approximately threefold, whereas children with AIDS have an extraordinary risk for leiomyoma and leiomyosarcoma (10,000-fold) compared with the general population. Incidences of other cancers such as cancer of the lip, squamous cancer of the conjunctiva, and brain tumors also have increased in AIDS patients.

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CHAPTER 7. BREAST CANCER

Marcia L. Chantler and Mohammad Jahanzeb

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I. Presentation

A woman with a new breast mass should have a complete history and physical examination. The differential diagnosis of a breast mass can be broad, including malignancies such as primary breast cancer, lymphoma, or sarcoma, or benign breast lesions such as cysts, fibroadenoma, and fat necrosis. Even skin conditions, such as sebaceous cysts, abscesses, or thrombophlebitis may occur with a palpable mass. The history and physical will help aid in the diagnosis, but ultimately a biopsy is confirmatory of the diagnosis.

A. History

A clinician can categorize the risk of a primary breast cancer based on the patient's age, presenting symptoms, history of breast pathology, and family history. A new breast mass in a woman older than 50 years should be considered malignant until proven otherwise, whereas in women younger than 35 years, cancer is possible but uncommon. Breast symptoms, including duration, tenderness, pain, relation to menstrual cycle, and nipple discharge should be elicited from the patient. Nipple discharge is a common complaint from women. There is increased concern of malignancy if the discharge is unilateral, spontaneous, or bloody, especially in a postmenopausal woman. The most common source of nipple discharge is an intraductal papilloma, which is a benign lesion.

A negative family history is not exclusive, given that most women in whom breast cancer develops do not have a family history of the disease. A personal history of prior malignancies such as breast or ovarian places a woman at greater risk for breast cancer through the association with the BRCA1 gene. See Table 7.1 for other associated risk factors to ask about in the medical history.

Family History	Relative Risk
First-degree relative, premenopausal	2–3
First-degree relative, postmenopausal	1.5–2.5
First-degree premenopausal relative with bilateral cancers	5.5
First-degree postmenopausal relative with bilateral cancers	4
Mother and sister	5–6
Second-degree relative	1–1.5
History of breast disease	
Nonproliferative	1
Proliferative disease without atypia	1.5–1.9
Atypical hyperplasia	4–5
Atypical hyperplasia and a first-degree relative	9–11
LCIS	7–10
Prior breast cancer	4
Hormonal factors	
Early menarche (<12 yr old)	1.3
Late menopause (>55 yr old)	1.5
Late parity (>30 yr old)	1.9
Current oral contraceptive use (OCP)	1.24
OCP previous 1–4 yr	1.15
OCP previous 5–9 yr	1.07
Estrogen replacement therapy	1.02–1.55

LCIS, lobular carcinoma in situ; OCP, oral contraceptive.

TABLE 7.1. ESTIMATED RELATIVE RISKS OF DEVELOPING BREAST CANCER ASSOCIATED WITH VARIOUS RISK FACTORS

B. Physical examination

The normal adult breast often has an uneven texture and feels nodular or lumpy. This is termed physiologic nodularity. It is often bilateral and may be evident throughout the entire breast or only in parts of it. Nodularity may increase premenstrually and during pregnancy.

The physical characteristics of a breast mass can be helpful in determining a diagnosis. A thorough breast examination should begin with the patient disrobed to the waist and sitting in the upright position. A careful inspection for skin changes, symmetry, contours, and retraction in four views; arms at sides, arms over head, arms pressed against hips, and leaning forward is first done. Changes in the appearance of the skin including color, thickening or *peau d'orange* appearance, or changes in breast contour such as masses, dimpling, or flattening suggest an underlying cancer. Inspection of the nipple for rashes, ulceration, and discharge also can help identify an underlying cancer or Paget disease of the breast. A thickened or broadened, retracted nipple also may indicate an underlying cancer.

For palpation of the patient's breast, the patient should be supine with her arms raised above head. With your fingers flattened, press down on the breast in a circular motion against the chest wall. Proceed in a uniform manner to examine the entire breast including the periphery, tail, and areola. By using a pattern such as concentric circles or a clock face, palpate the entire breast from clavicle to inframammary fold, midsternum to posterior axillary line and into the axilla for the tail of the breast, checking carefully for consistency of the tissues, tenderness, and nodules. Note the characteristics of any nodules including location, size, shape, consistency, demarcation, tenderness, and mobility. Palpation of the male breast may identify a firm disc of glandular enlargement, called gynecomastia.

The axilla should be examined with the patient in a sitting position. Press your fingers in toward the chest wall, trying to feel the central nodes. To locate pectoral nodes, grasp the anterior axillary fold and palpate inside the border of the pectoralis muscle. The lateral nodes are high in the axilla and are

palpated along the upper humerus. To identify subscapular nodes, palpate along the muscle in the posterior axillary fold. A complete examination for lymphadenopathy includes evaluation for supra- and infraclavicular lymph nodes as well.

Compressing the areola can elucidate spontaneous nipple discharge. Note the color, consistency, and quantity of any discharge. A nonmilky unilateral nipple discharge suggests underlying breast pathology and should be evaluated further.

II. Workup and staging of breast cancer

A. Evaluation of a breast mass

Physical characteristics of a palpable breast mass may be helpful in determining a diagnosis; however, a diagnosis should not be made exclusively based on physical examination. A biopsy ultimately provides the definitive pathologic diagnosis.

Ultrasonography can be useful to determine if a lesion is cystic or solid. A cystic mass may feel ballotable or tense with fluid. Aspiration of a simple cyst should reveal nonbloody fluid and result in complete resolution of the lesion. A biopsy is indicated if the fluid aspirated is bloody, the lesion does not resolve completely after aspiration, or the cyst recurs after repeated aspirations. Cytologic examination of the nipple discharge may reveal malignant cells, but the absence of malignant cells does not rule out a malignant lesion. Cytologic examination of the fluid is not routinely indicated, as the yield for positive cytology is low.

A solid mass is typically evaluated with diagnostic mammography. Mammography allows the physician to assess the radiologic characteristics of the mass and the remainder of breast tissue in the ipsilateral and contralateral breast. Ductal carcinoma *in situ* (DCIS) is often an incidental finding on mammography. DCIS does not occur as a palpable breast mass, but rather as the presence of clustered microcalcifications seen on mammography. The presence of clustered microcalcifications can alter further diagnostic and therapeutic interventions.

If a suggestive mass is identified, a biopsy can be obtained by using several different methods. Fine-needle aspiration (FNA) is a simple method for obtaining material for cytologic examination and can be performed in the clinician's office. False-negative rates for FNA can be as high as 9% even among the most experienced technicians (*Cancer* 1979;44:1458). If a negative result is obtained from FNA, a core (needle) or excisional biopsy should be done to obtain appropriate tissue for pathologic review. The majority of these biopsies also can be performed in the outpatient setting.

New techniques have been developed for nonpalpable breast masses identified only on mammography including needle localization and stereotactic core biopsies. Needle localization uses a hook-wire placed at the site of the lesion with the aid of mammographic views to guide the surgeon to the location accurately. The surgeon then removes the designated tissue surrounding the hook-wire. After the target lesion is excised, the specimen is subjected to mammography to ensure that the lesion was successfully removed.

Stereotactic-guided core biopsy is a new technique that uses a specialized mammographic machine and stereotactic table to localize the lesion accurately in three dimensions. The majority of nonpalpable mammographic lesions are candidates for stereotactic core biopsy, with the exception of lesions near the chest wall or behind the nipple, because of technical limitations of the stereotactic table. The sensitivity of the procedure varies with the type of lesion targeted and ranged from 71% to 100% (*Ann Surg Oncol* 1995;2:195). Nonpalpable masses also can be percutaneously sampled by using ultrasound guidance. The advantages to a percutaneous core biopsy include less pain, less scarring, and a lower cost compared with open surgical biopsies. Currently the roles of magnetic resonance imaging (MRI) and other imaging modalities are being investigated for their use in the evaluation of a breast mass and are not routinely recommended outside the setting of a clinical trial.

A core biopsy that confirms a benign lesion does not need further evaluation. If the biopsy reveals only normal breast tissue, further surgical biopsy is recommended if the lesion is suggestive of cancer. For less suggestive lesions and a normal biopsy, a 6-month follow-up mammogram is recommended.

Hormonal receptors (both estrogen and progesterone receptors) should be assessed on all patients with breast cancer. Thirty-three percent of all premenopausal and 67% of all postmenopausal breast cancers are estrogen receptor (ER) positive. Patients with tumors that express either ER or progesterone receptor (PR) have an improved prognosis and are more likely to benefit from hormonal therapy.

One of the most exciting areas of investigation in breast cancer is the HER2/neu-receptor protein. The HER2/neu protein is a transmembrane tyrosine kinase receptor. The overexpression of the HER2/neu-receptor protein occurs in approximately 25% of invasive breast cancers and is associated with ER-negative disease, high-grade histology, and is an overall poor prognostic factor. All breast cancers should be tested for HER2/neu overexpression (*Science* 1989;8:2127). Immunohistochemical (IHC) testing is commonly used to identify HER2/neu overexpression, but there is little standardization of reporting HER2/neu expression on breast cancer cells. IHC staining is reported as 0, 1+, 2+, or 3+ overexpression. Fluorescent *in situ* hybridization (FISH) can be used to measure HER2/neu gene amplification to confirm overexpression in patients with weakly positive IHC staining. Future prognostic factors may include measurement of other biologic markers such as S-phase fraction, DNA content (aneuploidy), cathepsin D protein, or epidermal growth factor receptor (EGFR) overexpression, which are all currently under clinical investigation.

B. Staging of breast cancer

The American Joint Committee on Cancer (AJCC) staging system provides a strategy for grouping patients with similar presence of disease and with respect to prognosis. The most important prognostic factor in women with breast cancer is axillary nodal status, followed by hormonal receptor status. As with other cancers, the AJCC has designated staging by TNM classification, based on tumor size, the status of regional lymph nodes, and the presence of distant metastases (Beahrs O, Henson D, Hutter R, et al., eds. *Manual for staging of cancer*. Philadelphia: JB Lippincott, 1992:149) (Table 7.2).

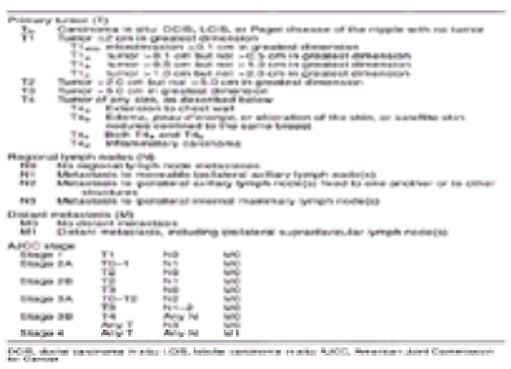

TABLE 7.2. TNM STAGING SYSTEM FOR BREAST CANCER

Therapeutic decisions are formulated according to staging categories. Radiology studies can be useful to complete the clinical staging for breast cancer. A chest radiograph can detect spread of breast cancer to the lungs. A bone scan can identify metastatic and pelvis disease to the bone. Computed tomography (CT) of the chest and abdomen can identify cancer that may have metastasized to other organs, including the liver and lymph nodes.

Laboratory tests do not aid directly in the clinical staging of breast cancer, but can allow the clinician to focus on possible metastatic sites of disease. A complete blood count (CBC) can detect abnormalities in blood cell lines that may suggest bone marrow infiltration. The spread of breast cancer to the liver or bones may cause abnormalities in blood chemistries, such as calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase. Abnormal blood tests give the physician an objective marker with which to assess clinical response after therapy in patients without identifiable measurable disease.

The levels of tumor markers CA 15-3, CA27-29, and carcinoembryonic antigen (CEA) can be elevated in breast cancer. CA 15-3 and CA 27-29 measure the

serum level of mucin-like glycoproteins, which are shed from tumor cells into the bloodstream. CEA is a cell-surface glycoprotein with increased expression found in a variety of malignancies, including breast cancer. Tumor markers have been evaluated for the ability to determine diagnosis, monitor therapy, and predict recurrence of breast cancer after curative surgery and radiotherapy. Low detection rates in early-stage disease indicates that tumor markers cannot be used to screen or diagnose patients with breast cancer (*J Clin Onco*l 1986;4:1542). However, in patients with metastatic disease and no other means of monitoring the disease, elevated tumor markers can assist in the monitoring of response to therapy through a subsequent increase or decrease in serum levels. Supporting clinical evidence should be used in conjunction with a increasing marker before modifying therapy.

III. **Therapy and prognosis**

A. **Ductal carcinoma *in situ***

DCIS (also known as intraductal carcinoma) is the noninvasive form of breast cancer. DCIS is being encountered more frequently with the increased use of screening mammography. These lesions are most often identified on mammography as clustered microcalcifications with or without a palpable mass. The traditional system for classifying DCIS was based primarily on architectural pattern and recognized five major subtypes: comedo, cribriform, micropapillary, papillary, and solid. DCIS is commonly subdivided into the comedo type and the noncomedo type (*Lancet* 1995;345:1154). This is based on the observations that the comedo type usually appears more malignant cytologically and is more often associated with invasion than are the other DCIS types.

A variety of local treatments have been proposed for DCIS, ranging from local excision to total mastectomy. A total mastectomy is a curative treatment for approximately 98% to 99% of patients with DCIS, but is a radical approach to a lesion that may not progress to invasive cancer during a patient's lifetime. Many patients may be candidates for breast-conserving therapy (BCT) and irradiation. However, treatment of DCIS with BCT and irradiation has never been directly compared with mastectomy. Available data on BCT with radiation show recurrence rates of 10% to 15% at 10 years, with approximately half of these recurrences being invasive carcinoma (*N Engl J Med* 1993;328:1581).

Whether radiation therapy (RT) is necessary for all patients treated with BCT remains uncertain. Retrospective data indicate that highly selected patients, with small, low-grade (no or slight comedo necrosis), with wide negative margins, have a low local recurrence rate after excision alone. In a large National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 study, women with localized DCIS and negative margins after excisional biopsy were randomized to breast irradiation (50 Gy) or to no further therapy. The event-free survival at 8 years for the irradiated patients was 75% compared with 62% for patients with lumpectomy alone. The occurrence of invasive cancer decreased from 13.4% to 3.9% with the additional of radiation (*Cancer* 1995;75:1310). Based on this clinical trial, lumpectomy with breast irradiation is an acceptable therapy for localized DCIS. Lumpectomy without radiation is controversial and is currently not recommended by breast cancer specialists. Axillary lymph node involvement is a rare event. A National Cancer Data Base review of more than 10,000 patients with DCIS who had an axillary lymph node dissection (ALND) demonstrated that only 3.6% of this group had axillary nodal metastases (*JAMA* 1978;239:1863); thus lymph node dissection is not routinely recommended.

In patients with a history of DCIS, after surgical management, tamoxifen has been shown to reduce the recurrence risk of both invasive tumors and DCIS. In an NSABP prospective trial randomly assigning women to lumpectomy and radiation followed by either placebo or tamoxifen (20 mg daily for 5 years), women in the tamoxifen group had fewer breast cancer events than did those taking placebo. The overall risk of an ipsilateral recurrence of any type (invasive or noninvasive) or a new contralateral breast cancer was reduced from 13% to 8.8% at 5 years (*J Natl Cancer Inst* 1998;90:1371). The benefits of tamoxifen therapy must be weighed against the potential risks of treatment.

B. **Lobular carcinoma *in situ***

Lobular carcinoma *in situ* (LCIS) is not detected on physical examination and is always an incidental finding on breast biopsies performed for another reason. From 80% to 90% of the cases of LCIS occur in premenopausal women and is more common in white than in African American women in the United States (Harris J, et al., eds. *Diseases of the breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:377). In contrast with DCIS, the histologic features of LCIS are homogeneous and easily recognized. The major issue in the management of LCIS is the risk for invasive carcinoma after diagnosis of LCIS.

LCIS is a misleading term. LCIS is not a premalignant lesion, but rather is a marker that identifies women at increased risk for subsequent development of an invasive breast cancer in either breast. The risk of developing invasive breast cancer is 8 to 11 times that of the general population at an approximate rate of 1% per year (Harris J, et al., eds. *Diseases of the breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:377). The majority of subsequent cancers are infiltrating ductal rather than lobular carcinomas. The risk of subsequent invasive cancer in a patient with LCIS is equal in both breasts. LCIS can be managed by observation alone after biopsy. Given that LCIS is known to be a multifocal lesion, there is no evidence that reexcision to obtain histologically negative surgical margins is required.

The NSABP tamoxifen prevention trial showed that the use of tamoxifen (20 mg daily for 5 years) is associated with a decrease in the risk of developing breast cancer by 56% in women with LCIS (*J Natl Cancer Inst* 1998;90:1371). The increased risk of breast cancer persists beyond 20 years, so careful observation and mammography should be performed indefinitely in these women. Radiation therapy has no role in the management of LCIS. Bilateral prophylactic mastectomies is an alternate option for women who are unwilling to accept the increase risk of bilateral breast cancers.

C. **The treatment of early-stage breast cancer (stages I, II, and IIIA)**

The treatment of stages I, II, and IIIA breast cancer uses a multidisciplinary approach, including surgery, adjuvant hormonal or chemotherapy, and radiation therapy.

1. **Surgical management**
   a. **Primary surgical approaches**

Options for surgical management of the primary tumor include BCT with lumpectomy followed by radiation therapy, mastectomy with breast reconstruction, and modified radical mastectomy alone. Surgical staging of the axilla is performed with all approaches to aid in determining prognosis and the role of adjuvant therapy. Prospective randomized clinical trials have shown that survival is equivalent between the surgical approaches (*N Engl J Med* 1995;332:907–911). The selection of a surgical approach depends on the location and size of the lesion, analysis of the mammogram, breast size, and the patient's attitude toward breast preservation.

The strategy behind BCT is to remove the bulk of the tumor surgically and to use moderate doses of radiation to eradicate any residual malignant cells left behind. Numerous trials have demonstrated high rates of local tumor control with satisfactory cosmetic results. Despite the favorable evidence, the use of BCT in the United States has shown relatively slow acceptance and geographic variation. Multicentric disease (two or more primary tumors in separate quadrants), extensive malignant-appearing microcalcifications, pregnancy, and previous breast or mantle irradiation are absolute contraindications for breast-conserving therapy. A history of collagen vascular disease and large pendulous breasts are relative contraindications to BCT because marked fibrosis and bone necrosis after adjuvant radiation may develop in these patients, with poor cosmetic result (*J Clin Onco*l 1992;10:356). The current standard therapeutic recommendation for BCT is surgery followed by radiation therapy. Attempts have been made to identify a subgroup of patients that has a low risk of local recurrence after BCT alone. Based on current available data, even in a highly selected group of breast cancer patients (based on clinical and histologic features), there is a substantial risk of early local recurrence after BCT alone when compared with BCT followed by radiation therapy (*N Engl J Med* 1995;333:1444).

A patient's age should not be a determining factor in the selection of BCT versus mastectomy. Women aged 65 years or older have overall and disease-free survival (DFS) rates similar to those of women younger than 65 years. In women with a strong family history of breast cancer, BCT has no difference in local recurrence or overall survival rates when compared with those of women without a family history of the disease. Further study of BCT is needed in women with known mutations in the BRCA1 and BRCA2 genes because of the high incidence of contralateral breast tumors in these patients.

   b. **Sentinel lymph node biopsy**

The presence of metastases to the axillary lymph nodes remains the most important prognostic factor in patients with breast cancer; therefore, ALND remains an important part of the surgical approach in breast cancer patients. In an effort to decrease the morbidity (arm discomfort and swelling) of

ALND while maintaining accurate staging, investigators have studied lymphatic mapping and sentinel lymph node (SLN) biopsy in women with breast cancer. Lymph node mapping and SLN biopsy was popularized by Morton et al. in melanoma patients in the early 1990s.

SLN biopsy has been evaluated in women with T1 and T2 disease, without multifocal involvement or clinically positive axillary lymph nodes (*N Engl J Med* 1998;337:941). The SLN is defined as the first node in the lymphatic chain that receives primary lymphatic flow, being at the highest risk for harboring occult metastatic disease in breast cancer patients with a clinically negative axilla. Vital blue dye and/or technetium-labeled sulfur is injected in and around the tumor or biopsy site. The surgeon can map the radioactive compound drainage to the axilla and identify the SLN, of which a biopsy is then performed. The SLN can be identified in approximately 93% to 97% of patients with breast cancer, with false-negative rates ranging from 0 to 10% (*N Engl J Med* 1998;337:941). The SLN is immediately examined by the pathologist to identify metastases. When an SLN biopsy is performed correctly and found to be negative on pathologic examination, it is currently believed that no further ALND is necessary. The appropriate management of the axilla in the sentinel-node–negative patients is unclear and needs further clinical investigation. If the SLN is positive for malignancy, possible treatment options include full ALND, axillary radiation, or no further surgery and adjuvant chemotherapy. Studies are currently under way to assess the efficacy and morbidity associated with each approach. The surgical level of lymph node involvement does not appear to add more prognostic information to the number of positive lymph nodes. Further randomized trials are needed to confirm that SLN biopsy and ALND procedures yield comparable overall survival rates.

c. **Breast-reconstruction techniques**

The change from a radical mastectomy to a modified radical mastectomy and advances in plastic surgery techniques have made breast reconstruction an option for most patients who elect to undergo a mastectomy. Overall, the goal of breast reconstruction is to create a cosmetic replacement of the surgically removed breast. The only contraindications to breast reconstruction are the presence of significant comorbid conditions that would interfere with the patient's ability to tolerate a longer operative procedure. A patient's age, need for chemotherapy, or poor long-term prognosis are not contraindications to breast reconstructive surgery (*Cancer* 1991;68:1167). Breast contour can be restored by the submuscular insertion of an artificial saline-filled implant or a transverse rectus abdominis myocutaneous (TRAM) flap. Silicone breast implants have not been available since 1992, because of the limited availability of data regarding their long-term safety.

Breast-reconstruction surgery has not been shown to increase the risk of local failure or impede the detection of local recurrence. In patients who may require postoperative chest wall irradiation, implants should be avoided because the risk of implant loss is high after radiation therapy. TRAM flap reconstruction can tolerate radiation therapy to the chest wall and regional nodes without significant loss of cosmesis in the adjuvant setting. Often surgery on the contralateral breast, such as reduction, may be necessary to achieve symmetry. Reconstruction of the nipple–areola complex is another secondary procedure that patients may elect to undergo to improve cosmetic appearance.

d. **The role of neoadjuvant chemotherapy**

Neoadjuvant chemotherapy has been shown to be as effective as postoperative chemotherapy with regard to survival of patients with primary operable breast cancer. In addition, neoadjuvant chemotherapy increases the opportunity for BCT by reducing the size of the primary tumor (*J Clin Oncol* 1997;15:2483). Chemotherapy regimens that result in high response rates include cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF), doxorubicin and cyclophosphamide (AC), and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), with the anthracycline-based regimens used most commonly. Newer neoadjuvant regimens with an anthracycline-based regimen followed by a taxane may achieve a pathological complete response at final assessment (*Oncologist* 2001;6:36). Further clinical trials using taxanes are currently under way. Neoadjuvant chemotherapy results in complete response rates ranging from 20% to 53% and partial response rates ranging from 37% to 50%, with total response rates ranging from 80% to 90% (*J Clin Oncol* 1997;15:2483). Neoadjuvant chemotherapy is usually given preoperatively for a total of four cycles or maximal tumor response. Surgical staging after neoadjuvant chemotherapy shows that 10% to 15% of women have a pathologic complete response that is associated with a favorable prognosis. Additional systemic chemotherapy may be considered in women with residual malignancy before or after radiation therapy.

2. **Radiation therapy**

Breast-conserving surgery followed by radiation therapy to the intact breast is currently considered standard treatment for the majority of patients with stage I or II invasive breast cancer. Several randomized trials have shown higher local recurrence rates with BCT alone compared with BCT with radiation therapy, but no significant survival benefit with radiation therapy. In the NSABP B-06 trial, more than 1,000 patients were randomly assigned to receive BCT with or without local breast irradiation. Irradiation reduced ipsilateral breast tumor recurrence from 36% to 12% in this group of patients. Further data analysis found no clinical or pathologic feature to allow the omission of radiation after lumpectomy (*Cancer* 2001;91(8 suppl):1679). Doses of 180 to 200 cGy/day are given to the intact breast over a 5- to 6-week period, to total doses of 4,500 to 5,000 cGy. A radiation boost to the tumor bed is often administered, although its necessity is currently controversial. For patients found to have negative axillary nodes at the time of dissection, regional nodal irradiation is not recommended. Patients with positive axillary nodes may benefit from regional nodal irradiation in addition to irradiation of the intact breast.

Available data suggest that, in postmastectomy patients with positive surgical margins, primary tumors more than 5 cm in size, or involvement of four or more lymph nodes, the risk of local recurrence is significantly high enough to consider adjuvant chest wall and axillary radiation therapy. Radiation therapy can decrease the rates of local recurrence in this group, even among patients who receive adjuvant chemotherapy (*N Engl J Med* 1995;333:1444). The British Columbia trial randomized 318 premenopausal women with node-positive breast cancer who were receiving chemotherapy either to receive or to not receive postmastectomy radiation therapy. At 15 years of follow-up, this trial demonstrated a 33% reduction in the rate of local recurrence and a 29% reduction in breast cancer mortality with postmastectomy radiation therapy. Radiation therapy should not be delivered concurrent with anthracycline chemotherapy because of the radiation-sensitizing effects of the drug, leading to higher radiation toxicities. Radiation therapy is typically given after completion of adjuvant chemotherapy, within the first 6 months after mastectomy.

3. **Adjuvant systemic therapy**

The viewpoint that occult metastases (or micrometastases) are commonly present when patients are initially seen with operable breast cancer is based on the fact that even after effective local treatment, metastatic involvement develops in many patients over time. Improvements in local control have been shown to provide, at best, only a small decrease in distant metastases. Given this, improving the long-term outlook for newly diagnosed breast cancer patients with early-stage disease can be accomplished only with improvements in systemic therapy. Beginning more than three decades ago, many clinical trials were organized to test the value of various drugs as an adjunct or adjuvant to local treatment. Adjuvant chemotherapy trials have demonstrated significant improvements in survival for treated patients compared with controls. Candidates for adjuvant systemic or hormonal therapy are chosen based on prognostic factors of the individual tumor associated with the risk of recurrence, including tumor size, axillary lymph node involvement, and hormonal-receptor status.

a. **Adjuvant hormonal therapy**

The laboratory discovery and subsequent measurement of estrogen receptors (ERs) and progestin receptors (PRs) in breast tumors have given the physician useful tools to aid in the treatment of women with breast cancer. The decision to recommend hormonal therapy should be based on the presence of hormone receptors in the breast cancer tissue. Hormone receptors can be routinely identified by a variety of immunohistochemical staining of breast tissue. The ER and PR belong to a large class of nuclear-receptor proteins, are present in normal breast and other tissues, and are expressed in up to 60% to 70% of breast cancers (*Cancer* 2001;91:1679). In both normal and tumor cells, estrogen binds to the ER, which is a large protein molecule located in the cytoplasmic and nuclear fractions of the cell. The receptor–hormone complex results in gene activation and transcription of messenger RNA (mRNA) and cell proliferation. The blockade of estrogen inhibits protein translocation, cell proliferation, and leads to the initiation of cell death. ERs and PRs can be used as both predictive and prognostic factors in women with breast cancer. Although ERs and PRs are associated together, PRs do not provide useful clinical information independent of the ER status (Table 7.3).

ER	PR	Response Rate
+	+	78%
+	–	34%
–	+	45%
–	–	10%

ER, estrogen receptor; PR, progesterone receptor.
From *N Engl J Med* 1989;320:479, with permission.

TABLE 7.3. RESPONSE TO HORMONAL THERAPY ACCORDING TO ER AND PR STATUS

The primary source of estrogen in the premenopausal woman is the ovary. In the postmenopausal woman, the predominant source of estrogen is peripheral conversion of adrenal androgens to estrogen by the enzyme, aromatase. Estrogen deprivation can be achieved by several different mechanisms. One method of reducing estrogen levels is with direct blockade of the ER in the target tissue, with drugs like tamoxifen. Another way to suppress estrogen synthesis is by inhibition or inactivation of the aromatase enzyme, with drugs like aromatase inhibitors or luteinizing hormone–releasing hormone (LHRH) agonists. LHRH agonists are initially associated with an increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH), leading to an initial increase in estrogen levels. Continued use of LHRH agonists causes a paradoxic suppression of FSH/LH from the pituitary gland, leading to a decline in circulating estrogen levels. The third mechanism for estrogen suppression is surgical or radiation-induced ovarian ablation.

The goal of adjuvant hormone therapy in breast cancer is to prevent the tumor from receiving stimulation from estrogen, leading to apoptosis in the malignant cell lineage. Hormonal therapy should be recommended to patients whose breast cancer contains the ER and/or PR protein, regardless of age, menopausal status, involvement of axillary lymph nodes, or tumor size. This recommendation is based on a substantial reduction in the likelihood of tumor recurrence and death at 15 years of follow-up. Adjuvant hormonal therapy should not be recommended in patients whose breast cancers do not express the ER or PR protein, because randomized clinical trials have not shown that hormonal therapy reduces the likelihood of ipsilateral or contralateral tumor recurrence or impact on overall survival (*N Engl J Med* 1989;320:479) (Table 7.4).

Selective estrogen receptor modulator	Tamoxifen Raloxifene Toremifene
Aromatase inhibitor	
Steroid base	Formestane (i.m.) Exemestane
Nonsteroid base	Aminoglutethimide Anastrozole Letrozole
Progestins	Megestrol acetate
Androgens	Halotestin
High-dose estrogen	Diethylstilbestrol
LHRH agonist	Goserelin Buserelin

LHRH, luteinizing hormone releasing hormone.

TABLE 7.4. CURRENT HORMONAL THERAPY

More than 20 trials have looked at the benefit of tamoxifen in the adjuvant setting compared with placebo. Many trials have focused on postmenopausal women, but an adequate number of trials include premenopausal women. The clinical response has been looked at for node-positive and node-negative patients, with duration of therapy ranging from 1 to longer than 5 years. Nearly all trials have shown a benefit in overall DFS, and two have shown an improvement in overall survival (*Br J Cancer* 1988;57:608; *Lancet* 1987;2:171–175).

The Early Breast Cancer Trialists Collaborative Group's (EBCTCG) meta-analysis included an overview of women with early-stage breast cancer who were randomized to adjuvant tamoxifen versus no tamoxifen (*Cancer* 2001;91:1679). This meta-analysis provides the best data for examining the relation between ER/PR status and the benefit from adjuvant hormonal therapy. The EBCTCG meta-analysis showed that women with ER-positive tumors treated with tamoxifen have a benefit in terms of a reduction of rates of recurrence and death, whereas those with ER-negative tumors do not have a clinical benefit (*Cancer* 2001;91:1679) (Table 7.5). These benefits appeared to be irrespective of age, menopausal status, or history of chemotherapy.

Receptor Status	Relative Reduction in Recurrence Rates (%)	Relative Reduction in Mortality (%)
ER+/PR+	37	16
ER+/PR–	22	18
ER–/PR+	23	9
ER–/PR–	1	1

TABLE 7.5. RELATIVE REDUCTION IN RECURRENCE AND MORTALITY ASSOCIATED WITH ADJUVANT TAMOXIFEN BY ER/PR STATUS

Early meta-analyses revealed no benefit in women younger than 50 years, but many of the trials included ER-negative patients and a maximal duration of therapy of 2 years. No conclusions could be adequately drawn from the data for women younger than 50 years. There are now convincing data that with tamoxifen, when used in ER-positive breast cancer patients for a duration of 5 years, women younger than 50 do have a benefit. This was first illustrated in the data on node-negative patients from the NSABP B-14 trial (*N Engl J Med* 1988;319:1681) and confirmed in later meta-analyses (Table 7.6) (*J Natl Cancer Inst* 1996;88:1529). These data were important in demonstrating that tamoxifen can be effective against breast tumor cells even in premenopausal women with higher circulating estrogen levels and helped oncologists to reformulate the standard of thought that premenopausal women could be treated only with chemotherapy. Whether tamoxifen is equivalent or superior to chemotherapy, as compared with postmenopausal women with ER-positive tumors, remains a question. Few studies have directly looked at this clinical question. In 1997, a large randomized clinical trial demonstrated that chemotherapy in combination with tamoxifen was more effective than tamoxifen alone (*J Natl Cancer Inst* 1997;89:1673). However, there was no arm with chemotherapy alone to assess the relative effectiveness of each modality used alone.

Age (yr)	Reduction in Recurrence (%)	Reduction in Death (%)
All patients	47	26
<40	54	52
40–49	41	22
50–59	37	11
60–69	54	33
>70	54	34

ER, estrogen receptor.
From *J Natl Cancer Inst* 1996;88:1529, with permission.

TABLE 7.6. EFFECTS OF TAMOXIFEN IN WOMEN WITH ER-POSITIVE TUMORS, DURATION OF 5 YEARS

In many trials, women with node-negative breast cancer had not demonstrated the same statistically significant differences in recurrence and survival rates because of fewer recurrences and deaths associated with node-negative disease. Yet women with node-negative, ER-positive disease should anticipate the same biologic response to tamoxifen as do node-positive patients. The NASBP B-14 trial looked exclusively at patients with histologically negative axillary nodes, in pre- and postmenopausal women with ER-positive tumors. Again a statistically significant reduction in recurrences and death occurred in both pre- and postmenopausal women when tamoxifen was given for at least 5 years as compared with placebo. Tamoxifen use was also shown to reduce ipsilateral breast, locoregional, and distant recurrences when compared with placebo, and also approximately 50% reduction in contralateral recurrence (*N Engl J Med* 1988;319:1681). Because of a more favorable side-effect profile compared with chemotherapy, tamoxifen is an attractive treatment option in women with node-negative disease and is proven to be beneficial in reducing recurrence rates.

The EBCTCG meta-analysis demonstrated the greatest reduction in recurrence and mortality when tamoxifen was used for duration of 5 years, compared with 1 or 2 years of therapy (*Cancer* 2001;91:1679) (Table 7.7). The current recommendation is to discontinue tamoxifen after 5 years in all patients outside the setting of a clinical trial. Although a greater reduction in recurrences has been demonstrated with longer treatment with tamoxifen, based on the NSABP B-14 and other clinical trials, there is no convincing evidence that treatment longer than 5 years is beneficial (*J Natl Cancer Inst* 1996;88:1529). There was a trend toward a detrimental effect after treatment for more than 5 years. The incidence of contralateral breast cancer was not further reduced with prolonged administration of tamoxifen. Switching to another hormonal agent, such as toremifene or raloxifene, after 5 years of tamoxifen has not been adequately studied in clinical trials and is currently not recommended. No data support the use of raloxifene, toremifene, or aromatase inhibitors as adjuvant hormonal therapy, although clinical trials are under way to look at the effectiveness of the combination of tamoxifen with aromatase inhibitors in the adjuvant setting.

Tamoxifen Duration (yr)	Reduction in Recurrence Rates (%)	Reduction in Mortality Rates (%)
1	21	14
2	29	18
5	50	28

ER, estrogen receptor.
From *Cancer* 2001;91(8 suppl):1679, with permission.

TABLE 7.7. REDUCTION IN RECURRENCE AND MORTALITY RATES OF BREAST CANCER BASED ON DURATION OF TAMOXIFEN THERAPY IN ER-POSITIVE PATIENTS

In patients receiving adjuvant chemotherapy, tamoxifen can be administered either after the completion of or concurrent with chemotherapy. Although there have been theoretic concerns about tamoxifen reducing tumor growth rates and interfering with the effects of chemotherapy, this has not been observed clinically (*N Engl J Med* 1988;319:1681). The NSABP B-16 trial looked at the use of chemotherapy with doxorubicin (Adriamycin) and cyclophosphamide and tamoxifen (ACT) versus tamoxifen alone in node-positive breast cancer patients 50 years and older with ER-positive tumors. NSABP B-16 updates at 8 years and 10 years showed a trend toward an improvement in the DFS and overall survival (OS) rates in patients treated with ACT rather than with tamoxifen alone (*J Clin Oncol* 1990;8:1005). There are currently no clinical trials that compare the use of concurrent versus sequential chemoendocrine therapy for adjuvant treatment of breast cancer. Clinicians may prefer to delay the start of tamoxifen until after any chemotherapy has been completed, which takes typically only 3 to 6 months. Evidence shows that chemotherapy and hormonal therapy are complementary adjuvant treatments in ER-positive patients, and use of one should not preclude the use of the other in this setting.

For ER-positive premenopausal patients, alternative strategies of hormonal therapy include ovarian ablation through surgery or radiation therapy to the ovaries and chemical suppression of ovarian function with LHRH agonists, such as goserelin. These strategies are used far less frequently in the United States than in Europe. In premenopausal women, ovarian ablation produces an improvement in recurrence rates and survival similar to that of an adjuvant chemotherapy regimen (*Lancet* 1996;348:1189–1196). Although ovarian ablation may be comparable to adjuvant chemotherapy in a selective premenopausal patient population, there is insufficient data to suggest that ovarian ablation should be substituted for adjuvant therapy as standard practice. LHRH agonists may be considered in premenopausal patients who refuse other hormonal therapies. Surgical or radiation-induced ovarian ablation may be considered in women with hereditary breast cancer syndromes who are at an increased risk of development of ovarian malignancies. The potential additive role of ovarian ablation to chemotherapy and/or tamoxifen is presently being explored in clinical trials.

Individual trials of other forms of adjuvant endocrine therapy, including aromatase inhibitors, progestins, and high-dose estrogen, have been reported, but data are insufficient to draw conclusions or make recommendations. With the exception of aromatase inhibitors, other hormonal therapies are associated with more adverse effects when compared with tamoxifen, and in the absence of additional data, are not currently recommended for adjuvant therapy in early-stage breast cancer patients.

b. **Adjuvant chemotherapy**

Since the 1970s, randomized trials have addressed many fundamental questions related to adjuvant chemotherapy. Over the past decade, data have emerged that more clearly define the subpopulations of patients with early-stage breast cancer for whom adjuvant chemotherapy is indicated as a standard component of treatment. Early trials focused on patients with node-positive disease because of the higher risk of recurrence and death that justified the added toxicities of chemotherapy regimens. Two of the initial adjuvant chemotherapy trials looked at the use of chemotherapy with melphalan alone or cyclophosphamide, methotrexate, and 5-fluorourcil, versus no chemotherapy. Both of these trials demonstrated a significant reduction in recurrence and a trend toward improvement in overall survival when compared with surgery alone. These initial clinical trials led to further investigational trials to identify the benefits of adjuvant chemotherapy in patients with breast cancer.

The EBCTCG conducted meta-analyses on all the major randomized clinical trials, with the most recent results being published in 1998 (*Lancet* 1998;352:930). Several major conclusions can be drawn from the meta-analyses:

1. Both pre- and postmenopausal women have a benefit from adjuvant chemotherapy.
2. Both ER(+) and ER(–) patients have a benefit from adjuvant chemotherapy.
3. Both node-negative and node-positive patients have a benefit from adjuvant chemotherapy.
4. Long-term chemotherapy (longer than 6 months) has not shown any benefit over shorter chemotherapy regimens.
5. Anthracycline-based chemotherapy regimens are superior to non–anthracycline-based chemotherapy regimens.

Overall, adjuvant chemotherapy has been demonstrated to reduce the risk of recurrence and mortality rates by 25% and 15%, respectively (*Lancet* 1998;352:930). Although these studies have not identified one standard regimen, they do provide important conclusions and a list of appropriate regimens to be considered by the practicing oncologist (Table 7.8). Some quantitative differences in benefits from adjuvant chemotherapy are evident in several clinical subsets that have formulated the current recommendations for adjuvant chemotherapy.

Cyclophosphamide/methotrexate/5-fluorouracil (CMF) × 6 cycles
5-Fluorouracil/doxorubicin/cyclophosphamide (FAC) × 6 cycles
5-Fluorouracil/epirubicin/cyclophosphamide (FEC) × 6 cycles
Doxorubicin/cyclophosphamide (AC) × 4 cycles
AC × 4 cycles followed by single-agent paclitaxel × 4 cycles (AC → T)

TABLE 7.8. CURRENT ADJUVANT CHEMOTHERAPY REGIMENS

For further information on chemotherapy regimens, see Appendix.

One subgroup analysis in the EBCTCG data shows a trend toward a greater risk reduction in younger than in older women (*Lancet* 1987;352:930) (Table 7.9). Relatively few women were aged 70 or older at presentation in the majority of these studies, and the results in this age subgroup are inconclusive and excluded from further analyses. The reason older women benefit less than younger women are not totally clear. Some investigators have suggested that women younger than 50 years might have an indirect protective effect from adjuvant chemotherapy through partial or total ovarian ablation from the systemic chemotherapy. Others have attributed this effect to age-related differences in tumor biology. The important conclusion from the meta-analysis is that all women, with the exception of those women 70 years or older showed a significant benefit in reduction of recurrence and mortality when given adjuvant chemotherapy. Therefore, being older than 50 years should not be a barrier to the use of adjuvant chemotherapy in women who would otherwise be at a substantial risk for tumor recurrence. It is no longer standard to offer adjuvant therapy to premenopausal women exclusively.

Age (yr)	Reduction in Recurrence (%)	Reduction in Death (%)
<40	37	27
40–49	34	27
50–59	22	14
60–69	18	8
>70	NS	NS
Overall	24	15

NS, not significant.
From *Lancet* 1998;352:930, with permission.

TABLE 7.9. EFFECTS OF ADJUVANT CHEMOTHERAPY WITH RELATIONSHIP TO AGE

Because of too few women older than 70 years in the meta-analysis, there is little direct assessment that one can make for that age group. It is likely that there is a survival benefit associated with adjuvant chemotherapy in this patient population as well. However, there is a real concern about the toxicity associated with the chemotherapy regimens in this older patient population and about the existing comorbid conditions that may influence the overall benefits in this group of patients.

ER expression does appear to influence the effectiveness of adjuvant chemotherapy based on the subgroup analysis of ER(+) and ER(–) patients in the meta-analysis (Table 7.10). ER-negative patients showed a trend toward a greater reduction in recurrence and mortality rates compared with estrogen-positive patients treated with adjuvant chemotherapy in both younger and older populations. In the 50- to 69-year-old group, estrogen-negative patients were twice as likely to benefit from adjuvant chemotherapy as were the ER-positive group. In all age ranges, the reduction rates for recurrence and mortality were statistically significant in both ER-positive and ER-negative patients, although the effects seem somewhat smaller in women with ER-positive tumors (*Lancet* 1998;352:930).

ER Status	Reduction in Recurrence (%)	Reduction in Mortality (%)
Age <50 yr		
ER negative	40	35
ER positive	33	20
Age 50–69 yr		
ER negative	30	17
ER positive	18	9

ER, estrogen receptor.
From *Lancet* 1998;352:930, with permission.

TABLE 7.10. EFFECTS OF ADJUVANT CHEMOTHERAPY WITH RESPECT TO ER STATUS

Initial clinical trials did not include node-negative patients because of the potential toxicities and relatively favorable prognosis in this subgroup. Approximately 25% of node-negative breast cancer patients will have recurrence of their breast cancer, with 25% of these occurring after 10 years. Although a majority of these patients will be cured with surgery alone, clinical trials have been trying to identify those patients with node-negative breast cancer who will benefit from adjuvant chemotherapy. Within each age group in the EBCTCG data, the proportional reductions in recurrence and mortality were similar for women with node-negative and node-positive disease with adjuvant chemotherapy (*Lancet* 1998;352:930) (Table 7.11 and

Table 7.12). Both node-positive and node-negative breast cancer patients may benefit from the effects of adjuvant chemotherapy, although the absolute number of node-negative patients that benefit from adjuvant chemotherapy may be smaller compared with the node-positive patients. The overall 10-year survival data from the EBCTCG showed an absolute benefit of 7% in node-negative and 11% in node-positive women younger than 50 years, and 2% in node-negative and 3% in node-positive women 50 years or older. It is clear from the data from the EBCTCG that adjuvant chemotherapy has an effect on recurrence and on long-term survival in both age groups and nodal status (*Lancet* 1998;352:930).

Age	Reduction in Recurrence (%)	Reduction in Mortality (%)
<50 yr		
Node positive	15	12
Node negative	10	6
50–69 yr		
Node positive	5	2
Node negative	6	5

From Lancet 1998;352:930, with permission.

TABLE 7.11. EFFECT OF ADJUVANT CHEMOTHERAPY WITH RESPECT TO AXILLARY NODE STATUS

Age	With Adjuvant Chemotherapy	No Adjuvant Chemotherapy	Absolute Benefit
<50 yr			
Node negative	78%	71%	7%
Node positive	42%	53%	11%
50–69 yr			
Node negative	69%	67%	2%
Node positive	49%	46%	3%

From Lancet 1998;352:930, with permission.

TABLE 7.12. EFFECT OF ADJUVANT CHEMOTHERAPY WITH RESPECT TO 10-YEAR SURVIVAL AND AXILLARY NODE STATUS

Adjuvant chemotherapy is routinely offered to women with a primary tumor of 1 cm or larger. However, within the subset of node-negative disease and primary tumor 1 cm or less in size, uncertainty about the prognosis and treatment recommendations prompted a retrospective analysis of data from five NSABP randomized clinical trials (*J Natl Cancer Inst* 2001;93:112). The meta-analysis included women with node-negative disease only. In the ER-negative subgroup of patients, there was no statistically significant difference in relapse or overall survival in the surgical versus the adjuvant chemotherapy groups. In the ER-positive patients, there was a significant increase in the 8-year relapse-free and overall survival rates with the addition of adjuvant chemotherapy and tamoxifen. The conclusion from the authors was that adjuvant chemotherapy and/or tamoxifen should be considered for the treatment of women with ER-negative or ER-positive tumors of 1 cm or less and negative axillary lymph nodes (*J Natl Cancer Inst* 2001;93:112). Criticism of the analysis regarding the true clinical benefit seen with adjuvant chemotherapy should be better explored. Surgery alone can be associated with a more than 95% cure rate in many patients with primary tumors less than 1 cm. The ability to predict accurately which patients will benefit from additional adjuvant chemotherapy is not reliable, and the risks of toxicity are not negligible. Therefore, as screening methods continue to improve, and tumors of less than 1 cm continue to be increasingly common, further clinical trials regarding treatment and the development of more precise prognostic factors are needed to help identify which patients will benefit most from adjuvant chemotherapy.

There is no subgroup of breast cancer patients for which chemotherapy is of no clinical benefit. The magnitude of the benefit varies by the risk of recurrence, thereby making it less desirable for women with a very low risk of recurrence. For example, in a woman with a risk of recurrence at 5 years of 10%, a 2% annual risk reduction would improve her 5-year recurrence rate to 9%. This number does not seem like a clinically significant decrease despite reaching statistical significance. Yet, surprisingly, as many as half of patients with breast cancer state that they would accept the toxic effects of chemotherapy for an incremental benefit of 1% survival advantage after 5 years. This makes it difficult to determine a “cutoff” of absolute benefit that is sufficient to recommend adjuvant chemotherapy. Clinical oncologists should individualize the role of adjuvant chemotherapy based on the patient, tumor characteristics, and confounding factors related to treatment when making formal treatment recommendation to each breast cancer patient.

Initial adjuvant chemotherapy regimens were given for up to 1 to 2 years. The optimal duration of treatment has not been adequately studied, and definitive data on the benefits of more prolonged treatment are lacking. Current literature now supports that four to six courses of treatment (3 to 6 months) appear to provide optimal benefit. Additional courses of chemotherapy add to treatment-related toxicity with no substantial improvement in overall outcome. Some examples include the NSABP B-15 and French Adjuvant Study Group. In the NSABP B-15 study, AC given every 3 weeks for four cycles was found to be equivalent in relapse-free survival rates to 6 months of CMF (*J Clin Oncol* 1990;8:1483). AC has never been compared with CAF or FEC in a randomized clinical trial. Alternatively, the French Adjuvant Study Group demonstrated that six cycles of FEC is associated with an increase in disease-free and overall survival compared with only three cycles of chemotherapy. For more details on the current recommendations on length of treatment with the various chemotherapy regimens, see Table 7.8 and the Appendix: Chemotherapy Regimens.

The 2000 NIH Consensus Conference on Adjuvant Therapy for Breast Cancer advocates the use of anthracycline-containing regimens, CAF, or FEC over non–anthracycline-containing regimens (CMF) based on statistically significant survival advantages (*NIH Consensus Statement* 2000;17:1). Multiple randomized clinical trials have addressed the clinical question of anthracycline-based chemotherapy compared with nonanthracycline regimens for adjuvant therapy in early-stage breast cancer. In one study by the National Cancer Institute of Canada (NCIC), CEF was compared with CMF in node-positive breast cancer patients. In this trial CEF was superior to CMF, with an improvement in recurrence rates and overall survival (*J Clin Oncol* 1998;16:2651). However, there also was a higher incidence of hospitalizations for febrile neutropenia in the anthracycline-based group. In a review of 11 clinical trials comparing anthracycline-based chemotherapy with CMF meta-analysis from the EBCTCG, an annual rate reduction of approximately 3% was demonstrated in both recurrence and overall survival between the two groups (*Lancet* 1998;352:930). However, one must consider whether the additional benefit from anthracycline-based chemotherapy regimens is warranted, given the higher incidence of toxicity, based on the individual breast cancer patient and tumor characteristics.

AC followed by paclitaxel (AC + T) had emerged in the United States as a standard adjuvant chemotherapy regimen based on the early results of the Cancer and Leukemia Group B (CALGB) 9344 phase III trial (*NIH Consensus Statement* 2000;17:1). The role of taxanes in the adjuvant setting raises concern in some breast cancer specialists, as results on their use in women with node-positive breast cancer is inconclusive. Initial data in 1998 from the CALGB 9344 trial showed a 22% and 26% reduction in the relative risk of relapse and death respectively in patients receiving AC + T compared with those who received AC alone.

Since 1998, additional follow up data have become available that question the true impact of paclitaxel in the adjuvant setting. The results of three key trials using paclitaxel were discussed at the National Institutes of Health Consensus Conference on Adjuvant Therapy in November 2000. An update of the CALGB 9344 trial at 52 months showed that patients who received paclitaxel continued to have a reduction in recurrence rates and death, but the size of this benefit was nearly half the rate of reduction seen initially (*NIH Consensus Statement* 2000;17:1). In an M.D. Anderson trial of nonadjuvant therapy with FAC plus paclitaxel × 4 versus FAC × 8 alone, the results did not show a difference in recurrence rates or overall survival

between the two groups (*NIH Consensus Statement* 2000;17:1). In the NSABP B-28 trial, at a median follow-up of 34 months, there was no apparent improvement in either recurrence rates or overall survival with the addition of paclitaxel to AC. In a subset analysis of the NSABP B-28 trial, patients with ER-negative tumors had a minor trend toward improvement in rates of relapse and death with the addition of paclitaxel, but did not reach statistical significance (*NIH Consensus Statement* 2000;17:1). Further follow-up of ongoing trials, as well as additional trials of taxanes in the adjuvant setting are needed the better to define the value of taxanes in the treatment of early-stage breast cancer.

Randomized clinical trials have looked at the optimal sequence of adjuvant chemotherapy and radiation postoperatively, and the current standard is to initiate adjuvant chemotherapy 3 to 6 weeks after surgery. It was shown that patients who received chemotherapy first had an improvement in overall survival and a reduction in local and distant recurrence rates (*N Engl J Med* 1996;334:1356). In the radiation-first treatment arms, a median delay of 17 weeks was observed after surgery before chemotherapy could be initiated. The radiation-first treatment group also had significant dose reductions in chemotherapy because of increased toxicity with myelosuppression. Radiation therapy can be safely delayed for several months after surgery until the completion of adjuvant chemotherapy with no impact on recurrence and survival rates. Delay of radiation is preferable for patients at high risk of disease recurrence to allow full doses of chemotherapy for maximal therapeutic benefit.

There are now no convincing data to support the use of any known biologic factor other than hormone-receptor status in selecting a specific adjuvant chemotherapy regimen in breast cancer patients. The HER2/neu or c-*erb*B2 protooncogene overamplification and subsequent overexpression of the gene product on the breast tumor cell surface occurs in approximately 25% of human breast cancers. This alteration in protein overexpression has been associated with a poor prognosis in breast cancer. Current prospective studies are needed to determine if HER2/neu overexpression is related to chemotherapy resistance and if HER2/neu overexpression should influence the choice of adjuvant chemotherapy regimens.

D. **Treatment of advanced breast cancer (stages IIIb and IV)**

Advanced breast cancer includes those subsets of patients with tumors larger than 5 cm in size (T3), inflammatory breast tumors (T4) with direct invasion of the dermis or chest wall, and any tumor with fixed or matted axillary lymphadenopathy (N2) or internal mammary lymphadenopathy (N3). Surgery is typically limited to a biopsy to confirm the diagnosis and identify receptor status. Neoadjuvant chemotherapy is indicated in this patient population and may facilitate tumor shrinkage to allow surgical resection with clear margins (see Sec. III.C.1.d., The role of neoadjuvant chemotherapy). Advanced breast cancer is associated with a poorer prognosis and a high rate of local and distant recurrences, leading to a similar treatment goals and modalities with metastatic breast cancer patients (Table 7.13).

Stage	5-yr Survival Rate (%)
0 (T_{is})	92
I	87
IIA	78
IIB	68
IIIA	51
IIIB	42
IV	13

From *Lancet* 1995;345:1154, with permission.

TABLE 7.13. STAGE GROUPING AND SURVIVAL

Metastatic breast cancer (MBC) remains an incurable disease with a median survival of 18 to 24 months, although a small subgroup of 3% to 5% of patients can remain in remission for longer than 10 years (Harris JR, Lippman ME, Morrow M, et al., eds. *Diseases of the breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:749–798). The primary goal of treatment for patients with metastatic disease is to prolong survival and palliate symptoms related to the disease, rather than curing patients. The management of MBC depends on the site and extent of metastases, hormone-receptor status, HER2/neu overexpression, and the presence of comorbid medical conditions.

Patients with MBC can be divided into two groups for treatment decisions, low and high risk. Patients in the low-risk group include those patients in whom MBC develops after a long disease-free interval, those with hormone receptor–positive tumors, and those with bone, soft tissue, or limited visceral organ involvement. High-risk patients include those with rapidly progressive disease or extensive visceral involvement, as well as those patients whose disease becomes refractory to hormonal therapy.

Low-risk patients may be treated initially with hormone therapy. Patients with ER/PR-positive tumors have response rates to first-line hormonal therapy as high as 60% to 70%, whereas at most, only 5% to 10% of patients with ER-negative tumors benefit. A small subset of tumors, approximately 5%, are ER negative, PR positive (Harris JR, Lippman ME, Morrow M, et al., eds. *Diseases of the breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:749–798). This could be due to false-negative determination of ER status. These tumors have response rates that are not substantially different from those of ER-positive tumors, although some evidence exists that ER-negative, PR-positive tumors may be associated with a worse clinical outcome. First-line hormonal therapy consists either of antiestrogen therapy such as tamoxifen, or the newer aromatase inhibitors. Present data show the second-generation aromatase inhibitors (anastrozole, letrozole, and exemestane) may produce higher response rates and longer remissions than tamoxifen (*J Clin Oncol* 2000;18:3758). The onset of action for hormonal therapy is slow, on the order of months, and is most effective in slowly progressive disease.

An important phenomenon related to hormone therapy is the “flare” response, or temporary worsening of signs and symptoms of the disease within the first few weeks to months of treatment. Scintigraphic flare on bone scan has been well described in the medical literature. This scintigraphic flare can mimic progressive disease early in the course of hormonal treatment in patients with bone metastases. This flare response typically signals that a clinical benefit will follow. Clinicians must be aware of this phenomenon to avoid premature discontinuation of potentially beneficial hormonal treatment.

Aromatase inhibitors work by blocking the peripheral conversion of testosterone to estrogen by the aromatase enzyme. The newer second-generation aromatase inhibitors have illustrated inhibition of more than 97% to 99% of the enzyme. The aromatase inhibitors have either a steroidal base (exemestane) or a nonsteroidal base (aminoglutethimide, anastrozole, and letrozole; Table 7.4). Both classes have comparable degrees of estrogen suppression. Aromatase inhibitors have challenged tamoxifen as first-line therapy for patients with MBC and have surpassed the use of megestrol acetate in patients who experience tamoxifen failure.

Anastrozole was the first aromatase inhibitor to show efficacy and safety at least equivalent to those of tamoxifen. Anastrozole was compared with tamoxifen as first-line therapy for MBC and was found to be at least as effective in terms of overall response rates (21% vs. 17%). Anastrozole showed an improvement in median time to progression (TTP), 11 months more than tamoxifen, 5.6 months (*J Clin Oncol* 2000;18:3758). This led to the recent approval of Anastrozole by the FDA as a first-line therapy for postmenopausal women with MBC. Anastrozole also is associated with fewer thromboembolic events and vaginal bleeding compared with tamoxifen. Currently letrozole also has been approved for the first-line treatment of women with MBC. Clinical trial data also support a benefit in the median TTP and improved overall response rates with the use of letrozole compared with tamoxifen (*J Clin Oncol* 2000;19:2596).

Initial clinical trials with aromatase inhibitors looked at the use of these newer agents as second-line therapy after tamoxifen failure in MBC. In one trial comparing anastrozole with megestrol acetate, similar response rates and median TTP were demonstrated (*Cancer* 1998;83:1142). Anastrozole also was associated with less edema, thromboembolic disease, and weight gain than was megestrol acetate. Similar finding were documented in clinical trials using letrozole or exemestane compared with megestrol acetate (Harris JR, Lippman ME, Morrow M, et al., eds. *Diseases of the breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:749–798). There have been no direct comparisons of aromatase inhibitors in the treatment of MBC. However, when indirect comparisons of the various aromatase inhibitors are made with megestrol acetate, similar initial response rates, ranging from 34% to 42%, and median TTP ranging from 4.7 to 5.6 months are seen among the aromatase inhibitors as a group. All three drugs are associated with less peripheral edema, thromboembolic complications, and weight gain when compared with progestins. Exemestane does have some androgen-related side effects with slightly

higher rates of weight gain than anastrozole and letrozole (*Eur J Cancer* 2000;36:86).

The results from a recent meta-analysis, including four trials with premenopausal women with locally advanced or MBC, suggest that patients treated with an LHRH agonist and tamoxifen had an improvement in TTP and survival compared with those treated with an LHRH agonist alone. No additional toxicity was associated with the combination of a LHRH agonist and tamoxifen compared with either alone. The results from this analysis suggest that combination hormonal therapy to promote maximal estrogen suppression may be beneficial in premenopausal women with breast cancer (*J Clin Oncol* 1992;19:343). Further clinical trials must be completed to evaluate fully the benefit identified in this meta-analysis.

Patients who have a complete response, a partial response, or even stable disease after initiation of a hormonal therapy may benefit from second- and third-line hormonal therapies when their cancer begins to progress. ER-positive status is important in predicting benefit from second-line and subsequent hormone manipulations. Very few ER-negative patients respond to second-line therapy. In ER-positive patients, although subsequent response rates become lower, they remain between 20% and 40%. Thus resistance to tamoxifen does not preclude a response to further hormonal manipulations, and a median duration of response of 12 or more months can be achieved with subsequent hormonal therapy in patients experiencing failure of tamoxifen. With each subsequent hormonal therapy, responses tend to become of shorter duration, and ultimately, the disease will become refractory to hormone treatment (Harris JR, Lippman ME, Morrow M, et al., eds. *Diseases of the Breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:749–798). Second-line, third-line, and subsequent hormonal therapy should be chosen based on the adverse side-effect profile of each drug. Systemic chemotherapy can be recommended in patients whose disease becomes refractory to multiple lines of hormonal therapy.

High-risk patients with rapidly progressive disease or extensive visceral involvement, as well as those patients whose disease becomes refractory to hormonal therapy, benefit from a number of chemotherapeutic agents that are active against advanced-stage breast cancer. Anthracycline-based combinations, such as CAF, can be used in MBC, and newer combinations with taxanes are gaining favor in MBC patients who have not received prior anthracyclines. Many single-agent drugs have activity in MBC as well, with the taxanes again being among the most active of the new agents (Table 7.14). Taxanes have demonstrated activity in anthracycline-resistant disease, as well as in patients who have received three or more chemotherapy regimens for MBC. Capecitabine has been shown to have a good antitumor effect in patients whose disease has recurred or progressed after anthracyclines and taxanes (Harris JR, Lippman ME, Morrow M, et al., eds. *Diseases of the breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:749–798).

Response Rates 30%–50%	Response Rates 10%–30%
Docetaxel	Cisplatin
Doxorubicin	Cyclophosphamide
Epirubicin	5-Fluorouracil
Paclitaxel	Ifosamide
Vinorelbine	Methotrexate
Capecitabine	Mitomycin-C
	Mitoxantrone
	Thiotepa
	Vinblastine
	Vincristine
	Liposomal doxorubicin

MBC, metastatic breast cancer.

TABLE 7.14. CHEMOTHERAPY AGENTS EFFECTIVE IN MBC

HER2/neu overexpression occurs in 25% to 30% of cases of MBC. Among patients with MBC, HER2/neu overexpression has been associated with relative resistance to treatment response with anthracycline- or taxane-based chemotherapy. Trastuzumab is a humanized monoclonal antibody to the HER2/neu protein. The drug has been approved for use in combination chemotherapy as first-line therapy, and as a single agent in second- and third-line therapy in MBC. In the original trials with trastuzumab as a single agent in first-line therapy, trastuzumab achieved response rates of 20% to 25% (*JCO* 2002). Among patients previously treated with chemotherapy, trastuzumab yielded response rates of 10% to 15% (*J Clin Oncol* 1996;14:737; *J Clin Oncol* 1999;17:2639). Preclinical models suggest that trastuzumab may potentiate the effects of chemotherapy when administered concurrently. In one clinical trial comparing the use of chemotherapy versus chemotherapy with trastuzumab, the combination with trastuzumab was associated with higher response rates, a longer TTP, and a statistically significant improvement in overall survival (*N Engl J Med* 2001;344:783). Neither the optimal combination of trastuzumab with chemotherapy nor the sequences of chemotherapy and trastuzumab have been determined. In one clinical trial, weekly paclitaxel and trastuzumab showed a superior median overall survival with paclitaxel plus trastuzumab compared with paclitaxel alone (*J Clin Oncol* 2000;19:2587–2595). Weekly trastuzumab in combination with vinorelbine also has been shown to be highly active as a first-line therapy as well as in patients who had received prior chemotherapy (*J Clin Oncol* 2001;19:2722; *SABC* 2001;429a).

Trastuzumab is overall well tolerated with mild adverse side effects as compared with standard chemotherapy. The use of trastuzumab in combination with anthracyclines has been associated with severe cardiac toxicity in up to 16% of patients. Trastuzumab should not be used in combination with this drug class (*N Engl J Med* 2001;349:783).

The overexpression of HER2/neu can be measured by IHC methods and FISH of the pathologic specimen. Initial trials with trastuzumab required IHC positivity of 2+ or 3+ for enrollment. Current clinical trials are under way to look more closely at data presented in abstracts from ASCO 2001, in which the use of trastuzumab based on FISH positivity was associated with higher response rates and an improvement in survival. Based on data presented in clinical abstracts, when FISH was applied to archived tissue sections that were 2+ and 3+ by IHC, a significant benefit of the addition of trastuzumab for FISH-positive patients was seen compared with FISH-negative patients. The authors advocated that FISH testing is superior to IHC for the selection of patients that will have a significant improvement from the addition of trastuzumab to chemotherapy in advanced or MBC (*Proc Am Soc Clin Oncol* 2001;20:85; *Proc Am Soc Clin Oncol* 2001;20:86).

E. **High-dose chemotherapy and stem cell transplant**

High-dose chemotherapy (HDCT) rationale is based on overcoming drug resistance and eradicating micrometastatic disease, based on the knowledge that breast cancer is a moderately chemosensitive disease, and there may be a dose–response correlation. Patients receive higher doses of chemotherapy with subsequent bone marrow toxicity rescue with the replacement of autologous peripheral blood stem cells. Many initial single-institution phase II studies showed promising results with HDCT in patients with locally advanced breast cancer and/or multiple positive axillary lymph nodes. The largest U.S. trial evaluating high-dose chemotherapy was conducted by the CALGB in patients with stage II or III breast cancer involving 10 or more axillary lymph nodes. Preliminary data from the study show a 3-year survival rate of 68% in patients treated with high-dose chemotherapy compared with a 64% survival rate in those who did not receive stem-cell support (*Proc Am Soc Clin Oncol* 1999;18:1). The follow-up is not yet long enough to define any benefit to HDCT. Moreover, toxicities have been significantly higher in the HDCT group. To date, the results of available clinical trials have not shown improved disease-free and overall survival in patients treated with HDCT plus stem-cell support. Outside the context of a clinical trial, HDCT cannot be recommended for patients with primary or MBC.

F. **Breast cancer and pregnancy**

Breast cancer is the most common cancer in pregnant and postpartum women, with an incidence of 1 in 3,000 pregnancies. With many women choosing to delay childbearing, it is likely that the incidence of breast cancer during pregnancy will increase. Delays in diagnosis are common, often due to breast tenderness and engorgement in pregnant and lactating women, hindering the detection of a discrete mass. Because of the delay, breast cancers are typically detected at a later stage than in the nonpregnant, age-matched population. Overall the survival of pregnant women with breast cancer may be worse than that in nonpregnant women at all stages. However, the decreased overall survival in pregnant women may be due primarily to delay in diagnosis (*Cancer* 1991;67:869). Pregnant and lactating women should be encouraged to practice breast self examination (BSE) and undergo a clinical breast examination as a part of the routine prenatal care.

If an abnormality is found on breast examination, further diagnostic studies should be undertaken. Mammography, with proper abdominal shielding, poses little risk of radiation exposure to the fetus. If needed, a biopsy can be safely accomplished under local anesthesia. To avoid false-positive diagnosis as a result of misinterpretation of normal pregnancy-related breast changes, the pathologist should be advised that the patient is pregnant.

Surgery is recommended as the primary treatment of breast cancer in pregnant women. Modified radical mastectomy is the treatment of choice, based on the toxicity to the fetus from radiation therapy associated with breast-conserving surgery. If adjuvant chemotherapy is necessary, it should not be given during the first trimester to avoid the risk of teratogenicity. Chemotherapy given after the first trimester is typically not associated with an increased risk of fetal malformations, but data on the immediate and long-term effects of chemotherapy on the fetus are limited. Studies using adjuvant hormonal therapy alone or in combination with chemotherapy also are limited. No conclusions have been reached regarding the use of these treatment options. Women receiving chemotherapy should be reminded to not breast feed, because many chemotherapy agents are secreted in breast milk. Radiation therapy should be withheld until after delivery because it may be harmful to the fetus at any stage of development. Termination of a pregnancy has not been shown to have any beneficial effect on breast cancer outcome and is not considered a therapeutic option. Termination of a pregnancy may be considered, based on the age of the fetus, and if treatment options, such as chemotherapy and radiation therapy, are limited by the continuation of the pregnancy.

Women who wish to bear children after treatment for primary breast cancer may seek advice as to whether pregnancy increases the chances of disease recurrence. Current data do not support that subsequent pregnancy adversely affects the survival of women with a history of early-stage breast cancer. This is based on limited retrospective data (*J Clin Onco*l 2001;19:1671). In one retrospective study from the International Breast Cancer Study Group (IBCSG), a superior survival was seen in women with early-stage breast cancer with subsequent pregnancies. This effect likely represents a healthy patient–selection bias, but also may be consistent with an antitumor effect of pregnancy (*J Clin Onco*l 2001;19:1671). Some physicians recommend that a woman wait 2 years after diagnosis before attempting to become pregnant. Most breast cancer recurrences are in the first 2 years after diagnosis; thus an early recurrence may affect a woman's decision to conceive.

G. Male breast cancer

Fewer than 1% of all breast cancers occur in men. About 1,500 new cases were diagnosed in the United States in 2001, and 400 men died of the disease (*CA Cancer J Clin* 2001;51:15). The average age at diagnosis is between 60 and 70 years, although the disease can affect men of all ages. Predisposing risk factors include radiation exposure, estrogen administration, and diseases associated with higher estrogen states, such as cirrhosis or Klinefelter syndrome. An increased risk of male breast cancer has been noted in families in which the BRCA2 mutation is identified. Infiltrating ductal carcinoma is the most common pathologic subtype, as in female breast cancer patients. About 85% of all male breast cancers are ER positive (*Am J Epidemio*l 1992;135:734). Lymph node involvement, hematogenous pattern of spread, prognostic factors, and overall survival are similar to those seen in female breast cancer patients. Primary surgical treatment consists of a modified radical mastectomy with ALND. Recommendations for adjuvant therapy are the same as those for a woman with a similar stage of breast cancer, as there is no evidence that response to therapy is different between men and women. In node-positive men, both adjuvant chemotherapy and hormonal therapy have been used and can reduce the risk of recurrence and increase survival to the same extent as demonstrated in women with breast cancer. For metastatic disease, hormonal therapy, chemotherapy, or a combination of both have been used with some success (*Am J Epidemio*l 1992;135:734). Hormonal therapies include tamoxifen, progestins, aminoglutethimide, and LHRH agonists, and orchiectomy. Although randomized clinical trial data on the use of aromatase inhibitors have been in women with MBC, one would not expect a difference in their use based on sex differences. The inhibition of conversion of adrenal androgens to estrogen by aromatase inhibitors should be just as effective in men with MBC as that demonstrated in clinical trials with women. Enrollment in men in MBC protocols will help further delineate the effectiveness of hormonal therapy and best quantify the adverse side effects related to hormonal therapy.

IV. Complications of therapy

A. Lymphedema

Lymphedema is a common and troublesome problem that develops in 15% to 20% of patients after breast cancer treatment (Harris J, et al., eds. *Diseases of the breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:1033). Physical discomfort and upper-extremity disability are associated with the swelling and arm enlargement, and recurrent episodes of cellulitis and lymphangitis are common. The incidence and degree of lymphedema are correlated with the extent of surgical dissection and axillary radiation. The use of SLN biopsy should decrease the incidence of lymphedema; however, the use of axillary radiation with SLN biopsy still introduces the risk.

Prevention of lymphedema after surgery or radiation therapy is based on the principle of avoidance of obstruction to lymphatic flow in the affected arm. Patients should be given instructions that include avoidance of blood pressure monitoring, blood draws or intravenous access, constrictive clothing, and heat or strenuous activity to the affected arm. Rehabilitation therapy with massage, compression garments, and intermittent pneumatic pumps can be effective in the long-term management of lymphedema. Surgery and diuretics are not effective treatment modalities.

B. Radiation therapy

Many tissues of the body require cellular proliferation for their function and can promptly display the side effects of radiation therapy. Acute toxicities associated with chest-wall irradiation typically involve the skin. Toxicities can be minimized with current radiation-delivery techniques and careful delineation of the target volume. Late toxic effects of radiation therapy, although uncommon, can include radiation pneumonitis, cardiac events, arm edema, brachial plexopathy, and the risk of second malignancies. The overall incidence of symptomatic radiation pneumonitis is approximately 1% (Harris J, et al., eds. *Diseases of the breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:540). There is a potential association with increased cardiac morbidity related to radiation in women with left-sided breast cancers. Radiation-induced injury to the brachial plexus is a rare clinical entity. The rate of second malignancies, primarily bone or soft-tissue sarcomas, after radiation therapy is very low, with long-term risk at 0.2% at 10 years. Another possible complication is the induction of another breast cancer. The latency period between exposure and the detection of a malignancy is at least 5 years. Tumor induction in the contralateral breast due to dose of exposed radiation also is a concern. The highest risk appears to occur in young (younger than 45 years) women, with the risk declining with the increasing age of radiation exposure. Smokers may have a small increased risk of lung cancer in the ipsilateral lung, given that the effects of smoking and radiation may be multiplicative in carcinogenesis.

C. Tamoxifen

Tamoxifen is extremely well tolerated by most patients with breast cancer. In large randomized trials with tamoxifen, fewer than 5% of patients withdrew from therapy because of related toxicities. The most common side effects from tamoxifen include hot flashes and vaginal discharge or irritation. Clonidine or the newer antidepressants can lessen the severity of hot flashes in some patients. In one NCCTG trial presented at ASCO 2000, venlafaxine was found to substantially reduce hot flashes compared with placebo (*Proc Am Soc Clin Onco*l 2000;19:9).

The development of endometrial cancer in women taking tamoxifen occurs at a rate 2 to 7 times greater than in women not taking the drug. Nearly all reported endometrial cancers have been in postmenopausal women. The endometrial cancers are typically of lower grade and stage, similar to those associated with estrogen therapy (*N Engl J Med* 1998;339:1609–1618). Endometrial hyperplasia and ovarian cysts also have been associated with tamoxifen use. Women taking tamoxifen should have yearly pelvic examinations, and any abnormal vaginal discharge or bleeding should be evaluated promptly. The value of endometrial biopsy, hysteroscopy, and transvaginal ultrasound as screening tools for endometrial cancer in asymptomatic women taking tamoxifen has not proven effective. An increased incidence of thromboembolic events also has been attributed to tamoxifen use. This complication occurs in fewer then 1% of patients given tamoxifen, but deaths due to thromboembolism have been recorded (*N Engl J Med* 1998;339:1609–1618). Retinopathy has been reported in women given high doses (40 mg daily) of tamoxifen. Conventional doses of tamoxifen can be associated with cataracts, and patients with visual complaints should be assessed carefully.

Tamoxifen also has some beneficial estrogenic effects. The drug has been shown to decrease total and low-density lipoprotein levels and decrease the incidence of cardiac disease in postmenopausal women. Controlled studies also have associated tamoxifen use with preservation of bone mineral density in postmenopausal women, but it is associated with a decrease in bone mineral density in premenopausal women (*N Engl J Med* 1998;339:1609–1618). Although tamoxifen is associated with an increased risk of thromboembolism and endometrial cancer, the benefit of tamoxifen outweighs the risk in the majority of women in breast cancer treatment.

D. **Chemotherapy**

Chemotherapy is associated with several well-characterized adverse side effects that vary according to the individual drugs in each regimen. For more details on side effects related to specific chemotherapy drugs, see Chapter 2. Common side effects of chemotherapy include nausea and vomiting, myelosuppression, alopecia, and mucositis. The combination of serotonin (5-HT_3) antagonists and dexamethasone helps control both acute and delayed nausea and vomiting far better; nausea remains a common complaint in breast cancer chemotherapy treatment. The localization of substance P in the brainstem region, associated with nausea and vomiting, has led to the use of neurokinin-1–receptor antagonists as a potential new antiemetic regimen in patients receiving chemotherapy (*N Engl J Med* 1999;340:190).

Anthracyclines are associated with a risk of cardiac toxicity. In a retrospective analysis, the overall incidence of drug-induced congestive heart failure (CHF) was 2.2% (*Ann Intern Med* 1979;91:710). The probability of developing anthracycline-induced CHF was related to the total dose of doxorubicin administration and advancing age. The current acceptable total cumulative dose of doxorubicin in standard adjuvant regimens is 360 mg/m ^{2}. Epirubicin, which is now FDA approved in the United States, is less cardiotoxic than doxorubicin at equimolar doses and can be administered at cumulative doses as high as 720 mg/m ^{2}. A high incidence of cardiotoxicity (18% to 21%) was noted with the combination of paclitaxel and doxorubicin in phase II trials. The presumed mechanism for increased cardiotoxicity is the concentration of polyoxyl-35 castor oil (Cremophor EL) in the formulation of paclitaxel (*N Engl J Med* 1997;332:1004). Data from more recent clinical trials suggest that the combination of paclitaxel and doxorubicin (AT) can be given safely as adjuvant therapy for a total of up to six cycles, with an overall incidence of CHF of 4% reported (*Proc Am Soc Clin Oncol* 1998;17:444). There are three ways to avoid the potential increased risk of cardiotoxicity with anthracyclines: building an interval between the dose of doxorubicin and paclitaxel, reducing the total dose of doxorubicin (240 mg/m ^{2}), or using docetaxel. There appears to be no pharmacokinetic interaction between docetaxel and doxorubicin, as docetaxel is not mixed with the preservative Cremophor EL. The indications for the use of pegylated liposomal doxorubicin (Doxil) also are expanding. Cumulative doses in excess of 500 mg/m ^{2} appear to carry considerably less risk of drug-induced CHF than is generally accepted with doxorubicin (*Ann Oncol* 2000;11:1029). More data are needed with randomized clinical trials to address fully the benefit of the use of Doxil in breast cancer adjuvant chemotherapy regimens. Dexrazoxane is a potential anthracycline chemoprotectant. At present, there is insufficient evidence on which to recommend the use of dexrazoxane in patients with cardiac risk factors or underlying cardiac disease who receive doxorubicin-based chemotherapy outside the setting of a clinical trial (*J Clin Oncol* 1999;17:3333).

Hypersensitivity reactions can occur during the infusion of either docetaxel or paclitaxel, although the incidence is higher with paclitaxel. Premedication with oral corticosteroids reduces the incidence and severity of hypersensitivity reactions. Paclitaxel administration necessitates premedication with diphenhydramine, 50 mg i.v., and an H_2 antagonist 30 to 60 minutes before the drug infusion, in addition to dexamethasone, 20 mg p.o, given 12 and 6 hours before the drug. The treatment of moderate to severe hypersensitivity reactions is with intravenous fluids, diphenhydramine, 50 mg i.v., with or without dexamethasone, 10 mg i.v., and epinephrine. Fluid retention is another problematic toxicity related to docetaxel. It is reversible after the discontinuation of the taxane. Dexamethasone, 8 mg p.o., q12 hours × 3 days (or six doses), beginning the day before the administration of the drug, is beneficial in ameliorating the side effect of fluid retention (*N Engl J Med* 1997;332:1004). Managing the edema at early stages (new-onset or 2-pound weight gain) with an oral diuretic reduces advanced fluid retention.

E. **Bone metastases**

Although patients with bone-only metastatic disease have a better prognosis than those with visceral metastases, bone metastases are a catastrophic complication of breast cancer that lead to pain, fractures, spinal cord compression, and hypercalcemia. Significant understanding of the biology of bone metastases have enhanced our knowledge of its pathogenesis and led to the development of new treatment strategies. Under the direct influence of metastatic tumor cells, a variety of cytokines are released, which are responsible for osteoclast stimulation and osteolysis. Chemotherapy and hormonal therapy specifically treat the cancer itself, but have a limited role in arresting the progression of osteolysis.

Traditionally, treatment of symptomatic bone metastases has consisted of potent analgesics, localized radiation, or surgery. Although improvements in pain and quality of life have been obtained from the use of these therapeutic options, the prevention of the progression of bone lytic metastases has been ineffective. Dramatic results from clinical investigations have shown that bisphosphonates have a potent inhibitory effect on osteoclast activity and subsequent bone resorption and osteolysis. Several studies have evaluated the use of bisphosphonates, either alone or as adjunctive therapy to primary cancer treatment, and have shown strong evidence of reduction in bone pain and a decrease in the progression of lytic bone metastases. Intravenous pamidronate infusion (90 mg i.v., over a period of 2 hours) was the first bisphosphonate to demonstrate that patients with skeletal metastases had fewer skeletal-related events and had a significant reduction in bone pain and analgesic use (*J Clin Oncol* 1998;16:2038). Zoledronic acid is an alternate intravenous bisphosphonate that is 1,000 times more potent than pamidronate and has been shown to be effective in the management of osteolytic metastases.

Initial clinical trials with pamidronate also showed a trend to improved overall survival and a potential antineoplastic effect. Further studies of bisphosphonates in the adjuvant setting have yielded inconsistent results. Starting bisphosphonates in patients without evidence of bony metastasis, even in the presence of other visceral metastases, is not recommended outside of clinical trials, despite a high risk for future bone metastasis. The NSABP B-34 trial is currently randomizing patients to the use of clodronate therapy versus placebo in patients receiving either adjuvant chemotherapy or hormonal therapy in early-stage breast cancer to look for an improvement in disease-free survival.

Bisphosphonates should be started when bone metastases are first diagnosed and continue for 24 months or for as long as active treatment is given for metastatic disease. Pamidronate and zoledronic acid are well suited for outpatient administration. Bisphosphonates are generally very well tolerated, with occasional transient “flu-like” symptoms or myalgias early in therapy. Pretreatment with analgesics or antipyretics may be useful. Renal toxicity has been demonstrated with rapid infusions (less than 1 hour) of pamidronate and escalating doses (more than 4 mg) of zolendronate. Pamidronate should be given as a 90-mg i.v. dose over a 1.5- to 2-hour period every 3 to 4 weeks. Zoledronic acid is given as a 4-mg dose over a 15-minute period every 3 to 4 weeks. Serum calcium, electrolytes (including phosphate and magnesium), creatinine, and CBC should be monitored on a monthly basis.

V. **Follow-up**

The scheme of follow-up should be individualized to reflect a patient's risk of recurrence. All women with one breast cancer are at an increased risk for the development of a new contralateral primary tumor. This risk is approximately 1% per year. The role of routine laboratory testing and imaging studies to detect metastatic disease when it is asymptomatic is controversial. A prospective, randomized trail has demonstrated no survival benefit for routine testing compared with a careful history and physical examination with further studies directed by symptoms (*JAMA* 1994;271:1593). The clinical role of tumor markers (CEA, CA 15-3) is unproven, and the use of these studies in follow-up will be elucidated by future clinical trials and research. Patients taking tamoxifen should have yearly gynecologic examinations because of the increased risk of endometrial carcinoma. Whether patients need a periodic ophthalmologic examination more often than the general age-matched population is unknown at this time (*N Engl J Med* 1998;339:1609–1618).

Current recommendations for follow-up office visits with an accompanying history and physical examination are every 3 months for the first year after diagnosis, and then every 4 to 6 months for the second to fifth year after diagnosis. Thereafter, an annual office visit and physical examination are appropriate. Particular attention in the physical examination should be placed on areas of metastasis, including bilateral breast examination, lymph nodes, liver, chest wall, and bones. A chest radiograph, routine laboratory data, and mammography should be performed yearly. A mammogram of the radiated breast is typically recommended every 6 months for the first 1 to 2 years (*Proc Am Soc Clin Oncol* 1994;13:77). However, mammography is more difficult to interpret after radiotherapy than after conservative surgery alone, and may lead to extra diagnostic tests and findings that will be negative at confirmation. The routine use of computed tomography scans or bone scans has been shown to be of no benefit and can be performed as indicated by the patient's symptoms.

VI. **Background**

A. **Epidemiology**

Breast cancer is the most commonly diagnosed malignancy in women (other than skin cancer) and follows only lung cancer as the leading cause of cancer deaths among women. In 2002, it is estimated 203,500 new breast cancers will be diagnosed in the United States, and 39,600 deaths will occur from the disease (*CA Cancer J Clin* 2001;51:15). A woman has a 12% lifetime risk of developing breast cancer and a 3.5% chance of dying of it. Although the incidence of breast cancer has been increasing steadily over the past two decades, mostly because of earlier detection through public awareness and mammography, the mortality from breast cancer has remained relatively constant since the 1950s. White, Hawaiian, and African-American women have the highest rates of breast cancer incidence. Asian and Hispanic women have lower incidence rates, up to two thirds the rates seen in white women. The lowest

incidence is among Korean, Native American, and Vietnamese women. In contrast to white women, black women are generally younger, have larger tumors at diagnosis, and a smaller percentage have hormone receptors in the tumor, which contributes to an associated poorer overall prognosis. However, in cases of similar clinical presentation, adjuvant treatment gives similar benefits to both black and white women (Miller BA, Kolonel LN, Bernstein L, et al., eds. *Racial/ethnic patterns of cancer in the United States 1988–1992.* Bethesda: National Cancer Institute, 1996: NIH Pub No. 96-4104).

B. **Identifiable risk factors**

Although the majority of women diagnosed with breast cancer have no known predisposition, risk factors for the development of breast cancer include age, family history, history of breast cancer or benign breast disease, and hormonal and environmental factors. The median age for the diagnosis of breast cancer is between the ages of 60 and 65 years. In addition, the incidence and risk of developing breast cancer increases with age (Table 7.15).

By age 30	1/2,212
By age 40	1/235
By age 50	1/54
By age 60	1/23
By age 70	1/14

From American Cancer Society. *Cancer risk report: prevention and control, 1997*. Atlanta: American Cancer Society, 1998, with permission.

TABLE 7.15. COMPARISON OF AGE AND RISK OF DEVELOPING BREAST CANCER

1. **Family history.** Fewer than 10% of all breast cancers are hereditary, yet women with a family history of breast cancer may be at an increased risk of disease (Table 7.1). The BRCA1 and BRCA2 genes have been identified and linked with inherited breast cancer. Women with mutations in the BRCA1 or BRCA2 gene have an estimated 40% to 85% lifetime risk of developing breast cancer (*J Natl Cancer Inst* 2000;92:1126). The BRCA1 gene is located on the long arm of chromosome 17 and is associated with a concomitant increase in ovarian malignancies. BRCA2 is located on the long arm of chromosome 13 and is associated with male breast and prostate cancer. Other familial syndromes associated with a genetic inheritance of breast cancer risk include Li–Fraumeni and Cowden syndrome. Li–Fraumeni syndrome is responsible for hereditary breast cancers, sarcomas, and other tumors types due to mutations in the tumor-suppressor gene, p53. Cowden syndrome is characterized by hereditary breast cancer, gastrointestinal malignancies, thyroid disease with mucocutaneous lesions, and is related to mutations in PTEN, a protein tyrosine phosphatase located on chromosome 10.
2. **History of breast cancer.** Women with a previous breast cancer have a threefold to fourfold increase in risk of a second breast cancer in the contralateral breast. Most studies report an annual risk of development of a second breast cancer of 0.5% to 0.7% (*J Am Col Surg* 1994;178:390). Whereas the risk of contralateral breast cancer persists for up to 30 years after the original diagnosis, the median time interval between primary diagnosis and contralateral disease is 4 years (*Cancer Causes Control* 1996;7:382).
3. **Benign breast disease.** Nonproliferative breast lesions such as cysts, fibroadenomas, or ductal ectasia are not associated with an increased risk for breast cancer. Proliferative breast lesions with or without atypical hyperplasia carry an increase in risk of development of breast cancer compared to that of women with nonproliferative lesions (*Cancer* 1996;78:1024). LCIS is associated with the highest risk for development of an invasive malignancy (Table 7.1).
4. **Hormonal factors.** Estrogen plays an integral role in the growth and development of breast cancer cells. This is reflected in the increase risk of developing breast cancer associated with longer exposure to endogenous estrogens, such as early menarche (before age 12), late menopause (after age 55), and first pregnancy after age 30 or nulliparity.

   Oral contraceptive (OCP) and estrogen replacement therapy (ERT) use and their association with breast cancer have been studied extensively. A recent meta-analysis published in *The Lancet* looked at 54 studies assessing the association of OCP use and breast cancer and identified a small, but statistically significant increase in relative risk in current OCP users and in those who had used OCPs in the previous 1 to 9 years. Overall, the meta-analysis found that 10 years or more after discontinuation of OCP use, the risk of breast cancer was identical among former OCP users and those who never used OCPs (*Lancet* 1996;347:1713). In studies evaluating the risk of ERT and the development of breast cancer, results have been contradictory. ERT is associated with a small increase in incidence of breast cancer. Risk appears to increase with current use and duration of use. Several recent studies suggested that breast cancer arising in postmenopausal women receiving ERT is histologically more favorable than that of women not taking ERT. Furthermore, the increased risk of breast cancer appears to be reduced after stopping ERT (*J Clin Oncol* 1996;14:997). Overall, the health benefits of ERT for postmenopausal women outweigh the risk of developing and dying of breast cancer.

5. **Environmental factors.** Women exposed to chest-wall radiation during childhood (ages 10 to 19) for Hodgkin disease have been shown to be at an increased risk for developing breast cancer throughout their lives. The risk associated with radiation exposure is inversely correlated with age, and it is relatively low if the exposure occurs after age 40 years. Other environmental factors, such as alcohol, dietary fat, or cholesterol intake, have not been shown conclusively to be associated with an increased risk of breast cancer.

C. **Histopathology of breast cancer**

Most invasive breast cancers are adenocarcinomas, which can be quite heterogeneous in histologic appearance. The adenocarcinomas can be classified into several different subtypes with varying prognostic implications. Infiltrating (invasive) ductal carcinoma accounts for approximately 80% of all breast cancers and originates from the cells lining the ducts of the breast. Infiltrating ductal carcinomas metastasize predominantly to the bones, liver, lungs, and brain. Lobular carcinomas make up 10% of malignant breast cancers and originate from the terminal ductules of the breast lobules. Lobular carcinomas are associated with bilateral tumors in up to 20% of cases, and also tend to be associated with multicentric disease within the same breast. Although the overall prognosis is similar to that for invasive ductal carcinomas, lobular carcinomas have a predilection to metastasize to the meninges, serosal surfaces, and to mediastinal and retroperitoneal lymph nodes.

Less common histopathologic types of breast carcinomas include medullary, tubular, mucinous, and papillary. These variants are typically well differentiated and carry a relatively favorable prognosis. Paget disease of the nipple is a specialized form of ductal carcinoma that arises from the main excretory ducts in the breasts and extends to involve the skin of the nipple and areola. Inflammatory carcinomas infiltrate widely throughout the breast tissue and involve the lymphatic structures in the dermis, producing swelling, erythema, and tenderness in the involved breast. Inflammatory carcinomas are not a special morphologic pattern, but imply widespread dissemination.

D. **Screening**

Historically, breast cancer has been diagnosed when a woman seeks medical attention for a breast mass or tenderness. Monthly BSE is frequently advocated as a screening tool for breast cancer, but there is little evidence for its effectiveness in reducing mortality rates in breast cancer. However, monthly BSE is inexpensive and may promote stronger health and personal awareness. The BSE is most useful in conjunction with a clinical breast examination (CBE) by an experienced physician and mammography. Between 14% and 21% of breast cancers are detected by a CBE. The American Cancer Society (ACS) recommends that a CBE should be performed every 3 years in women aged 20 to 39 years, and yearly in women older than 40 years (American Cancer Society. *Cancer risk report: prevention and control, 1997*. Atlanta: American Cancer Society, 1998).

Screening mammography is performed on asymptomatic patients to detect occult breast cancer. The current screening recommendations for average-risk patients is a mammogram every 1 to 2 years beginning at age 40 years. Currently no data support the role of a “baseline” mammogram between ages 35 and 40 years. For ages 50 and older, there is universal agreement that yearly screening mammography should be performed, and it is associated with up to a 30% reduction in breast cancer mortality in this age group (American Cancer Society. *Cancer risk report: prevention and control, 1997*. Atlanta: American Cancer Society, 1998). In women with a strong family history of breast cancer, annual mammography should begin 5 to 10 years earlier than the age at which a family member developed breast cancer. Screening for women with a genetic risk may begin as early as age 25 years. Presently, there is no role for

breast ultrasound or magnetic resonance imaging (MRI) as screening tests. Ductal lavage is an investigational technique using the introduction of a saline solution into one of the mammary ducts on the surface of the nipple through a thin, flexible catheter. The fluid collected from the ducts is then analyzed for malignancy.

E. **Current focus**

During the past decade, major advances in the treatment of breast cancer have resulted from analyses of large prospective randomized trials. To further the knowledge of the treatment of breast cancer, every effort should be made to enroll all patients in clinical trials. In the area of the treatment of breast cancer, many important questions remain to be answered.

In the context of hormonal therapies, further randomized clinical trials should be conducted the better to define the risks and benefits of continuing tamoxifen therapy for longer than 5 years. Other studies are needed in exploring the value of combined hormonal therapy and identify its role in the hormone-receptor–positive patient population. The new SERMs, aromatase inhibitors, and trastuzumab also should be examined in the adjuvant setting.

Current studies are looking at determining the clinical and biologic characteristics of breast cancer that may more accurately predict the effectiveness of specific adjuvant treatments in individual patients. Although adjuvant therapy has been found to produce significant improvements in DFS and OS, the ability to predict the value of these treatments in an individual patient is limited. The development of accurate predictors of treatment efficacy would permit better targeting of individuals for treatment and lower rates of toxicities and morbidity related to treatment. The integration of new technologies, such as tissue microarrays and proteomics may help to detect clinically important differences on a genetic level. The value of SLN biopsy and the development of sensitive assays for micrometastatic disease in lymph nodes and bone marrow also will make a large impact on clinical research.

New frontiers with molecular-targeted therapies and angiogenesis inhibitors, such as endostatin, anti-VEGF (vascular endothelial growth factor) compounds, EGF (epidermal growth factor) inhibitors, antisense compounds, and monoclonal antibodies will be important in the near future. Ongoing trials are evaluating a wide range of agents to reduce the risk of breast cancer, including differentiating agents, such as a variety of retinoids. Vaccine trials are currently under way in the therapeutic management and prevention of breast cancer.

Despite all the efforts medical science has made in the treatment of breast cancer, individual patients may differ in the amount of importance they place on the risks and benefits of treatment. Further studies to address a wide variety of quality-of-life issues should be done in selected randomized clinical control settings to examine the impact of both short- and long-term side effects of adjuvant treatment of breast cancer, particularly premature menopause and hot flashes, memory loss, fatigue, and weight gain.

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CHAPTER 8. CENTRAL NERVOUS SYSTEM TUMORS

Dennis Rivet, Michael Chicoine, Joseph Simpson, and Matthew A. Arquette

Approach to the patient with tumors of the central nervous system
General
Presentation
Brain metastases
Brain metastases
Presenting signs and symptoms
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Ependymoma
Meningioma
Meningiomas are benign
Pituitary adenoma
The anterior pituitary gland
Functional adenomas
Radiographically
Treatment
Primary central nervous system lymphoma
Primary central nervous system lymphoma
Imaging
Other useful tests
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Embryonal tumors
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Background
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Future directions
Suggested Readings

I. **Approach to the patient with tumors of the central nervous system**
   A. **General.** Tumors of the central nervous system (CNS) include a variety of diseases with highly variable presentations and natural histories. These rare tumors occur in both pediatric and adult populations. The histologic types are varied, but gliomas are the most frequent.
   B. **Presentation.** Most patients have signs or symptoms from one of three general categories: a progressive neurologic deficit, headaches, or seizure.
      1. **Evidence of localized brain dysfunction** due to the presence of a tumor results in a pattern of deficits relating to the specific location. This may result from physical compression or invasion of adjacent brain parenchyma by tumor. Deficits such as hemiparesis or altered mentation and/or consciousness may resemble a stroke or transient ischemic attack. A widely variable time course of symptoms often results in a delay in diagnosis of slow-growing tumors (e.g., meningiomas or well-differentiated gliomas).
      2. **Headaches** may result from mass effect itself or obstructive hydrocephalus. The classic pattern of being worse in the morning may be related to hypoventilation during sleep, causing hypercapnia and vasodilation, which increases the intracranial pressure. Posterior fossa tumors may produce hydrocephalus and severe headache accompanied by nausea, vomiting, lethargy, and visual problems. Emesis often yields temporary relief.
      3. **Seizures** are another common first manifestation of brain tumors. An idiopathic seizure for the first time after age 18 years should prompt aggressive investigation for a tumor. Locations such as the temporal lobe or cerebral hemisphere are more likely to result in seizure, whereas pituitary and posterior fossa tumors are unlikely.
      4. **Spinal neoplasms** also vary widely in their presentation based on their nature and location. The most common presenting symptom is pain, often worse when lying supine and localized to the region of the tumor. Other common manifestations include numbness, weakness, paresthesias, and bowel or bladder dysfunction.
      5. **Physical examination** of the patient with a CNS tumor should begin with a careful neurologic examination, assessment of the cranial nerves, motor and sensory examination, and assessment of reflexes and coordination. Funduscopic examination is used to assess for papilledema, a sign of increased intracranial pressure. A general physical examination and assessment of performance status is important for determining the overall health of the patient, comorbid conditions, potential sources of metastatic spread to the CNS, and functional status. The use of tests such as the Mini-Mental Status Examination, interpretation of proverbs, and the ability of the patient to follow commands may assess higher function.
      6. **Diagnosis and evaluation**
         a. **Radiographic imaging.** Since the inception of computed tomography (CT) scanning in 1973 and magnetic resonance imaging (MRI) in the mid-1980s, imaging of the nervous system has been revolutionized. Part of the increased incidence of neurologic malignancies has been ascribed to common use of these imaging techniques. The initial evaluation of patients suspected of having a brain neoplasm should consist of an MRI with and without the administration of gadolinium contrast. MRI is more sensitive than CT and provides multiplanar imaging. CT remains a useful evaluation in the setting of bony involvement of tumors, an acute neurologic deterioration, and to assess the degree of calcification. Ultrasound may be useful for the initial evaluation of the infant and for surgical planning. Positron emission tomography (PET) is often used to differentiate tumor progression from radionecrosis. Imaging modalities that are linked to the metabolic activity of tumors, such as functional magnetic resonance imaging (fMRI) are being refined and are useful in the depiction of the primary motor, sensory, and language cortex. Magnetic resonance spectroscopy is a developing technique that is currently being used to help differentiate between primary CNS tumors and metastases.
         b. **Classification.** Tumors can be divided based on location, cell type of origin, histologic appearance, or the age group they affect.
            1. **Grading of tumors.** Many different grading and classification schemes have been used over the years. The World Health Organization (WHO) grading scale is commonly used in diagnostic and treatment protocols. Table 8.1 lists the most common tumors with their typical WHO grade in the WHO classification scheme. Tumors are arranged by cell type and malignancy potential, or grade.

Most Common Tumors	WHO Grade
Pilocytic astrocytoma	1
Astrocytoma	1–2
Anaplastic (malignant) astrocytoma	3–4
Glioblastoma	4
Oligodendroglioma	1–2
Anaplastic oligodendroglioma	3–4
Mixed oligodendroglioma/astrocytoma	1–4
Ependymoma	1–2
Anaplastic (malignant) ependymoma	3–4
Primitive neuroectodermal tumor (PNET)	4
Medulloblastoma	
Cerebral or spinal PNET	
Schwannoma	1
Neurofibroma	1
Meningioma	1
Atypical meningioma	2–3
Anaplastic (malignant) meningioma	4
Primary malignant lymphoma	3–4
Pituitary adenoma	1

From AJCC cancer staging manual. 5th ed. Philadelphia: Lippincott-Raven, 1997:282, with permission.
WHO, World Health Organization.

TABLE 8.1. WHO CLASSIFICATION OF COMMON TUMORS

2. **A tumor's "malignancy" describes a tendency toward an aggressive growth rate** and infiltrative nature. The "benign" or lower-grade tumor suggests only slow growth, and these tumors may still have rare malignant transformation. A low-grade or indolent lesion may be incurable or cause severe morbidity, even death, because of its location. For these reasons, the terms malignant and benign are often misleading in describing CNS tumors. With a few notable exceptions, a tendency to metastasize is not a component of malignant behavior. In certain cases, medulloblastomas, ependymomas, and, less commonly, other gliomas disseminate to other locations, usually restricted to the neuraxis.
3. **Location.** The tentorium divides the intracranial space into infratentorial and supratentorial compartments. This anatomic distribution serves to separate both age incidence and typical clinical manifestations. The majority, approximately 60%, of pediatric intracranial malignancies occur in the posterior fossa or infratentorial location. They often have severe headache, vomiting, ataxia, and nystagmus or Parinaud syndrome (paralysis of upward gaze and convergence, rotatory nystagmus).

7. **General guidelines of treatment.** The specific role that surgery, radiation, and chemotherapy may play in the management of CNS tumors is dependent primarily on tumor type and classification. Some general principles of treatment are broadly applicable.
   a. **Surgery.** The goals of surgical treatment for tumors of the CNS are relief of symptoms, tissue diagnosis, and cytoreduction. Examples of symptoms that may be relieved after resection are seizures, headaches, and neurologic dysfunction related to mass effect from a tumor. Options for obtaining a tissue diagnosis include a resection of the tumor or a biopsy. Biopsy can be done by using a stereotactically guided needle technique or an open biopsy in situations in which the tumor cannot be safely or easily accessed with needle techniques. In general, surgical resection offers the greatest magnitude of cytoreduction and, although it is usually not curative for intrinsic gliomas, may cure many lower-grade CNS tumors. In all cases, consideration must be given to patient age, functional status, medical condition, neurologic status, likely diagnosis, prior treatments, and possible complications to determine when surgery is most appropriate.
   b. **Radiation** plays a significant role in the management of both primary and metastatic CNS tumors. The degree of success is determined by the responsiveness of such tumors to the doses of radiation therapy tolerated by normal brain tissue. When used as a definitive therapy, irradiation is given over a multiweek course of daily or occasionally twice-daily fractionations to a total dose expected to produce long-term tumor control or even cure. When used in a palliative sense, radiation courses are shorter, with a higher dose being delivered per fraction, and the aim being temporary relief of symptoms, although such relief can last for a year or more.
      1. **The tolerance of the CNS** to fractionated radiation therapy depends on volume treated, fraction size, and total dose. Typically, 5,400 to 6,000 cGy delivered at 180 to 200 cGy per day is considered tolerance for the nervous system, with the expectation that approximately 5% of patients so treated would develop symptoms of radiation injury within a 5-year period. These doses are adequate for rather durable control of such tumors as childhood medulloblastoma, certain low-grade astrocytomas, and a proportion of anaplastic oligodendrogliomas or ependymomas. It is less effective in producing durable long-term control of anaplastic astrocytoma or glioblastoma multiforme (GBM). The effective dose for long-term control for these latter two tumors has not been found and remains limited by normal tissue tolerance at present.
      2. **Approaches to increase radiation dose** above 60 to 70 Gy to restricted volumes have yielded results that suggest an alteration in relapse pattern may be achieved by focal escalation of dose by means of brachytherapy or radiosurgery. However, a major need is for development of agents that will either selectively sensitize tumor cells or alternatively protect the normal glial, neuronal, and vascular tissues incidentally exposure to irradiation.
      3. **When palliative treatment is given,** for example, for multiple metastases to the brain, or for spinal cord compression, the treatment course is usually approximately 2.5 to 3 weeks, with 250 to 300 cGy delivered daily. When a significant mass effect is exerted in either organ, steroids are generally begun before therapy and are tapered as tolerated.
      4. **Certain specialized radiotherapy treatments** are particularly useful for primary or metastatic brain tumors. These include radiosurgery, the use of a large single dose of irradiation with the Gamma Knife, or a modified linear accelerator (Linac) and intensity-modulated radiation therapy (IMRT). These techniques, where available, have the advantage of distributing radiation doses more precisely within a radiographically defined tumor with maximal sparing of surrounding normal brain tissue in either a single fraction or multiple fractions. These techniques are finding additional usefulness in primary tumors as well as in the management of patients with recurrence of CNS tumors.
      5. **Whole-brain radiotherapy** (WBRT) is used in three main situations. One is in the definitive treatment of medulloblastoma where craniospinal irradiation is used. Another is in the instance of multiple brain metastases when more focal treatment would be inadequate. Third is in the case of meningeal carcinomatosis, along with intrathecal chemotherapy. In nearly all other situations, partial brain irradiation, preferably with three-dimensional conformal radiotherapy techniques, is used. This is to spare the maximal amount of normal brain tissue from the potentially deleterious late effects of irradiation.
      6. **Stereotactic radiosurgery** represents the other extreme in terms of size and dose in radiation treatment of the CNS. This can be done with either a linear accelerator or the Gamma Knife. The principle here is to focus a very large single dose of radiation on one or a number of tumor targets, with minimal dose to the surrounding normal tissue because of very steep dose fall-off of 10% to 14%/mm. This technique can be used as a boost after partial brain irradiation for certain locally progressing gliomas or for retreatment of a small number of metastases. The doses typically used range from 1,400 to 2,400 cGy to the target boundary in a single fraction. This is in contrast to the usual daily dose for conventional radiation therapy of 180 to 200 cGy for definitive treatment or of 250 to 300 cGy for palliative whole-brain irradiation. In certain situations, radiosurgery alone is the treatment of choice (e.g., for acoustic neuromas, small inoperable meningiomas, and recurrent metastasis). The juvenile pilocytic astrocytoma in childhood and adolescence is a particularly focal type of glioma for which radiosurgery has been used in addition to partial surgical resection. In cases in which long-term survival is likely and CNS disease is limited, radiosurgery may be useful as a sole modality.
   c. **Chemotherapy** has a limited role in the treatment of primary and metastatic CNS tumors. Most commonly used chemotherapeutic agents are limited by their inability to cross the blood–brain barrier and low activity in these tumors. Although the median survival of patients with malignant gliomas is not improved by the use of chemotherapy in addition to other modalities, a subset of patients may enjoy prolonged survival with the addition of chemotherapy.
      1. **Active agents** in primary CNS tumors include the nitrosoureas, carmustine (BCNU), and lomustine (CCNU), alkalating agents including procarbazine and temazolamide, and vincristine.
      2. **Nitrosoureas** are associated with a delayed myelosuppression and are typically given on a schedule every 6 to 8 weeks. Single-agent BCNU is most often used in addition to radiation therapy and surgery in the treatment of glioblastoma multiforme (GBM).
      3. **Procarbazine, CCNU, and vincristine (PCV)** is used in the treatment of anaplastic astrocytomas and oligodendrogliomas. Procarbazine is a monoamine oxidase inhibitor and may be associated with hypertensive crisis in response to certain foods. Patients should be advised to avoid foods containing tyramine, including aged cheeses, red wine, and nuts. Allergies to procarbazine also are common. CCNU, an oral alkalating nitrosourea, may also cause delayed myelosuppression. Vincristine is associated with a syndrome of jaw pain associated with the first dose, and may cause a peripheral neuropathy.
      4. **Temozolomide** is a newer oral agent, similar to procarbazine and dacarbazine chemically, but with excellent CNS penetration. It has activity in anaplastic astrocytomas and some cases of GBM.
      5. **Other agents** that may have activity in some CNS tumors include platinum compounds and irinotecan. Gliadel wafers are an implantable depot form of BCNU that can be placed in the resection bed of patients with recurrent GBM. Methotrexate, given at high dose with leucovorin rescue or given intrathecally, is used in leukemia and lymphoma. Cytarabine also can be given intrathecally in hematologic malignancies. A liposomal formulation also is available for intrathecal therapy of lymphomatous meningitis.
   d. **Corticosteroids** are used in both primary and metastatic tumors of the CNS to control symptoms related to edema surrounding these tumors. Dexamethasone is most commonly used with initial doses of 4 to 10 mg i.v. or p.o. every 6 hours. This dose may be tapered over several weeks, as long as symptoms of the tumor do not worsen. Steroids may be started before radiation therapy for control of reactive edema during treatment. Generally, patients should be maintained on the lowest dose that controls symptoms, and a requirement for increasing doses may indicate progression of disease, whereas a decreasing steroid requirement is associated with response.

II. **Brain metastases**

A. **Brain metastases** from primary tumors that originate outside the CNS are overwhelmingly the most common intracranial tumors in adults. Autopsy studies have revealed the presence of intracranial metastasis in 24% of cancer patients. In those older than 65 years, the rate of CNS metastases increases to 42.7 per 100,000 population. More than 75% will originate from a primary tumor in the breast, respiratory tract, or melanoma in adults. In approximately 10% to 15% of cases, there may be no known primary tumor at the time of diagnosis. In the pediatric population, sarcomas and germ cell tumors are the most common sources.

B. **Presenting signs and symptoms** for intracranial metastases are similar to those of most brain neoplasms (i.e., focal neurologic deficit, headaches, and seizures). Tumors such as melanoma, choriocarcinoma, and renal cell carcinoma often occur with a symptomatic hemorrhage. Metastases may be single or multiple, and tend to be located at the grey–white junction. They are usually well circumscribed, demonstrate peripheral enhancement with the administration of contrast agents on CT or MRI, and often have a significant amount of associated edema. The finding of multiple lesions strongly supports the diagnosis of metastasis and is helpful in differentiating from primary tumors, infections, and other lesions. In a patient in whom a brain mass is discovered and no primary is known, the evaluation should focus on the lungs, as 65% of these patients will have a lesion on chest radiograph that represents a primary lung cancer or a pulmonary metastasis from systemic disease.

C. **Treatment** of metastatic disease should involve corticosteroids and, where appropriate, surgery and/or radiotherapy. Prognosis is related to age, Karnofsky

performance score (KPS), number of metastases, response to therapy, and progression of systemic disease. In older series, the median survival in untreated patients was 1 month. The addition of corticosteroids alone, typically dexamethasone (see earlier), prolongs survival to 2 months. WBRT combined with steroids increases the median survival to 3 to 6 months. Chemotherapy is seldom used and is usually reserved for asymptomatic, chemosensitive tumors.

1. **Solitary brain metastasis.** The current treatment of choice for solitary lesions in patients who are candidates for surgery is surgical excision combined with radiotherapy. Several randomized, prospective trials have demonstrated a survival benefit to resection plus WBRT over WBRT alone. Life expectancy increases to 12 to 14 months with combined surgery and radiation. Alternatively, many patients are treated with stereotactic radiosurgery, a technique of high-dose focal irradiation, if they have surgically inaccessible lesions or poorly controlled systemic disease. Several studies of radiosurgery have demonstrated survival benefit comparable to that with surgery. Current studies and areas of controversy are focusing on the role of surgery in multiple metastases, the need for postoperative WBRT versus stereotactic radiosurgery, and the role of stereotactic radiosurgery versus surgery in patients with small (less than 3 cm), accessible lesions.
2. Certain types of tumors originate in the CNS but still may metastasize, both within the CNS and systemically. Medulloblastoma, ependymoma, and hemangiopericytoma are all examples. Common systemic sites are bone and lung.

III. **Gliomas**

A. **Glial tumors** as a whole account for more than 50% of all primary brain tumors across all age groups. Glioma is a broad classification for tumors that derive from any of the glial cells types, mainly astrocytoma, oligodendroglioma, and ependymoma. Fifty to sixty percent of gliomas are GBM, the most malignant variety.

B. **Astrocytomas are divided into four grades** in the WHO classification, I to IV, each with distinctive behaviors.

1. **Grade I** tumors consist primarily of pilocytic astrocytomas, although other tumors of glial origin such as gangliocytoma and subependymoma are classified as grade I, indolent lesions. Pilocytic astrocytomas are slow-growing, circumscribed, often cystic lesions that occur in children and young adults. They tend to occur in the cerebellum, anterior optic pathways, and brainstem, and occur with chronic signs of neurologic dysfunction related to location, obstruction of cerebrospinal fluid (CSF) pathways causing hydrocephalus, and rarely, seizures. The clinical course is one of indolent growth or even regression, although frequently they recur after resection. When location allows, complete surgical excision is the preferred treatment and allows 80% to 100% 10-year survival. Long-term follow-up with serial imaging is warranted even when total resection has been performed, as it is not possible to predict which lesions might recur.
2. **Grade II** tumors are often classified as diffuse or low-grade astrocytomas and were previously called fibrillary astrocytomas. They have a wider range of histologic appearance and clinical behavior than do other astrocytomas. A high percentage of these tumors ultimately progress to higher grades, although the dynamics of progression are difficult to predict. Mean age at diagnosis is in the 30- to 40-year range, with a slight male predominance. Seizure is a common presentation along with chronic neurologic changes such as personality changes, speech difficulties, or visual disturbances. MRI often shows a lesion with decreased T_1 signal, increased T_2 signal, and no enhancement. These lesions usually occur in supratentorial locations, may be deep, diffuse, or relatively circumscribed, and are often difficult to differentiate from surrounding edematous brain. Treatment for these tumors is controversial because of the widely variable clinical courses and lack of prospective studies. A period of observation in a patient with a low-grade glioma may be reasonable; however, close neurologic and radiologic monitoring is appropriate. In addition, survival and time to recurrence have shown statistically significant improvement in retrospective studies looking at the role of surgical resection. The role of biopsy, aggressive surgical resection, and radiotherapy must be tailored to the individual patient. Median survival times are approximately 6 to 8 years, with a wide range of variability.
3. **Grade III** is often grouped along with the grade IV GBM, under the broad term “malignant,” as they are clinically more aggressive than diffuse or pilocytic tumors. Mean age at onset also is slightly older, usually 40 to 50 years. Several tumor types besides strictly anaplastic astrocytoma are given this grade, including mixed tumors, which are composed of both astrocytic and oligodendroglial components.

   These tumors may arise from preexisting low-grade tumors or be discovered *de novo,* and also can progress to GBM. The predominant location is the cerebral hemispheres, and there is usually a similar but more rapid clinical presentation as in the lower-grade lesions. Radiographically, they resemble low-grade astrocytomas but may demonstrate contrast enhancement. In terms of treatment, these tumors are grouped with GBM and treated similarly (see later). Prognosis is better, however. Patient age, histologic criteria, and KPS all individually influence survival. Treated with a combination of surgery, radiation, and chemotherapy, patients with anaplastic astrocytoma have a 60% to 70% 1-year survival and a 40% to 50% 2-year survival (*Cancer* 1985;56:1106–1111).

4. **Grade IV** GBM is the most common primary brain tumor and makes up the majority of tumors classified as high-grade or malignant. They are similarly believed to originate both *de novo* and from progression of lower-grade tumors. These are often designated primary and secondary tumors, respectively, with distinctive molecular genetic pathways of development (*Neurooncology* 1999;1:44–51). The location of GBM tends to favor the subcortical white matter of the cerebral hemispheres, and the mean age at onset is 65 years. There is often a rapid onset of symptoms. These tumors typically demonstrate a prominent, ring-like enhancement pattern on MRI. Despite many advances and an improved understanding of their genetic composition, prognosis remains very poor. When patients are aggressively treated with surgery and adjuvant therapy, mean survival is 12 to 14 months with a 2-year survival of 10%. Age and KPS remain significant independent predictors of survival.

   Surgery, radiation, and chemotherapy are all used routinely in the treatment of high-grade astrocytomas. Surgery alone is not curative but does improve the quality and duration of life in selected patients. Although no prospective, randomized trials have been performed to evaluate the role of aggressive resection, retrospective series have supported a survival advantage to complete resection. Radiation therapy is the mainstay of treatment in high-grade astrocytomas, demonstrating survival benefit regardless of the extent of resection. Chemotherapy also is frequently used with radiation, as it has been shown to offer some survival advantage. Other adjuvant strategies such as stereotactic radiosurgery, brachytherapy, and alternate routes of drug delivery are under investigation.

C. **Oligodendrogliomas** are a subtype of diffusely infiltrating, well-differentiated gliomas that compose 5% to 15% of all intracranial gliomas. They correspond to WHO grade II, with the more aggressive anaplastic variety being grade III. An oligodendroglial component may be present in mixed gliomas and predicts a more favorable outcome, compared with that of pure astrocytoma. Oligodendrogliomas have a predilection for the frontal lobes in 50% to 60% of cases and are rare in the cerebellum and spinal cord. Other characteristic features are a tendency to occur with seizures and the presence of calcification on diagnostic imaging. Prognosis is influenced by histologic features, age, and completeness of surgical resection. Most tumors will respond to chemotherapy, with the most experience being with PCV (procarbazine, CCNU, and vincristine). The frequent genetic alterations found for these tumors are loss of heterozygosity on chromosomes 19q and 1p. These deletions also have been shown to correlate with increased chemosensitivity (*J Natl Cancer Inst* 1998;90:1473–1479) and radiosensitivity (*Int J Radiat Oncol Biol Phys* 2000;48:825–830). Survival after surgery has been reported to be between 3 and 5 years.

D. **Ependymoma.** This subset of glial tumors comprises 5% to 8% of CNS neoplasms, and originates from the cells lining the ventricular system. They may occur throughout the neural axis but predominate in an infratentorial location (two thirds of cases) in the pediatric population. In children younger than 3 years, they make up 30% of intracranial tumors. In the spinal cord, they make up 50% to 60% of gliomas.

1. **Most ependymomas are WHO grade II,** with anaplastic ependymoma receiving a histologic designation of grade III. MRI appearance is heterogeneous with mixed areas of cystic regions, areas of old hemorrhage, and calcifications. They often track along CSF pathways into the cisterns and originate in the floor of the fourth ventricle. At the time of diagnosis, 12% will have seeded the spinal column with “drop metastases.”
2. **Presenting symptoms** depend on location, but infratentorial tumors tend to occur with headache, vomiting, cranial nerve palsies, and ataxia. In all patients with ependymoma, extent of surgical resection is an important prognostic factor, and complete surgical removal will cure a small percentage of cases. A complete resection is often not possible because of location, and radiation to the remaining tumor, or to the neural axis in cases of disseminated tumor, may offer some survival benefit. Overall, children have a poorer prognosis than adults, possibly related to an infratentorial predominance. Subtotal resection, age younger than 3 years, and anaplastic features are all associated with a poorer prognosis. Recurrence favors the original tumor site and usually remains a similar grade, although progression can occur. Overall, 5-year survival ranges are 30% to 40% in children and 40% to 50% in adults.
3. **Myxopapillary ependymoma,** a separate clinical and histologic entity, occurs in the conus medullaris–cauda equina region in young adults. They are WHO grade I lesions and carry a favorable prognosis after surgical excision.

IV. **Meningioma**

A. **Meningiomas are benign,** slow-growing, extraaxial tumors that are attached to the dura mater and arise from arachnoidal cap cells. They represent 15% to 20% of primary intracranial tumors and are a common incidental finding at autopsy. Advances in cranial imaging have increased the number of incidentally discovered, asymptomatic lesions. They may occur in almost any location but favor the falx cerebri, over the cerebral convexity, along the skull base at the sphenoid bone, olfactory groove, or parasellar region, along the tentorium cerebelli, within the ventricles, or along the spinal canal.

1. **The peak age incidence** is 45 years and with a female predominance of almost 2:1. In particular, this female predominance increases to almost 10:1 in spinal meningiomas. They are rare in children, except in association with either neurofibromatosis-1 (NF1) or NF2. Many histologic variants have been described and are not useful for predicting clinical behavior, except in determining grade. About 95% of meningiomas are WHO grade I. Based on histologic criteria, 4% to 5% are called atypical and WHO grade II, and approximately 1% are anaplastic WHO grade III. A majority express progesterone receptors, although the role they may play in formation and possibly in therapy is not clear.
2. **Most meningiomas cause symptoms by compression** of adjacent neural structures, and may be present for many years because of their slow rate of growth. They also may come to attention by causing seizures or in the evaluation of headaches. On imaging, they frequently demonstrate calcifications

and have a typical extraaxial location. MRI usually demonstrates isointensity before contrast administration with homogeneous gadolinium enhancement. An attachment to adjacent dura may be visualized on the MRI (a “dural tail”) and significant edema in the surrounding brain parenchyma may be seen.

3. **Treatment.** The decision about whether to treat an asymptomatic tumor is often difficult and requires consideration of multiple factors including location, patient age, general medical condition, and operative morbidity. Expectant management with serial imaging is often reasonable for incidentally discovered lesions. Surgical removal offers the greatest chance of cure for symptomatic lesions and is usually feasible, depending on location. Recent advances in radiotherapy techniques make this an option for treatment both in nonoperative cases and as adjuvant therapy. The chance of recurrence, even after complete extirpation, is significant and occurs as much as 20 years after treatment. Extent of resection and grade of tumor predict recurrence rates. Overall, the prognosis for patients with meningiomas remains good, with a 5-year survival of 90% to 95%. Grade I, typical meningiomas have a 10% to 20% recurrence rate, whereas atypical tumors recur in 30% to 40% of cases. Anaplastic tumors have nearly an 80% recurrence rate and a median survival less than 2 years.

V. **Pituitary adenoma**

A. **The anterior pituitary gland** (adenohypophysis) is the site of origin for 10% of all intracranial tumors, collectively referred to as pituitary adenomas. These are generally benign tumors, affect men and woman equally, and are incidentally found in as many as 20% of adults at autopsy. Incidence is increased in multiple endocrine neoplasia (MEN) type 1. Many classifications exist based on cell of origin, endocrine status, or histologic appearance. They may de divided into micro- (less than 1 cm) or macro- (more than 1 cm) adenomas, with the majority of tumors being smaller than 5 mm at the time of diagnosis.

B. **Functional adenomas.** It is useful to divide tumors clinically into functioning and nonfunctioning, based on whether they secrete active endocrine hormones. This may include the hypersecretion of adrenocorticotropic hormone (ACTH), prolactin, growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), or rarely, thyroid-stimulating hormone (TSH).

1. **The clinical presentation** may be endocrine disturbance, such as Cushing disease (ACTH secretion) and acromegaly (GH secretion); amenorrhea or galactorrhea; symptoms from mass effect on surrounding structures, such as the bitemporal visual loss from optic chiasm compression; or even pituitary apoplexy caused by tumor hemorrhage. Frequently these tumors are identified during an evaluation for headaches.
2. **In nonfunctioning tumors** or in tumors secreting inactive substances, the tumors are usually larger at the time of diagnosis. Compression of the surrounding pituitary gland may produce the insidious loss of function of other pituitary hormones or even an increase in the level of prolactin due to interference with the pathway through which dopamine provides negative regulation. This is known as “stalk effect” and may help differentiate prolactinomas from other tumor types.

C. **Radiographically** these tumors are demonstrated on MRI as masses in the region of the sella that may extend laterally into the region of the cavernous sinus or superiorly toward the optic apparatus. Enhancement is variable, and many microadenomas are too small to visualize on imaging. Angiography may rarely be necessary to help localize a tumor or determine the relation to the carotid arteries. The sella may be enlarged on skull radiographs.

D. **Treatment** depends on the clinical presentation and thus the cell type of origin. Overall management may include observation with serial imaging, medical treatment, surgery, and radiotherapy. All patients suspected of having a pituitary tumor require a thorough endocrine evaluation and, depending on tumor size, ophthalmologic evaluation.

Cushing disease, acromegaly, nonfunctioning tumors, and all macroadenomas are usually managed with surgery, possibly combined with various adjuvant therapies. Options include a transcranial or transsphenoidal sinus approach and depend on tumor size and anatomy. Treatment of prolactinomas is more variable, as these tumors often may initially be managed medically with dopamine agonists (e.g., bromocriptine) until definitive therapy with surgery or radiation therapy is completed. Radiotherapy, including stereotactic radiosurgery, plays a role in treatment of recurrences or in certain subtotally resected tumors. Prognosis also depends on tumor type and size. For nonfunctioning tumors and prolactinomas, in the majority (more than 80%) of cases, the growth of the tumor can be controlled for the life of the patient. Cushing disease can be controlled with surgery in 93% of microadenomas and 50% of macroadenomas. In cases of acromegaly, transsphenoidal surgery alone results in cure in 85% of microadenomas and 30% to 40% of macroadenomas. Results are improved with adjuvant therapies such as treatment with somatostatin and radiotherapy.

VI. **Primary central nervous system lymphoma**

A. **Primary central nervous system lymphoma** (PCNSL) is an unusual, aggressive form of non-Hodgkin lymphoma that does not represent spread from systemic disease. Rather, it is in most cases a tumor of B-cell origin and is staged I_E. The differentiation between spread of systemic lymphoma and PCNSL is not always clear and can make staging controversial. Although it was previously considered a rare tumor, the incidence has been increasing, as a result of the increased incidence of human immunodeficiency virus (HIV) and also in immunocompetent individuals. Patients receiving long-term immunosuppression and individuals with an inherited immunodeficiency also have an increased incidence. The median age at diagnosis is 52 years in immunocompetent patients and 34 years in immunosuppressed patients. The tumors may occur anywhere but are common in the frontal lobes, deep, periventricular regions, and in the posterior fossa. PCNSL favors an intraparenchymal location, whereas secondary lymphoma tends to occur in the leptomeninges. In all patients, the lesions may be multiple, with 70% to 80% of immunocompromised patients having more than one lesion. Ocular disease, in the form of lymphoma or uveitis, may accompany as many as 20% of all cases. The clinical presentation is usually a focal neurologic deficit or symptoms related to increased intracranial pressure, such as headache, nausea, and vomiting. Seizures are not common.

B. **Imaging** with MRI demonstrates often multiple, iso- to hyperdense lesions, with dense or ring-like enhancement, and generally a limited amount of surrounding edema. PET or single-photon emission computed tomography (SPECT) scan may be useful in differentiating ring-enhancing lesions in immunosuppressed patients as lymphoma or nonneoplastic entities, such as toxoplasmosis.

C. **Other useful tests** include Epstein–Barr virus polymerase chain reaction (PCR) of spinal fluid, which has a high correlation with PCNSL in HIV patients. A negative toxoplasmosis immunoglobulin G (IgG) serology helps to eliminate the diagnosis of CNS toxoplasmosis.

D. **Treatment.** Many tumors have a rapid and lytic response to corticosteroid treatment so they should be withheld until a diagnostic biopsy has been performed, unless there is severe mass effect. There is no benefit to surgical resection and stereotactic biopsy is the preferred method for obtaining tissue diagnosis.

1. **Radiation therapy.** These tumors are quite radiosensitive, and radiotherapy using WBRT is favored, given the diffuse, often multifocal nature of these tumors. Radiation increases survival to 12 to 18 months.
2. **Chemotherapy** has gained an increasingly important role in the treatment of PCNSL in immunocompetent patients. In a series of patients, administration of high-dose methotrexate (3.5 g/m^2) with leucovorin rescue, intrathecal methotrexate, procarbazine, and vincristine was followed by 45 Gy of WBRT and high-dose cytarabine. This resulted in a 94% response rate and an impressive median survival of 60 months.
3. **HIV-associated PCNSL** is associated with a particularly poor prognosis. Standard therapy is WBRT to 39 Gy. Median survival is 2 to 6 months. The role of chemotherapy is yet to be defined, although the institution of highly active antiretroviral therapy (HAART) may prolong survival, as opportunistic infection remains a leading cause of death in these patients. See Section VI, page 152.
4. **CNS toxicity,** including progressive memory loss and ataxia, may result from radiotherapy, especially from use of radiation therapy in older patients. Initial therapy with chemotherapy, and delaying or withholding radiation therapy until relapse in elderly patients are strategies for limiting these toxicities.

VII. **Embryonal**

A. **Embryonal tumors** encompass a wide variety of clinically important, mainly pediatric tumors that do not have a universally accepted classification scheme based on histopathologic criteria. They may demonstrate many different patterns of histologic differentiation. Some tumors included in this class are medulloblastoma, ependymoblastoma, medulloepithelioma, atypical teratoid/rhabdoid tumors, and all other tumors known as primitive neuroectodermal tumors (PNETs). As a group, they represent aggressive, malignant tumors and, with the exception of medulloblastoma, are rare. All are WHO grade IV tumors. Because medulloblastoma accounts for almost a fourth of all pediatric brain tumors and is the most common malignant brain tumor of childhood, it is considered in detail.

B. **Medulloblastoma** occurs primarily in children, 70% before age 16 years, with a peak incidence from ages 5 to 7 years. In adults, they very rarely occur after age 50 years. They also are uncommon before age 1 year, and 65% occur in boys. They are located in the vermis of the cerebellum, arising in the roof of the fourth ventricle in the majority of cases. As the age of the patient increases, they tend to occur more laterally, in the cerebellar hemisphere. It has not been established from what cell these tumors arise. In one third of patients, there is dissemination via the CSF pathways, and up to 5% may have systemic spread, usually to bone or lung.

1. **Presentation.** The majority of patients have symptoms of hydrocephalus or cerebellar symptoms such as ataxia, lethargy, headache, and vomiting. Radiographic features are a midline, well-demarcated, densely enhancing mass that is often hyperdense on noncontrast CT scan. Obstructive hydrocephalus is a common feature, and MRI may demonstrate foci of leptomeningeal dissemination.
2. **Treatment strategies** use a combined-modality approach. Surgical goals are to perform gross total resection when safe, as this improves survival. Invasion of the brainstem often limits resection. Additionally, CSF diversion (temporary ventricular drainage, ventricular shunt, or third ventriculostomy) often is necessary. In 30% to 40% of cases, permanent CSF diversion will be necessary. These tumors also are fairly radiosensitive, and craniospinal radiation is combined with surgery, except in children younger than 3 years, in whom chemotherapy is a preferable and efficacious alternative. Chemosensitivity is variable, and a variety of protocols are used with disease progression. Unfavorable prognostic factors are age younger than 3 years, subtotal resection, and dissemination at the time of diagnosis. In the last 30 years, outcomes have improved, with the 5-year survival currently from 50% to 70%.

C. **Neuronal tumors.** This group of tumors is varied in location and histology but shares some degree of differentiation into neuronal cell types. All of these tumors are unusual and relatively benign. All are WHO grade I or II and are almost always controlled with surgical excision alone.

1. **Gangliogliomas and gangliocytomas** are benign tumors of either ganglion cells and glial cells, or ganglion cells alone. Gangliogliomas may occur anywhere in the CNS but have a tendency to occur in the temporal lobe, where they are a frequent cause of medically intractable epilepsy. Rarely the glial component may demonstrate anaplastic or malignant features and designate the tumor as high grade. Surgery is usually curative.
2. **Desmoplastic infantile astrocytomas/gangliogliomas** are large, recently defined, cystic tumors of the cerebral cortex and often involving the leptomeninges, composed of poorly differentiated cells mixed with either neoplastic astrocytes or a neuronal component. They are often large, and typically cause macrocephaly in the affected infant.
3. **Dysembryoplastic neuroepithelial tumors** are hamartomata-like lesions that have been described in children and young adults, with a male predominance, and are found during resection of lesions for treatment of refractory epilepsy. They are usually supratentorial, retain a cortical topography, and may deform the overlying skull. They also may be associated with areas of cortical dysplasia.
4. **Central neurocytoma** is a tumor of young adults that characteristically occurs in the lateral and third ventricles in the region of the foramen of Monro. They histologically resemble ependymomas or oligodendrogliomas and are designated WHO grade II. Typically they cause obstructive hydrocephalus and occur with resulting headache, visual changes, or lethargy. In cases in which total resection cannot be performed, postoperative radiotherapy may be considered, although experience is limited.

VIII. **Tumors of special locations**

A. **Cranial nerves or extraaxial locations** may give rise to schwannomas, neurofibromas, and hemangiopericytomas.

1. **Schwannomas** are benign tumors arising from the Schwann cells located in a variety of places including the head and neck, peripheral nerves, and spinal nerves. They are well encapsulated, tend to favor sensory nerves, and very rarely undergo malignant change. Incidence peaks in the fourth through sixth decades and symptoms invariably relate to compression of surrounding neural structures. Schwannomas make up 29% of primary intraspinal tumors and, along with acoustic neuromas, make up the predominance of cases that require treatment.
2. **Acoustic neuromas** are technically schwannomas of the vestibular nerve and represent 5% to 7% of intracranial tumors, but 80% of tumors in the cerebellopontine angle (CPA). They are slightly more common in women and are increased in neurofibromatosis type 2 (NF2), for which they are pathognomonic when bilateral. Both in sporadic and NF2-associated cases, these tumors arise from a mutation that causes the lack of expression of the protein merlin, the product of the NF2 gene on the long arm of chromosome 22. Although they are histologically benign and are WHO grade I tumors, they may cause significant morbidity because of proximity to the brainstem and adherence to the cranial nerves. Symptoms include hearing loss, tinnitus, and dysequilibrium. MRI evaluation demonstrates a rounded, enhancing mass extending into the internal auditory canal. CT imaging of the temporal bone often shows expansion of the internal auditory meatus. Evaluation of individuals also must include audiometric testing to assess hearing quantitatively.

   The management of these tumors entails balancing the risks of surgery or radiosurgery to treat these lesions, with the natural history of continued observation. Both surgery and radiosurgery are options to control disease. Decisions regarding intervention consider the age and general medical condition of the patient, hearing status, patient symptoms, and the size of the tumor. Several surgical approaches exist, each with inherent advantages and disadvantages. Management decisions depend on these factors and are probably best made by a collaborative team including neurosurgeons, radiation oncologists, neurootologists, and neuroradiologists. Observation should include both serial audiograms and MRI evaluations. Decision making is further complicated in the patient with NF2 and bilateral vestibular schwannomas, as these patients tend to be first seen at a younger age and have a higher morbidity associated with resection.

3. **Neurofibromas** also are benign (WHO grade I) tumors associated with peripheral nerves that are infiltrative or intraneural in location and consist of a mixture of cells including Schwann cells, fibroblasts, perineurial-like cells. They can occur as solitary nodules associated with a peripheral nerve, often in a cutaneous location, or may be multiple. Patients with NF1 tend to have multiple lesions, which may involve spinal roots, and may have plexiform involvement of a major nerve. Neurofibromas are most often treated expectantly, unless there is suspicion of degeneration into a malignant peripheral nerve sheath tumor (MPNST).
4. **Malignant peripheral nerve sheath tumor.** In 3% to 5% of cases, usually when there is proximal major nerve or plexiform involvement, neurofibromas can develop into an MPNST. These are rare, aggressive tumors that are WHO grade III or IV and can develop sporadically or in two thirds of cases. They may develop from neurofibromas, often in the setting of NF1. The goal of treatment is a total resection with negative margins to prevent systemic metastases. They are generally chemo- and radioresistant. Prognosis is poor overall, with a 34% 5-year survival rate.
5. **Hemangiopericytomas** are rare tumors making up less than 1% of all intracranial tumors. Previously classified as angioblastic meningiomas, these tumors arise from pericapillary mesenchymal cells known as pericytes of Zimmerman. They are indistinguishable from those that occur extracranially and are usually found attached to the leptomeninges when they occur in the CNS. A tendency to metastasize systemically is well documented. They occur predominantly supratentorially, may affect children or infants in 10% of cases, and appear clinically like meningiomas with a more rapid onset. They are richly vascular and can be associated with significant intraoperative blood loss. The goal of treatment is gross total resection before systemic spread. Several studies have demonstrated a survival benefit to postoperative radiotherapy. In one series, 5-year and 10-year survival rates were 67% and 40%, respectively.

B. **Pineal region tumors.** Several tumor types commonly occur in the pineal region and are therefore considered as a group under this heading.

1. **Germ cell tumors.** Intracranial germ cell tumors generally occur in the midline, more often in the pineal region in male or the suprasellar region in female patients. Over half of the tumors that occur in the pineal region are germ cell tumors, and the majority of these are germinomas. These tumors are predominantly pediatric tumors, are unusual after young adulthood, and predominate in boys. They have an increased incidence in individuals with Klinefelter (XXY) syndrome and are more common in Asia, where they may make up as much as 15% of pediatric tumor series in Japan. They commonly occur with obstructive hydrocephalus because of their location and often cause Parinaud syndrome. Radiologic appearance is somewhat nonspecific, but generally these tumors appear as homogeneous, isodense lesions that enhance in the region of the pineal gland, sella turcica, and third ventricle. They often have a distinctive relation to the calcifications of the pineal gland parenchyma. The evaluation of someone with a suspected germ cell tumor includes evaluation of serum and CSF markers such as human chorionic gonadotropin (HCG), a-fetoprotein (AFP), and placental alkaline phosphatase (PLAP). These markers are suggestive of certain histologies and are useful in determining prognosis and response to treatment. As many as 35% of germ cell tumors may show metastasis throughout the CNS at the time of discovery, and therefore, with the exception of mature teratomas, most are considered malignant neoplasms.
   a. **Germinomas** are the most common type of germ cell tumor, and 30% will consist of a mixture of cell types. Germinomas make up 60% to 70% of germ cell tumors. They typically demonstrate positivity for PLAP, although HCG also may be present, as they are known to contain elements of syncytiotrophoblastic cells. These are distinct from choriocarcinoma tumors, which also are positive for HCG, but histologically have evidence of both cytotrophoblastic and syncytiotrophoblastic elements. Choriocarcinoma may commonly occur with intracranial hemorrhage, both when it occurs as a primary intracranial lesion and in cases of metastatic spread. Germinomas are exceptionally radiosensitive, and this fact is used as an adjunct to diagnosis. Response to a course of empiric radiation in a characteristic lesion and markers is often enough evidence to warrant further treatment as a germinoma.
   b. **The remainder of germ cell tumors** consist of teratomas, mature and immature, embryonal carcinomas, and yolk-sac tumors. Positivity for AFP helps distinguish teratomas and yolk-sac tumors. Embryonal carcinoma may express PLAP, although this is inconsistent.
2. **Pineal parenchymal tumors.** The cells that make up the pineal gland perform a diverse array of neuroendocrine functions, and when neoplasia occurs, a spectrum of differentiation from primitive to relatively terminal pineocytes is found. Tumors are classified as pineocytomas, pineoblastomas, or some intermediate forms, and make up 15% of tumors in the region of the pineal gland. All are classified as WHO grade IV lesions, with the exception of pineocytomas, which are WHO grade I. They appear similar to other tumor types in this area, and no serum markers are available. Pineocytomas tend to occur in adults, are slow growing, and may show a variety of phenotypes such as neuronal or glial. Pineoblastomas are more aggressive lesions that often disseminate throughout the CNS and resemble primitive neuroectodermal tumors histologically.
3. **Primitive neuroectodermal tumors.** These tumors compose 10% to 15% of pineal region tumors and are derived mostly from tumors of glial origin, such as ependymomas or astrocytomas. They occur in the third and fourth decades, have no gender predominance, and have no CSF markers.
4. The remainder of pineal region tumors consist of small numbers of miscellaneous tumor types such as meningiomas, craniopharyngiomas, and hemangiomas.
5. **Treatment** of all these lesions is multidisciplinary and somewhat controversial. The pineal region remains a difficult region to access surgically, although an aggressive approach has been advocated by centers with more experience in lesions of this region. Some tumors that are benign may be more amenable to aggressive surgical resection, such as meningioma, epidermoid, and mature teratoma. Stereotactic biopsy is generally safe, although it also carries risk for morbidity and the chance for sampling error because of the mixed nature of many lesions. Several series have demonstrated its usefulness and safety in initial management of pineal tumors and cysts. The role of radiotherapy, including stereotactic radiosurgery, and chemotherapy in these tumors is significant.

IX. **Background**

A. **Epidemiology.** Although brain tumors are rare compared with more common cancers of adulthood such as lung, breast, and colorectal, almost 30,000 new cases are diagnosed each year in the United States. Their annual incidence is 12 per 100,000, with half of these cases being malignant gliomas. In the pediatric population, brain tumors represent the most common solid tumor and have an incidence of two to five cases per 100,000. This comprises 40% to 50% of all tumors in children and 25% of cancer-related deaths.

The overall average age at onset is 53 years for all brain tumors, although there is considerable variability by site of origin and histologic type. Across multiple epidemiologic surveys, gliomas are slightly more common in men, whereas meningiomas favor women (2:1).

Controversy surrounds exactly which risk factors exist, and to what degree they play a causative role, in the development of brain tumors. All attempts at clarifying the epidemiology have some degree of methodologic problems, especially given the site and histologic heterogeneity. Some known associations and predisposing syndromes have helped to shed light on the role of tumor-suppressor genes in hereditary syndromes. Examples include the hereditary retinoblastoma (RB) syndrome, in which there is mutation of the *RB* tumor-suppressor gene. The neurocutaneous syndromes include NF1, NF2, tuberous sclerosis (TS), and von Hippel–Lindau syndrome (VHL). Other syndromes associated with CNS tumors are Li–Fraumeni syndrome (mutation of *p53*), Turcot syndrome, Gorlin syndrome (also known as basal cell nevus syndrome), and Cowden syndrome.

B. **Future directions** include investigation of gene therapy, immunotherapy, differentiation therapy, or combinations of these. Studies have been carried out by the Radiation Therapy Oncology Group (RTOG) evaluating the role of radiosurgery in the management of one to three brain metastases, as well as boost treatment for GBM. An ongoing RTOG trial currently is evaluating the use of a weekly radiosurgery boost along with conventional radiation therapy for GBM. The goal of such trials is focally to escalate the dose to obtain better local tumor control with sparing of normal tissue and limitation of toxicity. Similarly, radiation sensitizing with chemotherapy or other agents has been tested, with equivocal results thus far. Clearly there is a need to develop more and better chemotherapy regimens that can penetrate the CNS and are effective in the treatment of these tumors.

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CHAPTER 9. ENDOCRINE MALIGNANCIES

Steven Hunt and Gerard M. Doherty

Differentiated thyroid carcinoma
Presentation
Staging evaluation
Stage-directed approach to treatment
Follow-up
Disease-specific complications
Anaplastic thyroid carcinoma
Presentation
Staging evaluation
Stage-directed approach to treatment
Disease-specific complications
Medullary thyroid carcinoma
Presentation
Staging evaluation
Stage-directed approach to treatment
Disease-specific complications
Parathyroid carcinoma
Presentation
Staging evaluation
Stage-directed approach to treatment
Disease-specific complications
Pancreatic endocrine tumors
Presentation
Staging evaluation
Stage-directed approach to treatment
Disease-specific complications
Adrenal carcinoma
Presentation
Staging evaluation
Stage-directed approach to treatment
Disease-specific complications
Diffuse neuroendocrine system (carcinoid) tumors
Presentation
Staging evaluation
Stage-directed approach to treatment
Disease-specific complications
Suggested Readings

I. Differentiated thyroid carcinoma

A. Presentation

1. **History and risk factors.** Most differentiated thyroid cancers are first seen as a palpable mass in the neck. However, although solid thyroid nodules are relatively common, only about 10% are cancer. The evaluation of thyroid nodules is dependent largely on characterization by ultrasonography and fine-needle aspiration cytology. Solid nodules that are diagnosed as benign by fine-needle aspiration must be followed up over time. Factors that increase the likelihood of malignancy include patient age (younger than 20 or older than 50 years), growth during thyroid-stimulating hormone (TSH) suppressive therapy, residence in an iodine-deficient geographic area, and a history of thyroiditis, goiter, or head and neck irradiation. Neck pain, dysphagia, hoarseness, dyspnea, and cervical adenopathy are worrisome for more aggressive histologies, locally advanced disease, or metastases. Prior head and neck radiation is an etiologic factor in the development of papillary thyroid cancer, but not a prognostic factor in its outcome. Patients with a thyroid nodule and a history of childhood neck irradiation have a 33% to 37% chance of malignancy. Age at exposure and a radiation dose up to 2,000 cGy have been shown to have a linear relation with the increased risk associated with ionizing radiation.

   Occasional patients with differentiated thyroid cancer have a nodule that has been identified incidentally on imaging examinations, such as chest radiograph, cervical ultrasound, chest computed tomography (CT) scan, or fluorodeoxyglucose–positron emission tomography (FDG-PET) scan done for other reasons.

   Papillary thyroid cancer also has been associated with several inherited tumor syndromes (Gardner syndrome, Cowden disease, and familial polyposis coli). Thus a family history of thyroid cancer of uncertain type or other endocrine tumors should always elicit questioning regarding possible multiple endocrine neoplasia type 2 (MEN2; see medullary thyroid cancer [MTC]). A history of other family members with differentiated thyroid cancer is usually not due to a defined clinical syndrome.

2. **Physical examination**

   The examination of a patient with a diagnosis of thyroid cancer includes a general physical examination to evaluate both for metastatic disease and operative risk. Physical examination evidence of metastasis is usually confined to the neck. Careful examination of the thyroid gland itself, to identify direct invasion of other structures in the neck, such as the strap muscles or larynx, also should include characterization of, the contralateral lobe. The lymph nodes of the central and lateral neck should be carefully investigated; equivocal findings may warrant imaging by ultrasound or tissue sampling by fine-needle aspiration, if, this would affect the operative approach.

B. Staging evaluation

In the absence of specific symptoms, extensive staging is not indicated in patients with differentiated thyroid cancer. Patients should have a chest radiograph to evaluate for pulmonary metastases. The most sensitive staging evaluation is the intraoperative evaluation of the cervical lymph nodes and postoperative radioiodine scan. The pre- or posttreatment radioiodine scan is very sensitive for subclinical sites of regional or distant disease and cannot be performed until the thyroid has been removed. Whole-body scans are typically performed with iodine 131 doses of 1 to 5 mCi. Some clinicians prefer to assess for distant disease by a posttreatment scan, 4 to 7 days after a therapeutic ^{131}I dose. This avoids the use of a small ^{131}I dose for scanning before ^{131}I therapy, and the risk of “stunning” the residual thyroid tissue, decreasing uptake of the ^{131}I dose.

C. Stage-directed approach to treatment

1. **Extent of operative resection.** Differentiated thyroid cancer staging reflects the excellent prognosis of this tumor in general (Table 9.1). Although the American Joint Commission for Cancer (AJCC) staging system reflects the excellent prognosis for this disease, it does not really separate patients in a way that allows treatment planning. To try to select patients who might benefit from total thyroid ablation (total thyroidectomy and radioiodine therapy), some prognostic indices have been developed. These include the AGES (age, grade, extrathyroidal invasion, and size), AMES (age, metastasis, extrathyroidal invasion, and size), and MACIS (Table 9.2) systems. The MACIS system seems to be the one most easily applied in the immediate perioperative period, and the most consistently applicable, as it does not require tumor grading, which can be subjective. Some investigators have advocated using the MACIS system to select patients who have higher scores for total thyroid ablation. No prospective studies have been performed.

	Papillary or Follicular, Age < 45 yr	Papillary or Follicular, Age ≥ 45 yr	Medullary	Undifferentiated
Stage I	Any T, any N, M0	T1, N0, M0	T1, N0, M0	
Stage II	Any T, any N, M1	T2, N0, M0 T3, N0, M0	T2, N0, M0 T3, N0, M0 T4, N0, M0	
Stage III		T4, N0, M0 Any T, N1, M0	Any T, N1, M0	
Stage IV		Any T, any N, M1	Any T, any N, M1	All stage IV

Primary Tumor (T)	Nodal Involvement (N)	Metastases (M)
T1, T ≤1 cm within thyroid	N0, node negative	M0, no distant metastases
T2, 1 cm < T ≤4 cm	N1a, ipsilateral node(s) involved	M1, distant metastases
T3, T > 4 cm	N1b, contralateral, midline or mediastinal node(s) involved	
T4, any size extending beyond capsule		

From Fleming ID, et al., eds. *AJCC cancer staging manual*. Philadelphia: Lippincott-Raven, 1997, with permission.

TABLE 9.1. STAGING OF THYROID CANCER

Scoring System	Prognostic Factors Used
EORTC	Gender, tumor histology type, extrathyroidal invasion, distant metastases
AGES	Age, tumor grade, extrathyroidal invasion, tumor size
MACIS	Age, extrathyroidal invasion, distant metastases, completeness of resection, tumor size
AMES	Age, extrathyroidal invasion, distant metastases, tumor size
TNM	Primary tumor size, lymph node status, distant metastases
DeGroot class	Cervical node metastasis, distant metastasis, extrathyroidal invasion
SAG	Sex, age, grade
Mazzaferri system	Tumor size, cervical node status, multiple tumors (>3), extrathyroidal invasion, distant metastases

MACIS Calculation	
MACIS = 3.1	For age < 40, or (0.08 × age)
+ s	s = 0.3 × tumor size (cm)
+ 1.0	if tumor incompletely resected
+ 1.0	if local invasive
+ 3.0	if distant metastasis at presentation

MACIS Implications	
MACIS score	10-year survival
<6	100%
6–6.99	92%
7–7.99	60%
> 8	30%

Adapted from Usher B, Hay ID. Postoperative management of differentiated thyroid carcinoma. In: Doherty GM, Skogseid B, eds. *Surgical endocrinology*. Philadelphia: Lippincott Williams & Wilkins, 2001:87–108, with permission.

TABLE 9.2. PROGNOSTIC SCORING SYSTEMS FOR THYROID CANCER

The treatment for most differentiated thyroid cancer is operative resection. For patients with the most favorable prognoses, particularly women younger than 45 years with T1 or T2 tumors, thyroid lobectomy is adequate therapy. For people with a higher risk of recurrence, total thyroidectomy and adjuvant radioiodine therapy is selected. However, a large group of patients has prognoses between the best and worst groups, and the decision of which treatment is best applied for them is controversial. Because the prognosis is so good, the decision is affected substantially by the morbidity of the treatment. Thyroid lobectomy alone carries a low but real risk of unilateral recurrent laryngeal nerve injury and permanent hoarseness. Total thyroidectomy adds the risks of contralateral recurrent laryngeal nerve injury as well as permanent hypoparathyroidism. The risk of each of these complications is very low for total thyroidectomy performed by a surgeon experienced in thyroidectomy (about 0.5% for each) but can be substantially higher in the hands of those who perform thyroidectomy only occasionally. This issue must be taken into account when planning the treatment strategy for a patient with good-prognosis thyroid cancer.

For patients with T4 tumors, the surgical resection should be as complete as possible, including resection of involved strap muscles, pharyngeal muscles, or tracheal segments. The morbidity of laryngectomy is not generally necessary. If there is more than minimal gross residual disease, then external beam radiation therapy should be combined with radioiodine therapy to minimize the risk of local recurrence.

Patients with palpable metastatic lymph node disease in the neck should have a central and lateral cervical lymph node dissection, with careful preservation of function. In differentiated thyroid cancer, cervical lymph node metastasis does not have a substantial effect on prognosis, and so the morbidity of the operation must be weighed against the morbidity of the disease. This should always be followed by ^{131}I therapy.

2. **Radioactive iodine therapy.** Treatments with ^{131}I are typically given 6 to 12 months apart, during periods of thyroid hormone withdrawal. The TSH is allowed to increase to about 5 times the upper limit of normal before treatment is given, and the thyroxine is resumed after the ^{131}I dose. The ^{131}I treatment dose is tailored to the amount of residual thyroid tissue thought to be present; the less tissue present, the higher the ^{131}I dose. Typical doses if a significant thyroid remnant is present are 30 to 75 mCi. A posttreatment scan is useful to determine the extent of residual thyroid tissue (of which there is always some, even after "total" thyroidectomy), as well as thyroid cancer in the neck or elsewhere. Ablative doses are continued at 6-month intervals until there is no residual ^{131}I uptake. After thyroid-remnant ablation, doses are typically 100 to 200 mCi.

   Diagnostic thyroid scans, which can be performed by using exogenous recombinant human TSH (rhTSH) administration rather than hormone withdrawal, are then performed until there are two normal consecutive scans. The recommended dose of rhTSH is two injections on consecutive days, followed by ^{131}I dosing on the third day. If further disease is revealed on follow-up radioiodine scan, then therapy may include additional resection or ^{131}I treatment. Important preparation for radioiodine treatment or scanning also includes restriction of iodine intake to avoid saturation of the thyroid or cancer tissue. In particular, radiologic contrast agents contain substantial amounts of iodine and must not be administered. If there is a need to image the neck within 3 months of an iodine-based treatment or scan, then ultrasound or magnetic resonance (MR) scanning should be considered.

3. **Thyroid-stimulating hormone suppression.** In addition to radioactive iodine therapy, adjuvant therapy for thyroid cancer includes TSH suppression with thyroid-hormone replacement. TSH stimulates the growth of both normal thyroid tissue and differentiated thyroid cancer. Thus thyroid-hormone replacement is indicated for all patients with thyroid cancer, to suppress TSH secretion and eliminate this source of tumor growth stimulation. The level of TSH suppression is another issue for which there are few prospective data. However, hyperthyroidism associated with TSH suppression below the lower limit of normal may have cardiac or bone toxicity. It appears reasonable to suppress the TSH to an undetectable level for a period of time (5 to 10 years); if there is no evidence of tumor recurrence, then the thyroid hormone–replacement therapy can be decreased to allow the TSH to increase to the lower limit of normal.
4. **Distant disease.** For patients with distant (M1) disease, therapy should begin with total thyroidectomy to prepare for radioactive iodine therapy. Disease limited to small volumes of lung or bone metastases may be curable by one or more treatments with ^{131}I. Other forms of systemic therapy, such as doxorubicin, platinum, or taxane-based chemotherapy regimens are used rarely for patients with bulky, progressive disease that is not responding to therapy. In general, there is little or no role for systemic chemotherapy in patients with differentiated thyroid cancer.

D. **Follow-up**

Follow-up of patients who have had total thyroidectomy should include measurement of serum thyroglobulin levels at each follow-up. An increase in this level may be the initial indication of disease progression or recurrence. Physical examination and cervical ultrasound also are useful to evaluate for locoregional recurrence.

E. **Disease-specific complications**

The most frequent complications of thyroid cancer therapy are those noted earlier for total thyroidectomy. Injuries to the superior or recurrent laryngeal nerves can occur, as can hypoparathyroidism in patients who have bilateral operations. Radioiodine therapy can have short-term morbidity including neck pain or salivary gland pain.

II. **Anaplastic thyroid carcinoma**

A. **Presentation**

1. **History and risk factors.** Anaplastic thyroid cancer is the undifferentiated version of epithelial (papillary or follicular) thyroid cancer. It usually occurs as a rapidly growing mass in the neck and is frequently associated with pain, hoarseness, swallowing abnormalities, and overlying skin changes. The tumor usually occurs in patients older than 60 years. Some patients may have had a long-standing thyroid mass, which suddenly begins to change, as these

tumors may develop from preexisting thyroid cancer; however, this is usually not clear at presentation.

2. **Physical examination.** The examination is marked by the palpable mass in the neck, which is often fixed to surrounding structures such as the larynx, strap or sternocleidomastoid muscles, or adjacent adenopathy. Imaging with MR or ultrasound can be useful to delineate the relation between the mass and the neurovascular structures of the neck, particularly the carotid artery, which may be entirely surrounded.

B. **Staging evaluation**

All anaplastic thyroid cancer is stage IV, regardless of the anatomic extent of disease by staging studies (Table 9.1). This reflects the poor prognosis of this tumor. However, in planning rational therapy, the initial evaluation should seek to identify all sites of disease. The diagnosis should be established by cutting needle (core needle) biopsy if possible. Imaging should then include ultrasound or MR scan of the neck, as well as noncontrast CT of the chest. MR of the chest and abdomen may be added if there are abnormalities requiring further anatomic definition. FDG-PET has been used in a limited number of patients and may be useful to identify otherwise occult systemic disease.

C. **Stage-directed approach to treatment**

All anaplastic thyroid cancer should be managed as systemic disease. However, an important distinction may be made regarding the ability to control the local disease. Most patients have local disease in the thyroid bed of such an extent that the tumor cannot be resected. The tumor frequently surrounds the carotid arteries, the trachea, and the esophagus. However, occasional patients have more limited disease that can be resected. Patients who have disease in the neck that can be removed with limited morbidity appear to benefit from this effort at local control. This is not undertaken to affect survival, as that is generally dictated by metastatic disease; however, the only long-term survivors of this disease are those in whom resection was feasible.

All patients, including those who have had resection, should undergo external beam radiation therapy to the neck and other sites of focal disease. Anaplastic cancers do not typically concentrate iodine, and thus ^{131}I therapy is not generally a useful strategy. Patients also should receive systemic cytotoxic therapy. The most common regimen is low-dose doxorubicin (Adriamycin; 25 mg/m^2) administered concurrent with hyperfractionated external beam radiation therapy. Recently, promising data have been generated regarding paclitaxel as an alternative primary chemotherapeutic option.

E. **Disease-specific complications**

The most frequent and feared complications of anaplastic thyroid cancer are related to the local tumor invasion. These complications can include such bothersome problems as hoarseness from recurrent laryngeal nerve invasion or resection, or esophageal obstruction from tumor or radiation effects, and life-threatening issues such as tracheal compression or tracheo–innominate artery fistula. These problems should be managed as necessary. Tracheostomy, if possible, may be necessary for patients with impending airway obstruction. Gastrostomy may allow continued gastrointestinal access and nutritional support in patients with esophageal obstruction, which is as likely to be temporary because of the acute effects of high-dose external beam irradiation, as it is to direct esophageal invasion by tumor.

III. **Medullary thyroid carcinoma**

A. **Presentation**

Recent advances in the genetics of MEN type 2 allow direct DNA testing for mutation in the RET protooncogene of individuals at risk for MEN2 and subsequent prophylactic surgical management. This discovery has further emphasized the important distinction between the familial and sporadic forms of MTC.

1. **History and risk factors.** Patients with sporadic MTC and those with previously unrecognized familial MTC usually are first seen with a neck mass. The evaluation includes fine-needle aspiration (see earlier), which may then demonstrate MTC. Occasional patients have diarrhea associated with more advanced disease, although this is uncommon.

   Patients with a family history of MEN2 or familial MTC without the other features of MEN2 often now are seen without symptoms, but with positive genetic testing. These familial syndromes are all due to mutations of the RET protooncogene, and direct DNA testing is available. The presence of a germ-line mutation implies the predictable development of disease, given the near-complete penetrance of the genetic defect. Given this, presymptomatic thyroidectomy has become the treatment of choice for detected individuals. The timing of this intervention is important, as these individuals have C-cell hyperplasia (the direct precursor to MTC) at a young age. For patients with MEN2a (MTC, as well as lower risks of primary hyperparathyroidism and adrenal pheochromocytoma) or FMTC (familial medullary thyroid cancer, not including the risks of hyperparathyroidism or pheochromocytoma), the thyroidectomy can be confidently performed at about age 5 years, without significant risk of the presence of nodal or distant metastases. In contrast, in patients with MEN2b (MTC, as well as mucosal neuromas and pheochromocytomas), disease develops at an earlier age, and prophylactic thyroidectomy should be performed before age 2 years, to pre-date the development and spread of malignancy in most patients.

2. **Physical examination.** As for the patients with differentiated thyroid cancer, the examination of a patient with a diagnosis of thyroid cancer includes a general physical examination to evaluate for both metastatic disease and operative risk. Physical examination evidence of metastasis is usually confined to the neck. Careful examination of the thyroid gland itself, to identify direct invasion of other structures in the neck, such as the strap muscles or larynx, also should include characterization of the contralateral lobe. The lymph nodes of the central and lateral neck should be carefully investigated; equivocal findings may warrant imaging by ultrasound or tissue sampling by fine-needle aspiration, if this would affect the operative approach.
3. **Laboratory investigation.** A critical part of the evaluation for every patient with MTC is assessment for undetected pheochromocytoma. Each patient with known MTC should have 24-hour urine collection for catecholamines, vanillylmandelic acid, and metanephrines. Detection of a pheochromocytoma would raise the issue of a familial basis for the MTC, as well as mandate medical blockade of the catecholamine effects before anesthetic induction.

   In addition, every patient with MTC who is not known to belong to a family cohort with a RET protooncogene mutation, should have RET mutation screening.

   Finally, calcitonin is made by the C-cells of the thyroid gland, and by MTC, and serves as an extremely sensitive tumor marker. Each patient with MTC should have this measured at baseline, and the levels can then be used in the patient follow-up.

B. **Staging evaluation**

For patients with the initial presentation of MTC as an apparently localized intrathyroidal mass, no additional staging is necessary, beyond the laboratory evaluation outlined earlier. If a patient has additional palpable disease in the neck or unusual cervical symptoms, then additional imaging may help to define the extent of disease; MR scanning and cervical ultrasound are particularly useful.

The most complete staging information usually comes from the results of the total thyroidectomy and ipsilateral cervical lymph node dissection, which is the typical minimal operative intervention for these patients. The natural progression of nodal metastatic disease is via the cervical nodes into the mediastinal lymph nodes, and so chest MR scan or CT scan may reveal this disease in selected patients. In addition, of patients with persistent or recurrent disease as demonstrated by elevated calcitonin levels, a substantial fraction have minimal-volume metastatic disease in the liver. The most sensitive test for this disease is a diagnostic laparoscopy, as the disease is typically multiple tiny metastatic deposits immediately under the liver capsule.

C. **Stage-directed approach to treatment**

The only effective treatment for MCT is operative resection of all disease. The stage of the disease at presentation affects the operative planning and the extent of resection.

Genetically affected patients who have prophylactic thyroidectomy represent the earliest disease-treatment stage. These patients should have total thyroidectomy and central lymph node dissection. The management of the parathyroid glands is controversial. Our approach has been to deliberately remove and remotely autograft all parathyroid glands to allow complete central node dissection and protect the parathyroid gland from risk during any subsequent central neck procedure.

For patients with disease apparently limited to the thyroid gland, total thyroidectomy and functional neck dissection on the side of the tumor is the minimal

procedure we recommend. If there are other evident sites of adenopathy during the dissection, then formal dissections should include these areas as well.

There are no effective treatments for the management of systemic disease. However, the disease does tend to be indolent in its tempo of progression.

D. **Disease-specific complications**

The complications of MTC are similar to, although less frequent than, the local effects of anaplastic thyroid cancer. Patients with inadequately controlled disease in the central neck can have local complications, such as recurrent laryngeal nerve damage, airway obstruction, or esophageal obstruction. Complications of operative treatment can include damage to any of the local structures in the central or lateral neck, including the recurrent laryngeal, external branch of the superior laryngeal, and spinal accessory nerves, the parathyroid glands, and the thoracic duct.

IV. **Parathyroid carcinoma**

A. **Presentation**

1. **History and risk factors.** Patients with parathyroid carcinoma are first seen with either hypercalcemia or a neck mass. Patients may have symptoms and signs similar to those of benign primary hyperparathyroidism, including fatigue, lethargy, bone disease, and renal stones. In general, however, the hypercalcemia and symptoms are more severe than those in patients with benign disease, and symptoms of the higher calcium levels such as nausea, vomiting, dehydration, and polyuria are more frequent. Overall, the patients with parathyroid cancer are younger, and the gender ratio is equal, compared with the predominantly postmenopausal female population with benign hyperparathyroidism.
2. **Physical examination.** Palpable masses in patients with benign hyperparathyroidism are usually thyroid nodules. However, 30% to 50% of patients with parathyroid cancer have a palpable, firm mass in the central neck. Physical examination may further reveal palpable adenopathy.

B. **Staging evaluation**

Patients with primary hyperparathyroidism often have preoperative imaging with technetium–sestamibi scanning. However, this test may localize either parathyroid cancer or adenoma; it is not likely to distinguish between the two. If a question of parathyroid cancer is raised preoperatively because of a palpable neck mass or unusual sestamibi findings, then cervical ultrasound is the best test to try to delineate the nature of the mass.

For patients who have had a previous operation and diagnosis of parathyroid cancer, imaging localization of the persistent disease is mandatory before reoperation. Sestamibi scanning is useful to localize disease, but provides little anatomic information, and must be correlated with other studies. Cervical ultrasound is useful for delineation of disease in the central or lateral neck. MR scan is useful for cross-sectional evaluation; CT scan also can be helpful but provides less vascular detail. FDG-PET has been used in a limited number of patients and may complement the utility of sestamibi scan to localize disease regionally, and particularly to identify occult distant disease.

C. **Stage-directed approach to treatment**

Most patients who have parathyroid cancer have the diagnosis made in the operating room. At the time of neck exploration, in particular if parathyroid cancer is suspected, then the initial resection should be as complete as possible, always including the ipsilateral thyroid lobe, central cervical lymph nodes, and thymus, and in the absence of demonstrably abnormal lateral cervical nodes, a limited ipsilateral neck dissection (levels 2, 3, and 4). Resection of other local structures also may be necessary to achieve complete resection, such as partial tracheal resection, recurrent laryngeal nerve resection, or resection of strap muscles. There is no effective adjuvant therapy.

The only effective treatment for metastatic or locally recurrent disease is resection. To be useful, resection must be complete or nearly so. This may include resection of nodal or pulmonary metastases. Postoperative radiotherapy has been used in some patients, although effectiveness is difficult to judge.

D. **Disease-specific complications**

The main complication of parathyroid cancer is hypercalcemia. For patients with recurrent or metastatic disease, management of severe hypercalcemia often becomes a significant issue. Patients with severe hypercalcemia should be managed with saline hydration, furosemide diuresis, and administration of bisphosphonates. Octreotide may reduce calcium levels in some patients, through a mechanism that is not clear. There also are experimental calcimimetic agents that may be helpful in patients with severe hypercalcemia.

Complications of therapy may include recurrent laryngeal nerve injury, thoracic duct injury, or injuries to other cervical structures.

V. **Pancreatic endocrine tumors**

A. **Presentation**

1. **History and risk factors.** Patients with pancreatic endocrine tumors (PETs) can be separated by two main factors: hormonal function of the tumor and the presence of familial PET (MEN1 and von Hippel–Lindau [vHL]). Patients with functional tumors usually have symptoms of the hormonal syndrome (Table 9.3). Gastrin-producing tumors produce the Zollinger–Ellison syndrome; insulin-producing tumors produce neuroglycopenic symptoms. Together, these two tumor types account for more than 90% of the functional tumors.

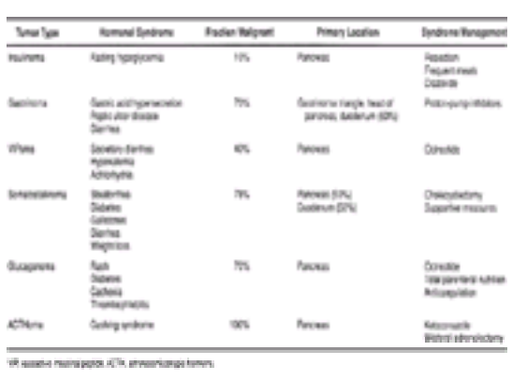

TABLE 9.3. PANCREATIC NEUROENDOCRINE TUMORS AND SYNDROMES

Nonfunctional tumors are neuroendocrine tumors without a demonstrable clinical syndrome, although they may produce pancreatic polypeptide and frequently demonstrate immunohistochemical staining for gastrin or insulin. They typically are seen because of local effects of the tumor mass. These patients have gastrointestinal or biliary obstruction, gastrointestinal bleeding, or cachexia. They frequently have liver metastases at diagnosis.

Patients with MEN1 typically have multiple neuroendocrine tumors in the pancreas and duodenum. The multiplicity of these tumors demands special consideration in the treatment planning.

2. **Physical examination.** The physical examination is typically unrevealing. Patients with metastatic disease may have palpable adenopathy, frequently in supraclavicular lymph nodes. Occasional patients may have an abdominal mass present at diagnosis.

B. **Staging evaluation**

1. **Laboratory investigation.** The biochemical evaluation depends on the clinical symptoms. Patients with symptoms suggestive of insulinoma should have a supervised fast for up to 72 hours, to document simultaneous neuroglycopenic symptoms, hypoglycemia, and hyperinsulinemia. Serum C-peptide levels and urine sulfonylurea measurements also should be performed to exclude factitious hypoglycemia.

Hypergastrinemia and simultaneous elevated gastric acid output document gastrinoma. Serum gastrin levels greater than 800 pg/mL and basal acid output greater than15 mEq/hour (or more than 5 mEq/hour after acid-reducing surgery) are diagnostic of gastrinoma. Lower levels of gastrin may require confirmation by stimulatory testing with secretagogues such as secretin or calcium. It is critical that the gastric acid analysis be performed, as most

elevated serum levels of gastrin are secondary to achlorhydria, as in pernicious anemia.

The less common functional tumors are all diagnosed by the measurement of elevated serum hormone levels in the appropriate clinical setting.

2. **Imaging.** Insulinomas are usually small, benign, and isolated to the pancreas. The most sensitive test for the identification of an insulinoma is intraoperative ultrasound. Given that, many experienced surgeons forego extensive preoperative testing in favor of a simple regimen designed to detect more extensive disease in the few patients who have this, and depend on the intraoperative ultrasound to identify the tumor. In some centers, preoperative endoscopic ultrasound has proved extremely accurate and useful in localizing the tumor. Older experience with more extensive localization, classically depending on angiography as the most sensitive test, has been largely obviated by these sonographic techniques. For the few patients with malignant insulinomas and metastatic disease, CT scans are the most useful test. Somatostatin-receptor scintigraphy is relatively insensitive for insulinomas, which generally express few type II somatostatin receptors on which the study depends.

   Gastrinomas are more frequently malignant than insulinomas, and their location is somewhat more variable, including a substantial proportion with primary tumors in the duodenum. Preoperative imaging for staging should always include a CT scan of the abdomen and pelvis and somatostatin-receptor scintigraphy. Further studies may be performed to address specific issues. These may include ultrasound or MR scan to resolve lesions identified in the liver, and plain films for possible osseous metastases. Intraoperative ultrasound is again useful for the staging during the resection. Stimulatory angiography, injecting a secretagogue for gastrin, such as secretin, into the arterial supply of a specific area with subsequent measurement of gastrin in the hepatic veins, may be occasionally useful to localize tumor further.

   Less common pancreatic endocrine tumors should always be evaluated with CT scan and somatostatin-receptor scintigraphy, as a starting point.

C. **Stage-directed approach to treatment**

   The only potentially curative treatment for PETs is complete resection of the primary tumor and any metastases. This should be planned for all patients if possible, regardless of function, as long as the patient's other medical problems permit resection. Preoperative preparation should include optimal control of any hormonal syndrome to prevent perioperative complications, and immunizations, in case splenectomy is indicated. Some surgeons use perioperative somatostatin-analogue therapy to try to decrease the incidence of clinically evident pancreatic fistula, but the value of this is unclear. Chemotherapy and radiotherapy do not have any defined role in the adjuvant setting.

   Patients with MEN1 or vHL may have multiple tumors in the pancreas. The planning of their resection requires special considerations. Our approach has been to try to do as complete a resection as possible with the preservation of pancreatic function. Often a subtotal pancreatectomy and enucleation of duodenal tumors is the best approach to achieve this.

   For patients with unresectable metastatic disease, systemic therapy may be useful. The timing of the initiation of systemic treatment is controversial. PETs are often quite indolent in their behavior, and the treatments have only marginal effects, so most clinicians reserve treatment until there is evidence of tumor progression. In some patients, this occurs rapidly; however, in others, there may be long periods of disease stability. The most common systemic antitumor therapy used is streptozotocin and 5-fluorouracil. The objective response rate in PET patients is 45% to 63%. Although some authors have advocated the use of somatostatin analogues as antitumor therapy, rather than merely treatment for the syndrome, most now believe that the antiproliferative effects of the somatostatin analogues are very limited.

   Interferon-a has been used with evidence of response in fewer than half of patients. The most frequent response is evident only by decreases in the biochemical parameters used to monitor the tumor burden (about 47%), and only a 12% objective tumor response.

   For some patients with substantial unresectable liver disease and symptoms, local treatments may be helpful. These may include hepatic artery embolization or hepatic tumor radiofrequency ablation.

D. **Disease-specific complications**

   The most frequent complication of PETs is liver metastasis and death. The often massive liver disease can impair liver function to the point of failure. The hormonal syndromes may be difficult or impossible to control with substantial amounts of disease in the liver, except for gastrinoma, which can always be treated with proton-pump inhibitors.

VI. **Adrenal carcinoma**

A. **Presentation**

1. **History.** Adrenal cancer is seen either because of symptoms of local mass effects or because of hormonal function. If hormonal effects do not cause recognition of the abnormality at an early tumor stage, then these tumors may reach a substantial size before local effects demand discovery. These tumors are often highly locally invasive, and frequently directly involve the liver and kidney on the right, or the pancreas, spleen, and kidney on the left.

   The most common functional tumors produce corticosteroids and Cushing syndrome. These patients have weight gain, typical changes in body habitus, changes in skin and hair, glucose intolerance, and infections. Less frequently, hyperaldosteronism or virilizing syndromes may develop; when solitary, these are less frequently malignant; however, any patient with a combination of hormonal syndromes almost certainly has cancer.

2. **Risk factors.** There are no clear risk factors for the development of adrenal cancer. A small number of MEN1 patients have had recognized adrenal carcinomas, but most adrenal lesions in MEN1 are benign adenomas.
3. **Physical examination.** Patients with Cushing syndrome may have the typical physical examination findings as noted earlier. In particular, the central obesity with a prominent dorsocervical fat pad and thin extremities may be discernible. Patients with virilizing tumors may have hair growth or precocious sexual maturation in children.

B. **Staging evaluation**

Adrenal cancer is staged mainly by the determination of local invasion and distant metastasis (Table 9.4). Radiographic evaluation should include CT scans of the chest, abdomen, and pelvis to evaluate local invasion and distant disease. MR scans may be useful, particularly in the evaluation of smaller adrenal tumors, where the signal characteristics may help to delineate the nature of the lesion.

Stage I	T <5 cm without regional extension
Stage II	T >5 cm without regional extension
Stage III	Regional extension and/or nodes positive
Stage IV	Distant metastases

TABLE 9.4. STAGING OF ADRENAL CANCER

Prognosis in adrenocortical carcinoma (ACC) depends on disease stage at presentation. Historically, approximately 70% of patients are first seen with advanced (stage III or IV) disease; however, more recent series have nearly 50% lower stage (I or II) patients. Patients have an overall median survival of 2 years, with 5-year and 10-year survival rates of 22% to 30%, and 10%, respectively. Patients with stage I or II disease have substantially better prognosis

overall (approximately 50% at 5 years); however, survival decreases quickly at stage III (median, 12 months, and only 20% alive at 5 years) and is very poor for patients with stage IV disease (median, 6 months, and 5% alive at 5 years).

C. **Stage-directed approach to treatment**

The only effective, potentially curative therapy for adrenal cancer is complete operative resection. This typically requires radical resection including the adrenal gland and adjacent structures such as the ipsilateral kidney, the pancreas, and spleen on the left, and the posterior portion of the right lobe of the liver on the right.

Treatment after apparently complete resection is controversial. The best-investigated, potentially effective systemic agent is mitotane (*o,p*-DDD). The beneficial effect of this therapy is limited at best, and the daily administration for 1 year has substantial toxicity. Adequate dosing must be determined for individual patients, but almost always is more than 4 g per day. Serum levels should be monitored and maintained at least 10 µg/mL, and preferably more than14 µg/mL. Mitotane is adrenolytic and increases the rate of metabolism of exogenously administered corticosteroid replacement. Patients must have exogenous corticosteroid administration, preferably with hydrocortisone, to avoid addisonian signs and symptoms. Replacement with prednisone or dexamethasone is significantly affected by increased metabolism. Mitotane is not proven to be effective in the adjuvant setting; this disease recurs frequently, and so a 1-year course of treatment is frequently used.

For patients with residual or metastatic disease, mitotane has a response rate of 20% to 30%, and the responses are generally of short duration. Radiation therapy may be useful for the palliative management of painful osseous metastasis. Cytotoxic chemotherapy has not shown any substantial or consistent effect for adrenal cancer.

For patients with recurrent disease, either in the chest or the abdomen, which is technically resectable, the best approach is metastasectomy. Whereas disease recurs in most of these patients, about one third will survive more than 5 years after the repeated resection, which none of, the unresected patients would be expected to achieve.

After treatment, patients should be followed up with urinary steroid profiles based on the pretreatment patterns of hormonal overexpression, as well as imaging with CT scan or MR scan. FDG-PET has been used in a limited number of patients and may be useful for some patients.

D. **Disease-specific complications**

The complications of adrenal cancer relate to either the direct effects of primary or metastatic tumor invasion, or the hormone production by the tumor. Direct effects of the tumor may be palliated in specific patients by resection, radiation therapy, or supportive care. Patients with Cushing syndrome may be very difficult to palliate. Ketoconazole may have some effect in limiting adrenal steroid production; however, it is not typically completely effective.

VII. **Diffuse neuroendocrine system (carcinoid) tumors**

A. **Presentation**

1. **History and risk factors.** Patients with carcinoid tumors (gastrointestinal neuroendocrine tumors) are first seen with either incidentally identified tumors, tumors with local effects (hemorrhage, obstruction, or perforation), or the carcinoid syndrome. Most occur in the midgut (appendix, ileum, jejunum), but they can occur in the foregut (bronchus, thymus, or gastric) or hindgut (rectal) as well.

   The majority of patients with carcinoid tumors are asymptomatic at tumor discovery, most frequently at appendectomy or sigmoidoscopy. In particular, small (less than 1 cm) incidentally discovered tumors of the appendix or rectum almost never metastasize or cause further disability. However, patients with malignant gastrointestinal neuroendocrine tumors, especially those larger than 2 cm, or which are outside of the appendix or rectum, are often multicentric or metastatic at discovery.

   Less frequently (2% to 6%), but more dramatically, patients with tumors that have access to the systemic circulation may have the carcinoid syndrome. This is characterized by intermittent flushing, diarrhea and nausea, valvular disease of the right side of the heart, and bronchial constriction. Not all patients express all of the aspects. Most of these patients have liver metastases and elevated urine 5-hydroxyindoleacetic acid levels (u5-HIAA). Survival is poor, less than 21% at 5 years, in patients with carcinoid syndrome.

2. **Physical examination.** Most patients have a normal physical examination. Patients with the carcinoid syndrome may have palpable liver enlargement, and those with long-standing flushing may have chronic violaceous skin. During flushing episodes, most patients have erythema over the face and upper body.

B. **Staging evaluation**

Patients should have a CT scan and somatostatin-receptor scintigraphy to evaluate for the presence and extent of liver and lymph node metastases. Late in the course of disease, tumor may spread to other sites as well. All patients should have a 24-hour urine collection for 5-HIAA measurement, and plasma chromogranin A determination. All patients with metastatic disease should have an echocardiogram to document any right-sided heart disease.

C. **Stage-directed approach to treatment**

The primary treatment for these tumors is resection. The application of this therapy may extend to radical resection of hepatic and nodal metastases, if present.

For tumors smaller than 2 cm confined to the appendix, appendectomy alone is adequate. For tumors of the appendix that are larger, or which extend to the serosa or the resection line, then right hemicolectomy is preferable. For most small (less than 2 cm) rectal tumors, local resection is adequate; however, for larger or invasive lesions, an appropriate anatomic resection is better. If disease from appendiceal, rectal, or small bowel tumor extends to mesenteric lymph nodes, then the nodes should be removed *en bloc*. This can be quite challenging, as the nodal metastases may be much larger than the primary tumor, and care must be taken to avoid massive bowel devascularization and resection.

Metastatic tumor should be resected for potential cure, if feasible. Total hepatectomy and transplantation is probably not reasonable for most patients because of high recurrence rates. Control of the disease and carcinoid syndrome may be aided by operative debulking, hepatic artery embolization, or radiofrequency ablation of the hepatic tumors. These approaches may slow tumor progression, and equally important, they may improve quality of life in patients with the carcinoid syndrome.

Systemic therapy to control the tumor growth generally starts with interferon-a and somatostatin-receptor analogues; objective responses occur in 8% to 18% of patients, and stabilization, in up to 67%. If there is progression, then the most common chemotherapy regimen is streptozotocin and 5-fluoruracil. Although other combinations with streptozotocin work as well (22% to 36% objective response rate), none is so well tolerated.

The systemic management of the carcinoid syndrome is made much easier by the availability of the somatostatin analogues. Octreotide is most frequently used and requires dosing 2 to 3 times daily, but with appropriate doses can control carcinoid symptoms well. Tachyphylaxis is nearly uniform, and so the doses must be increased over time. Newly available long-acting depot somatostatin analogues make the dosing more convenient, but still require adjustment of the administered dose and the interval (usually every 21 to 30 days).

D. **Disease-specific complications**

The complications of these tumors are mainly the hormonal syndrome that can occur (see earlier) and local effects of the tumor growth. In some patients, severe mesenteric and retroperitoneal fibrosis develops, presumably because of vascular effects of the hormones produced. The fibrosis can cause vascular occlusion and bowel infarction as a complication of the fibrosis.

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CHAPTER 10A. ESOPHAGEAL AND GASTRIC CANCER

Revathi Suppiah, Will Read, and Ramaswamy Govindan

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I. Esophageal cancer

A. **Subjective.** Patients with esophageal cancer usually have symptoms of dysphagia for solid foods to begin with and then semisolids and eventually liquids with the progression of the disease. Patients often do not have any symptoms until the esophageal lumen is greatly narrowed. Although dysphagia occurs in 95% of symptomatic patients, the other reported symptoms include regurgitation (40%), weight loss (50%), pain on swallowing (20%), or cough (20%). History should include particular questions on local effects of the tumor such as pain, cough, shortness of breath, and symptoms related to possible metastases.

B. **Objective.** Physical findings may suggest only cachexia and evidence of metastases such as supraclavicular lymphadenopathy, hoarseness from recurrent laryngeal nerve involvement, pleural effusion, hepatomegaly, or bony tenderness.

C. **Workup.** Symptoms or signs suggesting esophageal cancer should prompt further work that includes preliminary studies with CBC, liver-function tests to provide clues for possible liver metastases, chest radiograph to recognize pulmonary and mediastinal disease, and an esophagogram. Barium contrast studies can reveal an intraluminal mass with mucosal irregularities and/or strictures, but early lesions often show no abnormalities. An abnormal esophagogram should be followed with an endoscopy to detect radiologically occult neoplasms, to obtain brushings, or to perform biopsies of suggestive lesions. Many physicians use endoscopy as the primary tool for diagnosis of esophageal cancer without initial barium contrast radiography because flexible endoscopy has the ability not only to visualize the intraluminal tumor but also can be used to obtain a biopsy to establish a histologic diagnosis. An essential part of esophageal cancer staging, computed tomography (CT) predicts metastases in more than 90% of cases involving the mediastinal lymph nodes, tracheobronchial tree, pericardium, liver, and adrenal glands. Neoplastic growth of the esophagus may be visualized on CT, usually as a circumferential involvement of a particular region of the esophagus or as a focal region of wall thickening. Endoscopic ultrasound is an important tool for assessing tumor depth and thereby staging local disease and for detecting smaller lymph node involvement, particularly paraesophageal and celiac nodes. This procedure, involving insertion of an ultrasound probe into the esophagus and stomach, allows the most precise assessment of tumor depth involvement, length of esophagus affected, and magnitude of lymph node metastases. This procedure depends, to a great extent, on the skill of the individual performing the procedure. Positron emission tomography (PET) scans are increasingly used in the staging evaluation of patients with esophageal cancer.

D. **Staging.** Esophageal cancer staging depends on the tumor, node, metastases (TNM) system established by the American Joint Commission for Cancer (AJCC) and the International Union Against Cancer (UICC) (Table 10.1). In the AJCC/UICC staging classifications, the clinical, surgical, and pathologic stages are all established from the same TNM anatomic criteria. “T” pertains specifically only to the depth of primary tumor involvement, whereas length of the growth, extent of involved circumference, and extent of tumor obstruction play no role in staging. “N” indicates specified regional lymph node involvement by cancer. “M” pertains to distant metastases to lymph nodes other than the regional nodes, or to organs not affected by direct extension from the primary esophageal tumor. CT of the chest and abdomen should be the initial tests for staging purposes; thereafter, if the CT is negative for metastasis, endoscopic ultrasound or PET scans should be considered to attain a precise regional staging. Combining both CT and endoscopic ultrasound gives an overall stage accuracy of about 85%, which is significantly more precise than that obtained with CT alone.

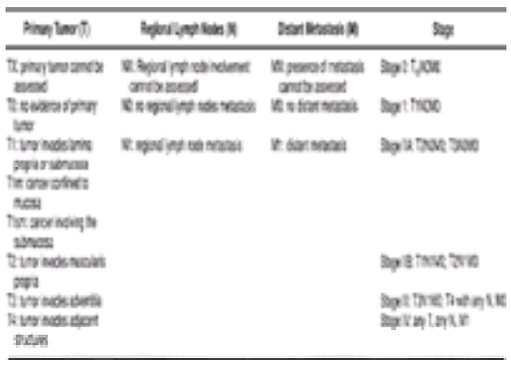

TABLE 10.1. STAGING CLASSIFICATION OF ESOPHAGEAL CANCER

E. **Therapy**

1. **Surgery as a single modality therapy.** Surgery is considered the standard therapy for stage I, II, and III esophageal cancers. Whereas the primary goal of surgery is cure, palliation of dysphagia is a significant secondary purpose. The best chance for surgical cure involves removal of the entire tumor and draining lymph nodes with adequate proximal and distal margins. Esophageal resection is a major surgery, with mortality rates ranging from 3% to 20%. After an esophagectomy, most patients are reconstructed with a primary esophagogastric anastomosis in the neck or chest. The three most frequently used approaches for resection are (a) an Ivor–Lewis approach in which a laparotomy and right thoracotomy are performed for esophageal resection and gastric mobilization with an anastomosis in the upper thorax, (b) a transhiatal esophagectomy through a cervical and abdominal approach with cervical anastomosis, and (c) a left thoracoabdominal approach with an anastomosis below the aortic arch. Curative surgery is accomplished in only about half of the patients, and median survival is 12 to 15 months. Locoregional relapse after surgical resection ranges from 15% to 25%.
2. **Surgery as a part of multimodality therapy.** Four prospective randomized studies, including the large North American Intergroup study, failed to reveal any survival advantage with the use of cisplatin-containing chemotherapy regimens when administered before surgery in patients who have resectable disease (*Gastroenterol Clin North Am* 1997;26:635–645). We do not recommend the use of preoperative chemotherapy in patients with resectable esophageal cancer outside the context of a clinical study. Although preoperative radiotherapy improves the resection rate and reduces the risk of locoregional dissemination of cancer during surgery, no statistically significant survival rates have been found with the use of preoperative radiotherapy alone (*Chest* 1998;113:112–119). However, the use of preoperative chemotherapy with radiation has been shown to have survival advantage in one study, although not confirmed by others (*N Engl J Med* 1996;335:462–467). Several phase II studies have reported higher pathologic complete response rates when patients with resectable esophageal cancer were treated with chemoradiation as opposed to chemotherapy alone. In view of the encouraging response rates reported in several phase II studies and the improved survival reported in one study, this approach has become a fairly acceptable

standard among the oncologists treating esophageal cancer. We strongly encourage enrolling patients with resectable esophageal cancer in prospective clinical studies.

Radiation therapy administered after surgery has been shown to decrease local relapse but has not been shown to improve survival rates (*Surg Gynecol Obstet* 1991;173:123–130; Fok M. *Surgery* 1993;113:138–147).

3. **Nonsurgical therapies**
   a. **Chemoradiation.** Patients who have metastatic disease confined to regional lymph nodes and are considered not to be candidates for surgical resection should be considered for combined-modality therapy with chemotherapy and radiation therapy. It has been clearly established that combined-modality therapy with cisplatin, 5-fluorouriacil (5-FU) and concurrent radiation therapy results in an improved 5-year survival rate compared with radiation therapy alone (*N Engl J Med* 1992; 326:1593–1598).
   b. **Radiation alone.** Radiation therapy alone as a curative modality in esophageal cancer is ineffective and should be resorted to only for palliation or in patients who are medically too unstable to undergo chemotherapy. The overall 5-year survival rate for patients given radiotherapy alone varies from 0 to 10% (*Int J Radiat Oncol Biol Phys* 1989;16:329–334; *Clin Radiol* 1982;33:347–352; *Int J Radiat Oncol Biol Phys* 1989;17:49–54). Intraluminal brachytherapy, performed through bronchoscopy or a nasogastric tube, offers an enhanced amount of radiation dose to the tumor but at the same time protects the adjacent organs such as the lung, heart, and spinal cord. Brachytherapy has been tried as the sole therapy (*Radiother Oncol* 1995;37:237–240) and as a boost subsequent to external-beam radiation therapy (*Int J Radiat Oncol Biol Phys* 1997;38:769–775). A significant drawback of brachytherapy is the effective treatment distance; any part of the growth that is more than 1 cm away from the location of the radioactive source will not acquire the optimal radiation dose. Brachytherapy as a sole treatment offers a local control rate of 25% to 35%, but significant toxicities limit its use.
   c. **Chemotherapy.** Chemotherapy agents effective in esophageal cancer include cisplatin, 5-FU, paclitaxel, docetaxel, vinorelbine, and irinotecan (*Semin Oncol* 1999;25:12–20). A combination chemotherapy regimen consisting of cisplatin and either a taxane or 5-FU is the most commonly used regimen in patients with esophageal cancer.
   d. **Other palliative procedures.** For patients who are not able to withstand or do not select surgery, various endoscopy-guided therapies such as mucosectomy, electrocautery, argon plasma coagulation, neodymium (Nd)/yttrium-aluminum-garnet (YAG) laser, and photodynamic therapy may substitute as palliative alternatives. Numerous palliative modalities (mechanical, thermal, and chemical) are available to relieve dysphagia in advanced esophageal cancer. Dilation with balloons or bougies is commonly performed for temporarily relief of dysphagia to tolerate consumption of a soft diet. Tubes or expandable metal stents may be placed within malignant strictures to preserve luminal patency and lessen dysphagia. With overall postinsertion complication of 20% to 40%, stents have the disadvantage of a high incidence of complications including hemorrhage, migration, and fistulization. High-power Nd/YAG laser may ameliorate dysphagia by coagulation and vaporization of the cancer growth through endoscopy, or the tumor may be ablated by photodynamic therapy (PDT).

F. **Course of the disease.** Esophageal cancer is highly lethal, causing death for more than 90% of affected patients. Three fourths have mediastinal node involvement or distant spread at the time of diagnosis. Death often occurs from progressive weakness secondary to metastatic disease or aspiration pneumonia from local disease.

G. **Complications.** Complications of the esophageal cancer itself on follow-up include hemorrhage, obstruction, tracheoesophageal fistula, and aspiration pneumonia.

   Complications of therapy include chylous effusions, anastomotic leak (after surgery), severe esophagitis, pain (secondary to radiation therapy), and the complications associated with cytotoxic chemotherapy.

H. **Epidemiology.** Esophageal cancer is a commonly found neoplasm and is the seventh most common cause of cancer death in the world. The vast geographic variation in the incidence of this cancer has led to numerous studies on the epidemiology of esophageal cancer. For instance, the incidence in the United States is about five per 100,000, although in black men, it may be as high as 18 per 100,000, whereas China and Iran have a greater incidence of 20 per 100,000. In parts of Africa, Central America, and Western Asia, the incidence is only 1.5 per 100,000 or even less. Moreover, within the United States alone, there are regional differences, with high incidences found in the southeastern coastal areas.

   Esophageal cancer comprises mainly squamous cell carcinoma and adenocarcinoma subtypes. Other histologic types, sarcomas, small-cell carcinomas, and lymphomas, are extremely rare. Of the two most common histologies, squamous cell tumors make up 98% of malignancies in the upper and middle one third of the esophagus, whereas adenocarcinoma is found predominantly in the lower third. Previously squamous cell carcinoma was the most frequent subtype, but in the past 20 years, the incidence of adenocarcinoma has been increasing rapidly in the western world and especially in white men.

   As in many cancers, the incidence of esophageal cancer increases with older age and is rarely found among patients younger than 40 years. Squamous cell carcinoma affects African-American men 6 times more than white men, whereas adenocarcinoma affects white men 4 times as much. All subtypes of esophageal cancers afflict men 3 times as often as women.

   Long-term use of tobacco and alcohol are predisposing factors for development of squamous cell carcinoma of the esophagus. Alcoholic smokers in the western world account for 90% of all squamous cell cases. Dietary factors involved in esophageal carcinogenesis are inadequate vegetable and fruit intake, along with deficiency of vitamins (particularly C) and trace elements such as molybdenum. Nitrosamines and their precursors (found in pickled vegetables, moldy or fermented foods, and smoked fish) are known to promote cancerous changes in the esophagus. Achalasia-induced squamous cell carcinoma accounts for about 2% to 7% of cases and is often localized to the middle third of the esophagus. In a patient in whom achalasia is not treated, the esophageal mucosa is burdened with stasis and chronic inflammation, promoting malignant transformation. Tylosis, a rare genetic syndrome, carries the highest risk of developing squamous cell carcinoma from chronic inflammation and stasis (1,000-fold risk). An autosomal dominant trait, it is characterized by hyperkeratosis of the palms and soles and may produce defective vitamin A metabolism. Cancer from benign esophageal stenosis also is known to occur but rarely. Squamous cell carcinoma in these cases is usually related to a caustic stenosis, especially lye-induced esophageal strictures, or may be due to esophageal webs and the Plummer–Vinson syndrome (sideropenic dysphagia). Other conditions associated with esophageal cancer are head and neck malignancies, celiac disease, and gastroesophageal reflux disease.

   Barrett esophagus (BE) predisposes to the development of adenocarcinoma of the esophagus (*Chest Surg Clin North Am* 1994;4:227–240). BE increases the risk of adenocarcinoma by 30 to 125 times that of the normal patient population (26). Other controversial risk factors are obesity, smoking, alcohol consumption, and dietary factors (4). In BE, the normal squamous epithelium of the esophagus is destroyed by chronic gastroesophageal reflux of acid, pepsin, and bile, and ultimately is replaced by a specialized intestinal columnar epithelium.

I. **Research initiatives.** The role of neoadjuvant therapy in patients with resectable esophageal cancer continues to be studied in clinical trials. Several combination chemotherapy regimens are being studied in this setting along with radiation therapy, as is addition of targeted therapies like celecoxib in conjunction with chemoradiation.

II. **Gastric cancer**
   A. **Subjective.** Gastric cancer usually occurs with nonspecific constitutional symptoms: chief among these is weight loss, which is among the presenting symptoms in 80% of patients. Other symptoms include anorexia, fatigue, or vague stomach pain. Symptoms of this type that persist for more than 2 weeks warrant evaluation, especially in a patient from a group at high risk for stomach cancer. Other symptoms may include dysphagia [from gastroesophageal (GE) junction tumors] or vomiting (from gastric outlet obstruction). Rarely, an early gastric cancer will occur with a paraneoplastic syndrome such as acanthosis nigrans or the sign of Leser–Trelat.
   B. **Objective.** Physical findings in gastric cancer are late manifestations of metastatic disease and can include cachexia and malignant ascites. Cancer markers, including carcinoembryonic antigen (CEA), may be elevated in some patients but have no proven diagnostic value. Several eponymic terms describe metastatic patterns in gastric cancer. *Virchow's node* describes metastasis to the left supraclavicular node. *Sister Mary Joseph's node* is a periumbilical metastasis. The ovaries may be preferred metastatic sites, and ovarian metastases are called *Krukenberg tumors*. *Blumer's shelf* describes a “drop metastasis” into the perirectal pouch, palpable on rectal examination.
   C. **Workup.** Flexible endoscopy is the procedure of choice for suspected gastric cancer: the endoscopist can visualize small lesions and obtain tissue biopsies. The latter are important to rule out gastric lymphoma, for which treatment is different. Gastric cancer may be seen as an ulcerating lesion, and biopsy of newly diagnosed ulcers is important to rule out cancer, especially if the ulcer is refractory to treatment. Endoscopy is used in the Japanese screening program for gastric cancer, which is credited for the increased proportion of early gastric cancers diagnosed in that country. As in esophageal cancer, endoscopic ultrasound may be used to gauge tumor depth. CT scans are used for further staging, although metastatic peritoneal deposits invisible on CT may be discovered on subsequent laparotomy. Gastric cancer is surgically staged with the AJCC TNM criteria (Table 10.2). These criteria require removal of

at least 15 lymph nodes, and thus at least a D1 dissection (see later).

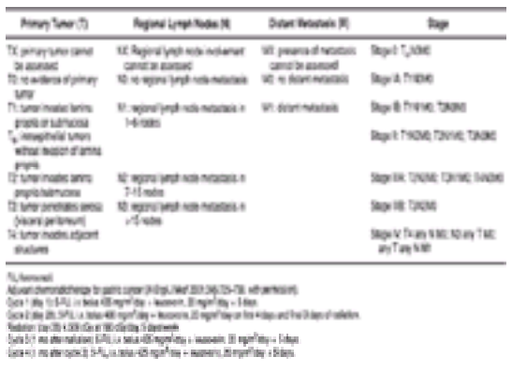

TABLE 10.2. STAGING CLASSIFICATION OF GASTRIC CANCER

D. **Therapy**

1. **Surgery.** Surgery is the only curative therapy for gastric cancer. Patients with cancers localized to the distal stomach may be cured with subtotal gastrectomy. Other sites should be treated with total gastrectomy. United States patients with resected stage I cancer have a 5-year survival of 58% to 78%. Stage II survival ranges from 20% to 34%, and stage III, from 8% to 20%. There continues to be controversy over the extent of surgery required. In Japan, the standard of care is a D2 lymph node dissection, which in addition to gastrectomy, removes the perigastric nodes along the greater and lesser curvature (the N1 group of nodes) as well as the nodes along the left gastric artery, the common hepatic artery, the celiac artery, and the splenic artery (the N2 group of nodes). The tail of the pancreas and the spleen also are sometimes removed in a D2 dissection. Japanese investigators credit this extensive dissection for the superior outcomes in Japanese patients; stage for stage, survival is double or triple that of American patients (*Cancer* 2000;88:921–932). Other possible reasons for the better outcomes in Japan are that the disease is different (i.e., more intestinal-type, well-differentiated cancer) or stage migration occurs. Stage migration occurs when more thorough investigation finds less obvious sites of disease spread in some patients. These patients are upstaged, and by removing them from the cohort, the patients who remain have improved outcomes on average. Outside of Japan, the D2 dissection is associated with greater morbidity, and controlled, randomized studies have not shown D2 dissection to be better than the more limited D1 dissection, in which only the N1 group of nodes is removed (*N Engl J Med* 1999;340:908–914). D1 dissection is the generally accepted standard in the United States, although it is likely that many patients receive even less than this; in a recent study of 556 patients with resectable gastric cancer, despite the recommendation by investigators that patients undergo a D2 dissection, only 10% of patients actually received this. Only 36% received a D1 dissection, and 54% received less than D1 (D0). In addition, it is unclear whether GE-junction tumors should be resected and staged like esophageal or gastric tumors. The ideal type and extent of surgery for gastric cancer continues to be debated.
2. **Surgery as a part of multimodality therapy.** Until recently, studies did not show better outcomes with the addition of chemotherapy and radiation to surgery (*Cancer* 1999;86:1657–1668). The recently completed INT-116 study showed that the group of patients with gastric and GE-junction tumors who received adjuvant 5-FU and radiation after surgery had a significantly improved 5-year median survival (36 months vs. 27 months) compared with patients who underwent surgery alone (*N Engl J Med* 2001;345:725–730). As mentioned earlier, a criticism of this study was that many patients received suboptimal lymph node dissections. Nevertheless, adjuvant chemoradiation has become the standard of care in U.S. patients.
3. **Nonsurgical therapies**
   a. **Chemoradiation.** Chemoradiation may be considered as primary treatment for unresectable patients with GE-junction tumors, as described in the section on esophageal tumors. Only surgery has been proven to improve survival in gastric cancer; other modalities should be considered palliative. Therefore chemotherapy and radiation should not be combined as primary treatment except as part of a clinical trial.
   b. **Chemotherapy.** Small studies have suggested that quality of life and overall survival can be modestly improved with chemotherapy (*Oncology [Huntingt]* 1998;12:44–47). Several combination regimens have been studied in advanced gastric cancer, including FAMTX (5-FU, doxorubicin, and methotrexate) and ELF (etoposide, 5-FU, and leucovorin). Although response rates are higher for combination regimens (40% to 50%) than those with single agents (10% to 20%), median survival for treated patients is the same, ranging from 6 to 8 months. Therefore single-agent 5-FU is a reasonable and tolerable standard for palliation of these patients. The addition of cisplatin or irinotecan might be considered in patients for whom more aggressive treatment is desired off study. Other active single agents include irinotecan, etoposide, and capcitabine; the latter two have oral formulations that may be convenient for patients. Available treatments for these patients are unsatisfactory, and enrollment in clinical studies is encouraged.
   c. **Other palliative procedures.** Debulking/diverting surgery may improve quality of life in selected patients with discrete obstructing tumors. Radiotherapy may palliate bleeding or painful metastases. Other procedures are similar to those discussed for esophageal cancer.

E. **Course of the disease.** Like esophageal cancer, gastric cancer is aggressive: up to 80% of U.S. patients undergoing complete resection will soon develop local and distant recurrences and die of their disease. This contrasts with Japanese patients, who often are first seen with earlier disease and have a 50% rate of cure.

F. **Complications.** Complications of gastric cancer include hemorrhage, obstruction and inability to eat, and malignant ascites. Anastomotic leaks are the most common complication of gastrectomy; other complications arise from pancreatic and splenic resections when these are included.

G. **Pathology.** Of gastric cancers, 90% or more are adenocarcinomas, the remainder being non-Hodgkin lymphomas (NHLs) and leiomyosarcomas (GI stromal tumors). It may require immunohistochemistry to distinguish NHL from adenocarcinoma of the stomach, but this is an important distinction, as NHL patients may not require surgery. The Lauren classification divides gastric adenocarcinomas into the intestinal and diffuse types. The intestinal type arises from a background of intestinal metaplasia and shows differentiation resembling that of a colonic adenocarcinoma. Intestinal type is predominant in epidemic areas, affects older patients, and metastasizes first to the liver. The diffuse type is poorly differentiated, predominant in endemic areas, affects younger patients, and tends to metastasize as peritoneal implants and malignant ascites. Outcomes are generally better for patients with intestinal type. The Borrmann classification divides adenocarcinomas by their growth pattern. Types I and II are polypoid and heaped-up ulcers, respectively, and are associated with the intestinal type. Type III is an ulcerated, infiltrating tumor, and type IV, diffusely infiltrating; this last type also is referred to as *linitis plastica* or “leatherbottle stomach.” These are associated with the diffuse type of adenocarcinoma. GE-junction tumors are usually the diffuse type. The boundaries between these groupings are not sharp, and some tumors are not easily categorized.

H. **Epidemiology.** The epidemiology of gastric cancer is interesting. Gastric cancer was once the most common malignancy in the United States, but has decreased in incidence since the 1930s (*Carcinogenesis* 1999;20:2195–2208). Estimated new cases for 2001 are 13,400 (4.8 per 100,000) for men and 8,300 (2.9 per 100,000) for women (*Ca Cancer J Clin* 2001;51:15–36); this is down from a combined rate of 28.8 per 100,000 in 1930. Worldwide, gastric cancer is surpassed only by lung cancer in frequency and is the most frequent cancer in Japan, where the incidence reaches 93.3 per 100,000. Therefore high-incidence areas are labeled “epidemic,” whereas in the remainder of the world, gastric cancer is “endemic.” The high incidence in Japan has resulted in the creation of an endoscopic screening program, which is credited for the high frequency of early-stage cancers (50%) in Japanese patients. In contrast, more than 80% of Western patients have advanced cancers at diagnosis.

   The intestinal and diffuse types of gastric cancer differ in regard to epidemiology and risk factors. The intestinal type is associated with consumption of large amounts of salt and preserved foods, and possibly with *Helicobacter pylori* infection. These irritants lead to intestinal metaplasia of the stomach, which can then transform into frank malignancy. Other predisposing factors include achlorhydria associated with pernicious anemia, and previous partial gastrectomy for peptic ulcer. It is thought that the lack of stomach acid in these conditions predisposes to intestinal metaplasia. Despite this, long-term use of H_2 blockers is not a risk factor. The intestinal type of gastric cancer is prevalent in Japan, where preserved and salty foods are widely consumed. The decrease in the incidence of gastric cancer in the United States may relate to the availability of refrigeration and a dietary shift toward fresh foods. Asian patients may have genetic predispositions increasing cancer risk as well, as the rate decreases in Japanese immigrants to the United States who adopt local diets, but remains elevated compared with the populace as a whole. The diffuse type is more sporadic and is not associated with diet; the increased proportion of this more aggressive type among gastric cancers in the United States may in part be responsible for the worse outcome of American gastric cancer patients. There is a genetic predisposition to gastric cancer in some families, although the specific mutations responsible are not yet known. In contrast to the declining incidence of intestinal-type adenocarcinomas, diffuse-type adenocarcinomas of the esophagus and gastric cardia (among which are included GE-junction tumors) are increasing in the United States. The incidence of these cancers has doubled among white American men in the past 25 years, with similar increases in Northern Europe. The reason for this increase is not clear (*JAMA* 1991;265:1287–1289).

I. **Research areas.** The success of the recent intergroup trial has renewed interest in adjuvant chemoradiotherapy; experimental approaches include neoadjuvant or intraoperative chemotherapy as well as intraperitoneal chemotherapy. The presence of Epstein–Barr virus (EBV) in a subset of gastric adenocarcinoma may permit virus-targeted therapy for this subset of tumors.

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CHAPTER 10B. PANCREATIC AND HEPATOBILIARY CANCERS

Benjamin Tan and Joel Picus

Pancreatic cancer
Clinical presentation
Diagnosis, workup, and staging
Therapy
Complications
Follow-up
Background
Current focus
Other pancreatic tumors
Hepatocellular cancer
Clinical presentation
Diagnosis, workup, and staging
Therapy
Complications
Follow-up
Background
Current focus
Gallbladder carcinoma and cholangiocarcinoma
Clinical presentation
Diagnosis, workup, and staging
Therapy
Follow-up
Background
Current focus
Suggested Readings

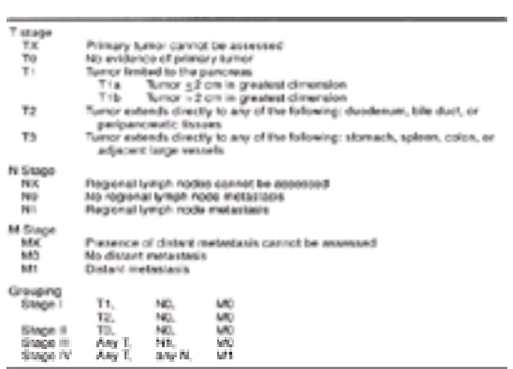
I. Pancreatic cancer

A. Clinical presentation

1. **Subjective.** Many patients are first seen with advanced pancreatic cancer because of lack of early clinical symptoms. Nonspecific complaints such as anorexia, weight loss, abdominal discomfort, nausea, vomiting, or fatigue are common. **Epigastric pain,** caused by splanchnic nerve or celiac plexus infiltration, may be gnawing or severe and may radiate to the back or the shoulder. Painless **jaundice** occurs because of common bile duct compression by tumors located in the head of the pancreas. Often patients notice pale stools or darkening of their urine color. **Wasting,** anorexia, and weight loss are common. **Gastric outlet or duodenal obstruction** due to local invasion of the tumor may occur.
2. **Objective.** Jaundice with a palpable gallbladder (**Courvoisier sign**) is pathognomonic of pancreatic cancer in the absence of cholecystitis or cholangitis. Widespread disease may be evidenced by left supraclavicular lymph node enlargement (**Virchow's node**), an umbilical mass (**Sister Mary Joseph's node**), or a palpable pelvic mass on rectal examination (**Blumer's shelf**). Migratory superficial phlebitis (**Trousseau syndrome**) also may be associated with pancreatic cancer. Paraneoplastic syndromes such as the panniculitis–arthritis–eosinophilia syndrome may arise from tumor-induced lipase release.

B. Diagnosis, workup, and staging

1. **Pathology.** CT-guided percutaneous fine-needle biopsy is the recommended procedure for locally advanced or metastatic pancreatic cancer. Laparoscopic biopsy or endoscopic ultrasound–guided (EUS) biopsy may be done in cases of potentially resectable pancreatic cancer. Most tumors are adenocarcinomas arising from the exocrine pancreas. Tumors of the endocrine pancreas, such as insulinomas, gastrinomas, and vasoactive intestinal peptide (VIP)omas are rare.
2. **Radiology.** Accurate radiologic staging of pancreatic cancer is necessary to characterize the primary pancreatic mass, determine the presence of nodal and distant metastatic disease, and assess the resectability of the tumor. Initial workup for a jaundiced patient includes an abdominal **ultrasound,** which can differentiate between a cyst and a solid mass and assess the presence of bile duct dilatation. **CT scan or magnetic resonance imaging (MRI)** is the study of choice for staging and determination of tumor resectability. Triple-phase **spiral CT** improves detection of tumor involvement of the celiac axis and mesenteric vessels. Other less commonly used tests, including **EUS** may enhance determination of portal vein as well as regional lymph node tumor involvement. Diagnostic and therapeutic **endoscopic retrograde cholangiopancreatography (ERCP)** can be performed to differentiate between a malignant intrapancreatic common bile duct stricture, which is characterized by a double-duct sign or proximal dilatation of the pancreatic and common bile ducts, from benign strictures from choledocholithiasis. If bone pain is present and alkaline phosphatase is elevated, a **bone scan** is needed to exclude bony metastases.
3. **Laboratory tests** such as CBC, chemistries, and liver-function tests should be done initially. Serum markers such as CA19-9, if elevated, may be used later to monitor response to therapy.
4. **Staging.** See Table 10.3.



T stage			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Tumor limited to the pancreas		
	T1a Tumor ≤2 cm in greatest dimension		
	T1b Tumor >2 cm in greatest dimension		
T2	Tumor extends directly to any of the following: duodenum, bile duct, or peripancreatic tissues		
T3	Tumor extends directly to any of the following: stomach, spleen, colon, or adjacent large vessels		
N Stage			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Regional lymph node metastasis		
M Stage			
MX	Presence of distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Grouping			
Stage I	T1,	N0,	M0
	T2,	N0,	M0
Stage II	T3,	N0,	M0
Stage III	Any T,	N1,	M0
Stage IV	Any T,	any N,	M1

TABLE 10.3. STAGING OF PANCREATIC CANCER

C. Therapy

1. **Resectable pancreatic cancer.** Fewer than 25% of patients have resectable pancreatic cancer. Clinical criteria for resectable disease include T1 to T2 tumors or selected T3 lesions with isolated involvement of the superior mesenteric vein, portal vein, or hepatic artery without encasement of the celiac axis, and a patent superior mesentery artery with no extrapancreatic disease. Patients who undergo complete resection for localized pancreatic cancer have long-term survivals of 20%, with median survivals of 15 to 20 months with current therapy.
   a. **Surgery.** Patients with localized pancreatic cancer should be evaluated for surgical resection. Accurate preoperative assessment of operability with imaging studies will decrease positive-margin resections. Peritoneal implants, unsuspected liver metastases, and other intraabdominal disease may be detected at the time of surgery or on laparoscopy, thereby precluding resection. **Pancreaticoduodenectomy,** whether standard or pylorus sparing, is the treatment of choice and the only potentially curative therapy for localized pancreatic adenocarcinoma. This should be considered in patients with good performance status of 70% or higher on the Karnofsky scale. This standard procedure entails six defined steps including the Cattell–Braasch maneuver exposing the superior mesenteric vessels, Kocher maneuver, portal dissection, partial gastric resection, jejunectomy, and then pancreatectomy with retroperitoneal lymph node dissection. Surgery alone results in a median survival of 12 to 14 months. Local recurrences and distant metastases occur frequently, thereby limiting survival.
   b. **Adjuvant therapy.** The addition of postoperative 5-FU–based chemoradiation increases median survival to 18 to 22 months in patients with resected localized pancreatic cancer. **External-beam radiation (40 Gy) with concurrent 5-FU (500 mg/m^2/day for 6 days) chemotherapy** was demonstrated to improve survival in patients with completely resected pancreatic cancer in a small Gastrointestinal Tumor Study Group (GITSG) trial (*Arch Surg*

1985;120:899). Median survival was 20 months for patients receiving postoperative chemoradiation compared with 11 months in patients who had surgery alone. These results were confirmed by another study from Johns Hopkins (*Ann Surg* 1997;225:621). Therefore patients with resected pancreatic cancer should be offered adjuvant therapy or participation in trials using multimodal therapy. **Adjuvant combination chemotherapy** with 5-FU, doxorubicin, and mitomycin with no radiation also improved survival (23 months) compared with surgery alone (11 months) (*Eur J Cancer* 1995;29:698).

c. **Neoadjuvant therapy.** Patients with marginally resectable lesions should be considered for protocols using neoadjuvant chemoradiation. Although there are no randomized trials available to support neoadjuvant therapy versus postoperative therapy, advantages to this approach include the following: (a) no delay in delivering multimodal therapy because of prolonged postoperative course; (b) pancreaticojejunal leaks may be reduced with neoadjuvant therapy; and (c) patients with subclinical metastasis initially and progression during the preoperative regimen are spared a major operation. In an Eastern Cooperative Oncology Group (ECOG) trial, mitomycin and 5-FU with radiation rendered 45% of patients resectable with median survivals of 15.7 months (*J Clin Oncol* 1998;16:317). Rapid-fractionation preoperative chemoradiation using a 2-week course of 5-FU, 300 mg/m^2 daily for 5 days per week with 30 Gy, followed by surgery and electron beam intraoperative radiation, resulted in excellent locoregional tumor control and a 23% 3-year survival rate (*J Clin Oncol* 1998;16:3843).

2. **Locally advanced pancreatic cancer** confers a median survival of 6 to 10 months. Approximately 40% of patients diagnosed with pancreatic cancer have locally advanced disease. Patients with clear encasement of the celiac or mesenteric plexus or occlusion of the superior mesenteric portal vein (SMPV) are generally unresectable.
   a. **Chemoradiation.** The GITSG demonstrated a median survival advantage of 5-FU chemotherapy with 40 Gy radiation (9.6 months) compared with radiation alone (5.2 months) or chemotherapy alone (5.1 months) (*Cancer* 1981;48:1705; *J Natl Cancer Inst* 1988;80:751). However, the benefit is seen mainly in those with good performance status. Occasional cases of downstaging, which allows for successful resection, have been reported with chemoradiation.
3. **Metastatic pancreatic cancer.** The median survival of patients with metastatic pancreatic cancer is approximately 3 to 6 months.
   a. **Chemotherapy. Gemcitabine** is the standard of care in patients with unresectable or metastatic pancreatic cancer. When compared with **5-FU,** gemcitabine improved quality of life with a trend toward improved median survival and 1-year survival rates (5.7 months and 18% vs. 4.4 months and 2%, respectively) despite achieving very low response rates. The standard dose of gemcitabine is 1,000 mg/m^2 as a 30-minute infusion given weekly for 7 weeks, followed by a 1-week break, and then three weekly administrations every 28 days (*J Clin Oncol* 1997; 15:2403). 5-FU is the most extensively studied agent for pancreatic cancer either as a continuous infusion of 1,000 mg/m^2/d for 5 days or as bolus injections of 400 to 500 mg/m^2/d for 5 days. Combination with doxorubicin or mitomycin offers no added benefit. Ifosfamide, streptozocin, and taxanes show marginal activity against pancreatic cancer. **Supportive care** or participation in clinical trials should be offered to patients for whom front-line chemotherapeutic regimens fail.

D. **Complications**
   1. **Pancreatic insufficiency** may occur because of tumor involvement of the pancreas. Approximately 10% of patients with pancreatic cancer have **diabetes.**

      Severe **pain** may be treated with celiac axis blocks in addition to narcotic analgesics. Radiation may palliate pain from bony metastases.

   2. **Surgical complications.** Patients who undergo the Whipple procedure may have gastric-dumping syndromes, anastomotic leaks, fistula formation, and nutritional deficiencies. Postoperative sepsis, hemorrhage, and cardiovascular events may occur. Stent complications such as occlusion, infection, or migration require stent replacement.

E. **Follow-up.** For patients with resected pancreatic cancer who have completed adjuvant chemoradiation, physical examination, CBC, chemistries, liver-function tests, and CA19-9 may be monitored every 3 months, with CT scan every 6 months.

F. **Background**
   1. **Pancreatic cancer** is the fifth leading cause of cancer death in the United States. Only 1% to 4% of patients will be alive 5 years after their diagnosis. Cigarette **smoking** increases risk for developing pancreatic cancer by twofold to tenfold. Exposure to nitrosamines, alcohol, and chronic pancreatitis may be associated with pancreatic cancer. Rare familial syndromes such as the multiple mole melanoma syndrome may be associated with increased risk for pancreatic cancer. Genetic alterations with mutated p16, p53, and DCP4 with K-*ras* point mutations have been noted frequently in pancreatic cancer specimens. Approximately 30% of pancreatic cancers are HER2/neu positive.

G. **Current focus.** Topoisomerase I inhibitors and taxanes have shown promising activity against pancreatic cancer. Combinations of gemcitabine with cisplatin, 5-FU, irinotecan, rubitecan, and taxanes are under current investigations. Gemcitabine, given on a constant-infusion rate of 10 mg/m^2/minute, may improve 1-year survival compared with the standard 30-minute gemcitabine administration pending further evaluation (*Proc Am Soc Clin Oncol* 1999;18:273). Strategies to combine gemcitabine safely with radiation by using very low gemcitabine doses also are under investigation.

   Novel approaches such as targeting of *ras* protein farnesylation with farnesyl transferase inhibitors are ongoing. The tyrosine kinase HER2/neu is overexpressed in pancreatic cancer and may be targeted by monoclonal antibodies. Blockade of epidermal growth factor (EGF) receptors and inhibition of other tyrosine kinase also are being investigated.

H. **Other pancreatic tumors.** Tumors of the endocrine pancreas are rare and heterogeneous. The islet cell tumors include insulinomas, gastrinomas, VIPomas, glucagonomas, somatostatinomas, and other nonfunctional tumors.

   Insulinomas are b-cell pancreatic islet tumors producing insulin and causing recurrent hypoglycemia during fasting or exercise. Elevated insulin, proinsulin, and C-peptide levels are diagnostic. **Gastrinomas** produce gastrin and are associated with **Zollinger–Ellison syndrome,** causing peptic ulcers and diarrhea. This may be associated with MEN1. An elevated fasting serum gastrin level of more than 1,000 pg/mL or an increase of more than 200 pg/mL after secretin challenge are diagnostic. **VIPomas** are associated with large-volume watery diarrhea, hypochlorhydria, hypophosphatemia, and hypokalemia. Necrolytic migratory erythema can herald **glucagonomas,** which also are associated with diabetes, weight loss, cheilosis, and glossitis. **Surgical excision** is preferred, if possible. Chemotherapy with doxorubicin and streptozotocin was better than 5-FU with streptozotocin in advanced islet cell tumors (*N Engl J Med* 1992;326:519). Octreotide treatment may improve symptoms of both VIPomas and glucagonomas (see Chapter 9).

II. Hepatocellular cancer

Approximately 1 million new cases of hepatocellular carcinoma occur worldwide annually, and it is the most common primary cancer of the liver. Hepatitis B and C as well as cirrhosis are major risk factors.

A. **Clinical presentation**
   1. **Subjective.** Most patients have nonspecific symptoms such as weakness, anorexia, malaise, weight loss, upper abdominal pain, abdominal fullness, or swelling. Hematemesis may occur because of esophageal varices. Jaundice occurs because of biliary duct obstruction.
   2. **Objective.** Common physical signs include hepatomegaly, ascites, jaundice, abdominal bruits, and wasting. Splenomegaly may occur because of portal hypertension or portal vein occlusion. Other signs from the patient's underlying liver disease may be present, including palmar erythema, dilated superficial abdominal veins, gynecomastia, testicular atrophy, and pedal edema. The **Child–Pugh Score** is a good prognostic index and may influence management of patients with HCC. Both clinical (encephalopathy and ascites) and laboratory parameters [albumin, prothrombin time (PT), and total bilirubin] are scored, depending on severity. Patients with no encephalopathy or ascites, albumin greater than 3.5 g/dL, and total bilirubin of 1 to 2 mg/dL, and only a 1- to 4-second prolongation in PT have a Child A score (Table 10.4).

	Points		
	1	2	3
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Ascites	None	Mild	Moderate–severe
Encephalopathy	None	Mild	Moderate–severe
Prothrombin time (seconds above normal)	<4	4–6	>6
Grade			
Childs A, 5–6 points			
Childs B, 7–9 points			
Childs C, 10–15 points			

TABLE 10.4. CHILDS CLASSIFICATION OF HEPATIC CIRRHOSIS

B. **Diagnosis, workup, and staging**

1. **Radiology. Ultrasonography** has been used for screening high-risk populations in conjunction with tumor markers and chemistries. **Spiral CT scans** or **MRI** scans are done to determine the extent of the tumor, the number of lesions, and any extrahepatic involvement of HCC. **CT-scan angiography** may show characteristic increased arterial blood flow with decreased portal blood flow and may delineate tumors that are amenable to chemoembolization or intraarterial chemotherapy.
2. **Laboratory tests** should include hepatitis screening, liver-function tests, albumin, PT, total protein, albumin, lactate dehydrogenase, ammonia levels, and creatinine. Hypercalcemia, hypoglycemia, hypercholesterolemia, and erythrocytosis and other paraneoplastic syndromes may occur. Thrombocytopenia, anemia, or leukopenia may reflect underlying portal hypertension and hypersplenism. **a-Fetoprotein (AFP)** is elevated in 60% to 90% of cases. The **des-g-carboxy prothrombin (DCP)** also may be increased in HCC. However, chronic hepatitis also may increase both AFP and DCP.
3. **Diagnosis/Pathology.** Serum AFP levels of more than 4,000 ng/mL in hepatitis B or C antigen–positive patients and more than 400 ng/mL in surface antigen–negative patients are sufficient for a presumptive diagnosis of HCC. **Liver biopsy,** preferably a core biopsy, is required for a definitive diagnosis of HCC. Histologic examination may reveal nodular or diffuse HCC of trabecular, scirrhous, acinar, or fibrolamellar type. The fibrolamellar type is usually not associated with cirrhosis or an elevated AFP and carries a better prognosis than other types.
4. **Staging.** See Table 10.5.

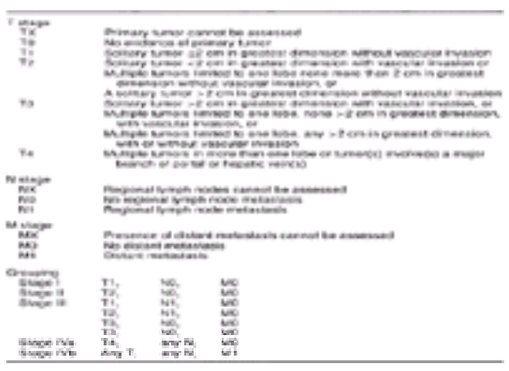


TABLE 10.5. STAGING FOR HEPATOCELLULAR CANCER

C. **Therapy**

1. **Limited HCC (TNM stages I and II)**
   a. **Liver resection** is the treatment of choice in patients with HCC with no chronic liver disease and in a small subset of cirrhotic patients with HCC. Optimal candidates for excision are Child–Pugh class A cirrhotics with normal serum total bilirubin, no clinically relevant portal hypertension, and small solitary lesions. Five-year survival with resection is similar for cirrhotic and noncirrhotic patients with HCC (45%), but patients with tumors less than 5 cm have a 60% 5-year survival compared with those with tumors larger than 5 cm (30%). Vascular invasion and hepatic transaminitis also are adverse prognostic features (*J Clin Onco*l 2000;18:1094). However, in one large series, only 14.4% of HCC patients were disease-free 10 years after curative resection (*Cancer* 1989;63:2201).
   b. **Orthotopic liver transplantation** (OLT) also is considered the first-line option in cirrhotic patients with tumors smaller than 5 cm, fewer than four total lesions, no vascular tumor involvement, and no hepatitis B infection. OLT is preferable in patients with hepatic insufficiency and multiple tumors and may offer better long-term survivals in cirrhotics because it also treats the underlying pathology. Overall 5-year survivals were reported to be approximately 70% (*N Engl J Med* 1996;334:693; *Hepatology* 1998;27:1572). Preoperative chemoembolization may limit disease progression while awaiting orthotopic liver transplantation, with excellent survival outcomes (*Liver Transpl Surg* 1999;5:192; *Liver Transpl Surg* 1995;1:242). Several studies have focused on adjuvant and neoadjuvant intraarterial or systemic chemotherapy, chemoembolization, or radiation. Strategies incorporating primary liver resection in cirrhotic patients with resectable lesions followed by salvage OLT on recurrence and deteriorating liver function may provide an alternative option, especially if the waiting list is long (*Hepatology* 1999;31:899).
   c. **Ultrasound-guided percutaneous 95% ethanol injections,** used in patients with Child A cirrhosis and tumors smaller than 5 cm, may produce greater than 60% 3-year survivals (*Cancer* 1992;69: 925).
   d. **Cryosurgery** may cause tumor necrosis but demonstrated only a 20% 3-year survival in 60 patients with HCC (*Cancer* 1988;61:1889).
2. **Unilobar HCC** with multiple lesions, with or without portal vein invasion or thrombosis, may be considered for aggressive presurgical intrahepatic chemotherapy or chemoembolization followed by resection or transplantation, resulting in 3-year survivals of 20% to 60%. **Extensive or extrahepatic HCC** or medically inoperable limited HCC can be treated with supportive care or any of the following palliative alternatives.
   a. **Chemoembolization** may be used to shrink tumors and palliate symptoms; however, two prospective randomized trials showed no survival advantage (*N Engl J Med* 1995;332:1256).
   b. **Chemotherapy** has generally been ineffective in extensive HCC. Single-agent **doxorubicin** may result in less than 20% response rates but no prolongation of survival (*Cancer* 1988;62:479). Other agents with marginal efficacy in HCC include 5-FU, interferon-a, mitoxantrone, cisplatin, and etoposide. **Combination chemotherapy** generally did not augment single-agent cytotoxic efficacy but only increased toxicity. Recently, cisplatin, doxorubicin, interferon-a, and 5-FU produced 26% response rates including complete responses in hepatitis B virus (HBV)-related HCC (*Clin Cancer Res* 1999;5:1676).
   c. **Intraarterial fluorodeoxyuridine (FUDR)** with mitomycin or leucovorin, doxorubicin, and cisplatin yielded response rates of 40% and median survivals of more than 1 year (*Cancer* 1992;29:920; *J Clin Onco*l 1994;12:1204).
   d. **Radiation therapy** may produce local control in symptomatic patients. Radiation should be limited to a total of 30 Gy to reduce risks of radiation-induced hepatic damage. **Three-dimensional (3D)-conformal radiation** allows higher radiation doses (up to 70 Gy) with acceptable toxicity.
3. **Recurrent HCC.** Tumor recurrences occur in more than 70% of patients after excision, especially in patients with stage IVA HCC, tumors larger than 5 cm, vascular infiltration, and more than five lesions (*J Clin Onco*l 1999;17:324). Late recurrences may be seen in patients with fibrolamellar tumors. Surgical treatment should be again be considered, if possible.

D. **Complications.** Budd–Chiari syndrome, due to tumor invasion of the portal and hepatic veins, may be fatal. Tense ascites compromising respiration may require palliative paracentesis.

Needle-tract implantation is rare with liver biopsies and may require more extensive surgery. Fulminant hepatic failure may occur with chemoembolization and other local therapies.

E. **Follow-up.** Physical examination with chemistries, liver-function tests, and CBC every 3 months is typical. If AFP was initially elevated, this should be monitored every 3 months for 2 years and then every 6 months. Ultrasound or CT scan surveillance may be done every 6 months for the first 2 years and then annually.

F. **Background. HCC** arises from long-standing cirrhosis from HBV or HCV infection, or excessive alcohol intake. Persistent HBV infection increases the risk of HCC by 100-fold and causes 80% of HCC in the world, mainly in Southeast Asia and Africa. In the United States and Japan, where HCC incidence continues to increase, HCV infection causes 50% to 70% of HCC cases. HCC develops in 1% to 4% annually of patients with HCV cirrhosis. Multistep genetic alterations may be induced by viral DNA integration, concurrent inflammatory necrosis, and hepatocellular regeneration. Loss of heterozygosity on several chromosomes has been noted, especially in association with HBV-positive tumors (*Hepatology* 2000;31:1073). Deletions of p16 and p53 mutations may play significant roles in hepatocarcinogenesis in HCV and aflatoxin-related HCC.

G. **Current focus**

1. **Adjuvant therapy** with polyprenoic acid and intraarterial, radiolabeled lipiodol to prevent tumor recurrence after curative resection has shown benefit but requires confirmation (*N Engl J Med* 1996;334:1561; Lau. *Lancet* 1999;353:797). **Interferon-b,** at 6 million units twice weekly after curative resection of HCV-related HCC, suppressed tumor recurrence in one small study (*Hepatology* 2000;32:228). However, this must be validated in a larger randomized study.
2. **Prevention** of HCC by using anti-HBV vaccine has decreased the incidence of HCC by approximately 50% in Taiwan (*N Engl J Med* 1997;336:1855). Response to interferon-a in chronic HBV and HCV hepatitis may reduce risk for HCC (*Ann Intern Med* 1995;122:664; *Lancet* 1995;346:1051). Lamivudine

(ribavirin) may eradicate HCV and therefore decrease HCC risk.

III. **Gallbladder carcinoma and cholangiocarcinoma**

Gallbladder cancer is the most common biliary tract tumor and represents the fifth most common gastrointestinal (GI) malignancy. **Cholangiocarcinomas** may occur anywhere throughout the biliary tract and are usually grouped into intrahepatic and extrahepatic types. **Intrahepatic** cholangiocarcinomas usually are peripheral in location because they arise from small biliary canaliculi. **Extrahepatic cholangiocarcinomas,** including **Klatskin tumor,** may occur in the major biliary ducts including the common bile duct, hepatic ducts, and even in the pancreatic portion of the bile duct.

A. **Clinical presentation**
   1. **Subjective.** Early gallbladder cancer and cholangiocarcinoma may be asymptomatic. Jaundice, abdominal discomfort or pain, anorexia, weight loss, pruritus, and fatty food intolerance may occur in more advanced stages. Occasionally cholangiocarcinomas may occur as hepatic abscesses.
   2. **Objective.** Except for jaundice, physical examination is usually normal. Occasionally ascites, hepatomegaly, or an abdominal mass may be detected.

B. **Diagnosis, workup, and staging**
   1. **Laboratory tests.** Baseline CBC, chemistries, and liver-function tests should be done. Alkaline phosphatase and bilirubin levels are usually elevated. An elevated g-glutamyl transferase (GGT) may indicate intrahepatic disease. Leukocytosis, anemia, hypoalbuminemia, or prolonged prothrombin times also may be seen. **CA19-9** levels may be elevated, but CEA and AFP levels are typically normal.
   2. **Radiology. CT scan or ultrasound** may detect thickened gallbladder, a liver mass, or dilated intrahepatic or extrahepatic ducts. CT scan is more helpful in assessing the extent of disease or involvement in surrounding structures or lymph nodes. **Cholangiogram,** either by percutaneous transhepatic (PTC) or endoscopic retrograde (ERC) technique, may show the site of high-grade or complete biliary obstruction. **Hepatic arteriography and portal venography** should be performed in patients with potentially resectable disease. **Magnetic resonance cholangiopancreatography** is a noninvasive alternative under investigation at present.
   3. **Pathology. Percutaneous fine-needle aspiration biopsy, bile samples, ductal brush biopsy, or intraductal biopsies** may confirm diagnosis of biliary cancers. Gallbladder tumors are usually adenocarcinomas of the scirrhous type, with squamous or mixed histologies in only 15% of cases. Most cholangiocarcinomas are adenocarcinomas of papillary, nodular, or sclerosing types. Adenosquamous, mucoepidermoid, or leiomyosarcomas also may occur.
   4. **Staging.** See Table 10.6 and Table 10.7.

T stage			
T1	Tumor invades mucosa or muscle layer		
T2	Tumor invades periductal tissue		
T3	Tumor invades adjacent structures		
N stage			
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph nodes		
M stage			
M0	No distant metastasis		
M1	Distant metastasis		
Grouping			
Stage I	T1,	N0,	M0
Stage II	T2,	N0,	M0
Stage III	T1,	N1,	M0
	T2,	N1,	M0
Stage IVa	T3,	N0–1,	M0
Stage IVb	T1–3,	N0–1,	M1

TABLE 10.6. STAGING FOR CHOLANGIOCARCINOMA

T stage			
T_{is}	Carcinoma in situ		
T1	Tumor invades mucosa or muscle layer		
T2	Tumor invades perimuscular connective tissue		
T3	Tumor perforates the serosa and/or directly invades one adjacent organ		
T4	Tumor extends >2 cm into the liver and/or into two or more adjacent organs		
N stage			
N0	No regional lymph node metastasis		
N1	Metastasis in cystic duct, pericholedochal, and/or hilar lymph nodes		
N2	Metastasis in peripancreatic, periduodenal, periportal, celiac, and/or mesenteric lymph nodes		
M stage			
M0	No distant metastasis		
M1	Distant metastasis		
Grouping			
Stage 0	T_{is},	N0,	M0
Stage I	T1,	N0,	M0
Stage II	T2,	N0,	M0
Stage III	T1,	N1,	M0
	T2,	N1,	M0
	T3,	N0–1,	M0
Stage IVa	T4,	N0–1,	M0
Stage IVb	T1–4,	N2,	M0
	T1–4,	N0–2	M1

TABLE 10.7. STAGING FOR GALLBLADDER CANCER

C. **Therapy**
   1. **Operable gallbladder cancer and cholangiocarcinoma**
      a. **Resection. Gallbladder carcinoma** that invades only the mucosa and not the muscularis layer requires cholecystectomy alone. More extensive involvement may require porta hepatis lymphadenectomy with wedge resection of the gallbladder bed. Intrahepatic or peripheral **cholangiocarcinomas** can be resected in up to 70% of cases versus only 20% in hilar extrahepatic lesions. The type of surgery depends on the site and extent of the tumor. Biliary stents may be placed before surgery to relieve obstruction. Distal tumors are treated with pancreaticoduodenectomy with *roux-en-y* anastomosis. Proximal lesions are treated with hilar resection with *en bloc* liver resection and lymphadenectomy. Bile duct excision with lymphadenectomy with a frozen section to assess margins is recommended for tumors in the middle third of the duct.
      b. **Adjuvant therapy.** Radiation with low-dose infusional 5-FU (225 to 300 mg/m^2/day) throughout radiation may be offered to patients with completely resected gallbladder cancer or cholangiocarcinoma. However, no randomized data are available to define this as a standard regimen. Patients with positive margins after resection may require additional resection or may be offered adjuvant chemoradiation.
   2. **Inoperable gallbladder cancer and cholangiocarcinoma**
      a. **Biliary stents** should be placed on patients with inoperable cholangiocarcinoma with obstructive jaundice. **Surgical bypass** may be necessary to palliate symptoms.
      b. **Chemotherapy. 5-FU** alone offers a 15% to 20% response rate in cholangiocarcinoma. **Gemcitabine** appears promising but requires additional controlled studies. Other agents with activity against cholangiocarcinoma include mitomycin, doxorubicin, and carmustine. Combination chemotherapy with continuous-infusion 5-FU, leucovorin, and mitomycin or 5-FU with cisplatin resulted in partial responses in small studies. 5-FU with interferon-a resulted in a 34% response rate and a 12-month median survival in patients with cholangiocarcinoma and gallbladder cancer (*J Clin Oncol* 1996;14:2311).
      c. **Chemoradiation.** Focal hepatic radiation at 70-Gy doses with concurrent hepatic artery fluorodeoxyuridine resulted in a 68% response rate and prolonged survival in patients with unresectable hepatic lesions including cholangiocarcinoma (*J Clin Oncol* 2000;18:2210; *J Clin Oncol* 1993;11:1286).
      d. **Radiation therapy** may help palliate symptoms. Percutaneous stent placements may allow brachytherapy or radiation implants to shrink obstructing tumors.

D. **Follow-up.** Patients with resected biliary neoplasms should be monitored every 3 months with physical examination, chemistries, liver-function tests, and tumor markers, if initially elevated. CT or MRI scan should be done every 6 months for 2 years, and then annually.

E. **Background. Gallbladder cancer** risk factors include cholelithiasis, chronic cholecystitis, porcelain gallbladder, gallbladder polyps, typhoid carriers, and exposure to nitrosamines or azotoluene. It affects women more than men (2.7:1 ratio) and is diagnosed most frequently in the elderly (median age, 70 years). Known risk factors for cholangiocarcinoma include hepatolithiasis, ulcerative colitis, choledochal cysts, and liver-fluke infections. Cholangiocarcinoma occurs in 6% to 36% of patients with **primary sclerosing cholangitis (PSC).** Survival is extremely poor for PSC patients with cholangiocarcinoma, even with liver transplantation. Alcohol consumption is a risk factor for developing cholangiocarcinoma, and elevated CA19-9 may discriminate PSC patients with or without cancer (*Hepatology* 2000; 31:7).

F. **Current focus.** Palliative options currently being studied include photodynamic therapy with ERCP in unresectable hilar cholangiocarcinomas; this improved

quality of life and gave palliation.

SUGGESTED READINGS

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CHAPTER 10C. COLORECTAL MALIGNANCIES

Elaine M. Majerus, Elisa Birnbaum, and Joel Picus

Presentation
Subjective
Objective
Workup and staging
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Treatment
Epidemiology and risk factors
Suggested Readings

I. **Presentation**

A. **Subjective.** Colorectal cancer (CRC) is seen because of symptoms or because of a positive screening test for the disease. It is relatively asymptomatic until the tumor is large. Most of the symptoms are nonspecific and are found not uncommonly in patients without CRC. Symptoms associated with CRC are often related to the location of the tumor within the bowel; therefore right-sided lesions more often have symptoms of anemia and occasionally melena. Left-sided lesions more commonly cause obstruction, tenesmus, constipation, bright-red blood per rectum, and other changes in bowel habits. Other symptoms on presentation include fatigue, anorexia, failure to thrive, and right-upper-quadrant pain associated with liver metastasis.

The most common symptoms, though, are those associated with anemia. These symptoms can vary from vague weakness to shortness of breath to angina pectoris. Because the bleeding is insidious, patients often have an iron-deficiency anemia and symptoms of pica. Because CRC is a cause of anemia, it is important to evaluate any person with an unexplained anemia for CRC, especially men and postmenopausal women.

B. **Objective.** Signs found on physical examination for CRC include those of anemia such as pallor in the conjunctivae and the nail beds. Rarely a palpable mass will be present in the abdomen or the rectum. Patients also may have gross blood or melanotic stool in the rectal vault. If liver metastases are present, patients may have hepatomegaly and tenderness to palpation in the right upper quadrant. On barium enema, an apple-core lesion can be seen, which suggests colon cancer. *Streptococcus bovis* bacteremia or endocarditis also are signs of CRC, and persons diagnosed with these should be evaluated for colon cancer.

II. **Workup and staging**

A. **Initial evaluation.** A CBC will give information about an iron-deficiency anemia that may be present. CRC most often metastasizes to the liver, lung, adrenals, ovary, and bone. Liver-function tests may be elevated in a person with metastatic disease to the liver. An elevation in the levels of alkaline phosphatase can be seen in association with liver and bone metastases. A CEA determination is often obtained for prognostic value and to monitor after treatment. An increase in CEA after treatment is often seen with recurrence. A chest radiograph is sufficient to rule out pulmonary metastasis. Many would advocate an abdominal CT scan to evaluate the liver and other abdominal organs for metastatic disease.

All patients should have the remainder of their bowel evaluated by colonoscopy or barium enema to rule out synchronous lesions. Up to 3% to 5% of patients have another focus of CRC in their bowel. Patients also should have a tissue biopsy before therapy to confirm the diagnosis.

B. **Surgical staging.** Surgery is important for accurate staging of CRC. The preferred staging system for CRC is the AJCC TNM system.

T1, invasion of the submucosa
T2, invasion into the muscularis mucosa
T3, invasion through the muscularis mucosa into the subserosa
T4, invasion through the visceral peritoneum or direct invasion into adjacent organs
N0, no lymph node metastases
N1, metastases in one to three lymph nodes
N2, metastases in four or more lymph nodes
M0, no distant metastases
M1, distant metastases present

Clinical stages are delineated in Table 10.8. It uses the degree of tumor invasion, the presence of positive lymph nodes, and the presence of distant metastasis to classify the disease in one of four stages.

	T	N	M
Stage I	T1 or T2	N0	M0
Stage II	T3 or T4	N0	M0
Stage III	Any T	N1 or N2	M0
Stage IV	Any T	Any N	M1

TABLE 10.8. COLORECTAL STAGES

Although the AJCC TNM staging system is the preferred staging system today, the Duke staging system with the Astler–Coller modification is often referred to in older literature. Duke's A is equivalent to T1, N0, M0. B1 indicates invasion through the muscularis propria and is equivalent to T2, N0, M0. B2 indicates invasion through the serosa without lymph node involvement and corresponds to T3, 4, N0, M0 (stage II). Duke's C indicates positive lymph node

involvement or stage III disease, and Duke's D indicates distant metastasis or stage IV disease. Historically, approximately 40% are first seen with localized disease; 40%, with regional disease; and 18%, with distant metastasis.

III. **Prognosis**

The four stages have great significance in the prognosis and treatment of the disease. In the United States between 1973 and 1997, the 5-year overall survival with CRC was 61%. Stage I was associated with more than a 95% 5-year survival. Stage II had an 87% 5-year survival. Stage III had a 55% 5-year survival, and stage IV was associated with a less than 5% 5-year survival and a median survival of around 11 months. Five-year survival correlates well with cure of the disease.

Other prognostic factors include the number of positive lymph nodes. Increasing N stage is associated with decreased survival. Tumor invasiveness also is associated with poorer outcomes. Those with invasion through the bowel wall into adjacent organs or into veins tend to do worse than do those with the same stage without invasion. Some histologic classifications also have prognostic value. Colloid tumors and signet-ring tumors are associated with a poor outcome. Some molecular markers and chromosomal abnormalities portend a poor prognosis. These include aneuploidy, chromosomal deletions, mutant p53 or K- *ras,* overexpression of bcl-2, and loss of expression of E-cadherin. Overexpression of certain repeat sequences in conjunction with 17 p deletion is associated with increased response to chemotherapy. Whether these markers connote independent prognostic significance is still a subject of investigation. Testing for these markers, though, is not generally available.

IV. **Treatment**

A. **Colon cancer**

1. **Surgery.** Surgery is undertaken with an intent to cure in 75% of those with colon cancer. Many of the remainder also will require surgery to prevent obstruction, perforation, or bleeding.

   Wide excision of the tumor with a distal margin of approximately 5 cm is recommended for curative surgery. The length of colon and mesentery resected is determined by the vascular anatomy. If the tumor is adherent to or invades another organ, an *en bloc* excision also must be done. This excision prevents seeding and allows the possibility of cure. If the surgical intent is palliation instead of cure, a simple resection or diversion is used to lessen morbidity from the procedure.

   Prophylactic total abdominal colectomy is a controversial subject among colorectal surgeons. Most recommend this for those with FAP, whereas others believe that a total colectomy should be offered to patients with HNPCC and those with a colon cancer before age 40 years (see Sec. IX). Prophylactic oophorectomy has been advocated for women with CRC, but this also remains controversial.

   New advances in surgery for CRC include sentinel lymph node mapping and laparoscopy. Sentinel lymph node mapping is done by injecting a dye and or a radioactive tracer into the tumor to determine which lymph nodes are drained from the tumor. In breast cancer, this has been used extensively to gain the most prognostic information from a less extensive lymph node dissection. The use of sentinel node mapping for CRC remains investigational. Laparoscopic colectomy also is being done with increasing frequency, although its use for patients with CRC is controversial. Concerns with this approach include inadequate resection and staging, as well as trocar site implants. Advantages, as with other laparoscopic approaches, include decreased recovery time, decreased postoperative pain, and shorter hospitalizations. In the short term, outcomes have been equivalent for open and laparoscopic approaches. Long-term follow-up comparative studies are in progress.

2. **Chemotherapy.** Adjuvant chemotherapy is administered to prevent relapse, which occurs mainly at distant sites with colon cancer (Table 10.9). Whereas 5-FU with levamisole was used in the past, treatment with 5-FU and leucovorin is now the standard of therapy for stage III colon cancer. 5-FU works by inhibiting the synthesis of thymidine, which can be incorporated into DNA and RNA. Leucovorin (folinic acid) increases binding of 5-FU to thymidylate synthase, which increases its antimetabolite role. This leads to apoptosis in rapidly dividing cells. 5-FU is cytotoxic only in those cells undergoing DNA synthesis and cell division.

Roswell Park Memorial Institute regimen[a]
Leucovorin, 500 mg/m^2 i.v. infused over 2-h period
5-FU, 500 mg/m^2 i.v. bolus 1 h after leucovorin begun
Repeat every 7 d for 6 wk. After 2 wk off, the cycle is repeated

Mayo Clinic regimen[b]
Leucovorin, 20 mg/m^2 i.v. over 30-min period
5-FU, 425 mg/m^2 i.v. bolus every day for 5 d. Cycle is repeated every 4 wk

Saltz metastatic colon cancer regimen[c]
Irinotecan, 125 mg/m^2 over 30-min period
Leucovorin, 20 mg/m^2 i.v. bolus
5-FU, 500 mg/m^2 i.v. bolus
Given 4 of every 6 wk.

[a]A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. *J Clin Oncol* 1987;5:1559–1565, with permission.
[b]Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989;7:1407–1417, with permission.
[c]Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000;343:905–914, with permission.

TABLE 10.9. COLORECTAL CHEMOTHERAPY REGIMENS

The survival in stage III colon cancer is significantly improved by adjuvant therapy with 5-FU and leucovorin. The 5-year disease-free survival rate in stage II/III was 74% for those treated with 5-FU and leucovorin after surgery, as compared with 58% for those with surgery and then follow-up alone (*J Clin Oncol* 1997;15:246–250). Overall survival of 74% versus 63% also was reported, which is a significant improvement at 5 years. Another study with Duke's B and C cancers treated with 5-FU and leucovorin showed an overall survival of 76% at 5 years. When only Duke's C cancers were considered, the overall survival was 70% (*J Clin Oncol* 1999;17:1349–1355). Other studies have shown similar improved outcomes with this treatment. Based on these data, we recommend adjuvant therapy with 5-FU and leucovorin for 6 months in patients with stage III (Duke's C) colon cancer.

Because the mortality rate is higher with stage III disease, it is clear that adjuvant chemotherapy improves outcome. Controversy remains, though, over adjuvant chemotherapy for stage II disease. Because the 5-year survival rate is 75% to 80% in stage II colon cancer, the relative reduction in deaths is predicted to be small. One study of 998 Duke's B colon cancer patients found that 5-FU plus leucovorin increased overall survival to 83% from 81% without treatment, which reached statistical significance. (*Proc Am Soc Clin Oncol* 1996;15:205). Another pooled analysis of 1,016 patients randomized to 5-FU and leucovorin versus observation after resection showed a trend toward improvement in overall survival (82% vs. 80%), but the difference was not significant. (*J Clin Oncol* 1999;17:1356). Because there seems to be only a small benefit to treating stage II disease, the focus of research is to identify subgroups within the stage II colon cancer population that will be more likely to benefit from treatment.

Other ongoing trials attempt to identify the role of irinotecan in the adjuvant therapy. These studies compare survival with irinotecan, a topoisomerase I inhibitor, with 5-FU and leucovorin versus survival with 5-FU and leucovorin alone. Accrual of 1,600 patients for this study is completed.

Irinotecan, which has been used as a second-line treatment for metastatic colon cancer was shown to prolong survival when used in conjunction with 5-FU and leucovorin, in metastatic colon cancer. Progression-free survival was extended from 4.3 months to 7 months, and overall survival was increased to 14.8 months from 12.6 months. Quality of life also was superior with this drug treatment, with a smaller decrease in baseline functioning. Patients also had less fatigue, anorexia, and pain (*N Engl J Med* 2000;343:905–914). Since this study was published, a higher mortality from gastrointestinal syndromes and vascular syndromes was reported when irinotecan was administered with 5-FU and leucovorin as compared to other regimens including 5-FU and leucovorin alone (*JCO* 2001;3801–3807).

Because the liver is a common and frequently the sole site of metastases, therapies have been directed at colon cancer metastatic to the liver. These include surgery and hepatic artery and portal vein chemotherapy. When metastatic disease is limited to the liver; about 25% of these persons can have resection of the liver metastasis. The rationale for hepatic artery infusion of chemotherapy is that hepatic metastases derive their blood supply mainly from the hepatic artery rather than the portal vein. Several drugs are extensively metabolized by the liver. Therefore direct infusion in the hepatic artery (HAI) will allow increased concentration of the active chemotherapeutic agent at the metastases with little comparative systemic exposure. 5-FU and

leucovorin and the 5-FU analogue floxuridine have been used. The advantage of floxuridine is its high clearance by the liver and its activity in CRC. By direct infusion into the hepatic artery, its systemic effects are limited. This relatively high peak concentration also can be a disadvantage if extrahepatic metastases are present. The technology that is used most frequently is an implantable device that slowly pumps out its contents at a steady rate, powered by the heat of the body. Although the surgical technique for implanting these devices can be challenging, specialized centers can implant them with lower mortality and morbidity. A German study showed a higher response rate of 45% versus 20% with hepatic artery infusion of floxuridine when given for unresectable liver metastases but no statistically significant difference in overall survival (*J Clin Oncol* 2000;18:243). Despite thorough staging, the most common site of recurrence remains the liver, therefore a United States Cancer and Leukemia Group B (CALGB) trial is currently under way to address a role for hepatic artery infusion in survival of colon cancer metastatic to the liver.

One of the major toxicities of HAI therapy with floxuridine is biliary sclerosis, which can lead to liver failure and even death. In a randomized trial, the addition of dexamethasone (Decadron) to the HAI mix has shown a considerable decrease in this particular side effect. An additional use of this technique is the “adjuvant” setting, after the resection of liver metastasis. One study has shown that giving HAI with floxuridine and dexamethasone plus systemic chemotherapy with 5-FU and leucovorin after resection of liver metastasis results in improved actuarial survival rates at 5 years to 61% for HAI plus systemic chemotherapy versus 49% in the systemic chemotherapy-alone group (*N Engl J Med* 1999;341:2039).

Portal vein infusion (PVI) has been shown to reduce recurrence and prolong survival in some studies. A meta-analysis of trials using continuous PVI after surgery showed a small (5% absolute improvement) but significant improvement in survival for Duke's stage A, B, and C as compared with controls who had no adjuvant therapy (*J Natl Cancer Inst* 1997;89:497). An NSABP trial did not show a benefit, and this approach is rarely used now.

B. **Rectal cancer.** Surgery also is used in rectal cancer to cure the disease and plays a role in palliative therapy. The rectum is the distal 15 cm of the large bowel and resides within the bony pelvis. Local recurrence for rectal cancer is high, and adjuvant therapy often is needed to make a tumor resectable; 50% of those who have surgery will be cured. Surgery in the pelvis can be technically demanding because there is a decreased area in which to work. The surgical approach includes a complete mesorectum resection and wide lateral excision. These methods (often in conjunction with radiation or chemoradiation) have been associated with decreased recurrence. Approaches aimed at sphincter preservation, obviating the need for colostomy can often be performed if a 2-cm margin can be obtained. Low anterior resection, coloanal anastomoses, transsacral approach, and transanal local excision can be done on appropriately selected patients. In general, the most distal tumors are more likely to require abdominoperineal resection, particularly if the tumor invades the anal sphincter.

Compared with colon cancer, rectal cancer is much more likely to recur locally rather than distally. Only about 25% of patients have distant metastases. Therapy is therefore tailored to prevent local recurrence in stage II and III cancers. Currently surgery, along with 5-FU and radiation, is used to treat rectal cancer, leading to significant improvements in overall survival as compared with treatment with surgery alone. This usually involves surgery followed by concurrent radiation and 5-FU. Areas of study involve the timing of radiation and 5-FU in relation to surgery and bolus versus continuous intravenous infusion (CIVI) 5-FU. One Intergroup study has shown that overall survival can be improved to 70% by using the CIVI regimen versus 60% with bolus infusion (*N Engl J Med* 1994;331:502–507). Ongoing studies are designed to compare preoperative and postoperative combined-modality therapy. Possible advantages to preoperative therapy are improved sphincter preservation and decreased tumor stage. These advantages result from a potential shrinkage of the tumor by preoperative radiation, allowing a better chance of sphincter preservation. In addition, it has been hypothesized that radiation delivered preoperatively is more effective because the tumor is better oxygenated and lower, but more effective doses can be used, leading to less morbidity. Most American centers are adopting preoperative radiation therapy as a standard, especially for low-lying tumors. The timing and use of chemotherapy remains a subject of investigation, especially for tumors that shrink dramatically before surgery. Newer drugs are being introduced to synergize with the radiation therapy.

Other agents being studied for the treatment of CRC include oral fluoropyrimidines such as tegofur-uracil (UFT), which is widely used now in Japan, and capecitabine (Xeloda), which was recently approved in the United States. Because they can be taken orally, they may be preferred by patients to 5-FU and leucovorin because they have been proven to be equally efficacious in recent phase III trials in the United States and Europe. Oxaliplatin, a platinum analogue, has been shown to produce responses in metastatic CRCs and 5-FU–refractory disease. In the presence of 5-FU and leucovorin, a marked synergistic effect is seen. With combined regimens, the response rate was increased for refractory cancers and when used as first-line therapy. Further studies with oxaliplatin are ongoing. Future targets of therapy include vascular endothelial growth factor (VEGF), the epidermal growth factor (EGF) receptor, p53, and cyclooxygenase (COX)-2. Monoclonal antibodies against VEGF and the EGF receptor have been used in CRC trials.

V. **Complications**

A. **CRC related.** Complications that can result from CRC often produce the symptoms of which patients complain. These include bowel obstruction, anemia, and abdominal pain. More serious complications can include peritonitis after perforation, fistula formation, and malnutrition. Complications also can result from sites of metastatic disease. Liver metastases can lead to hyperbilirubinemia and coagulopathies, and advanced pulmonary metastases may result in cough or shortness of breath. Pain also may develop at sites of metastases.

B. **Treatment related.** Complications of treatment are commonly related to surgery and chemotherapy but also can occur with radiation therapy. Postoperative mortality rates are 1% to 5%. Major morbidity includes bowel and bladder dysfunction, sexual dysfunction, anastomotic leaks, and bowel obstruction. The need for a permanent colostomy can be psychologically upsetting.

Chemotherapy also has many side effects and is not tolerated by everyone, especially those with a poor performance status. Anorexia, nausea, and vomiting are usually mild when associated with the standard treatment of 5-FU and leucovorin; however, mucositis and diarrhea can be severe and dose limiting, particularly with irinotecan or the Roswell Park regimen. These and other agents also can cause delayed effects like myelosuppression, and therefore blood-count monitoring is necessary. Myelosuppression can be manifest as increased infections with neutropenia, anemia symptoms, and bleeding with thrombocytopenia. Leukopenia can be the dose-limiting toxicity, especially with the Mayo Clinic regimen. The nadir of the white blood cell count usually occurs between days 9 and 14 after treatment. 5-FU is metabolized mainly in the liver, so dose reductions should be considered in cases of liver dysfunction. Other side effects include alopecia, palmar–plantar erythrodysesthesia, hyperpigmentation, conjunctivitis, cerebellar ataxia, chest pain, cardiac arrhythmias, and seizures.

VI. **Follow-up**

With the risk of recurrent CRC being nearly 50%, studies are ongoing to address how closely and extensively patients should be monitored to detect recurrence. One controversial area remains the measurement of CEA levels. In one study, CEA monitoring cost $5,696 per resectable occurrence (*Ann Surg* 1998;228:59–63). Colonoscopy is widely recommended 1 year after surgery and then every 3 years after that to detect new primary lesions. Routine chest radiograph and CT scans also have been evaluated in the detection of recurrence and improving survival but are not routinely recommended now. Often when recurrent malignancy is found, the tumor is inoperable.

VII. **Role of screening**

Screening methods used to detect CRC include fecal occult blood testing (FOBT), endoscopy, and barium enema. CRC is suitable for screening tests because early detection is associated with improved survival, and its incidence is high enough that screening can be cost effective with acceptable positive predictive values. Available screening tests also have acceptable sensitivity and specificity that make them variably effective in early detection. The tests also have various risks and practical acceptability for patient and physician.

FOBT is the least expensive, at less than $10, and most widely used screening test for the detection of CRC. There are problems with its sensitivity, which has been reported to be from 18% to 93%, with a specificity of more than 90%. Prewetting the paper is associated with a higher sensitivity but lower specificity. The sensitivity and specificity also can be affected by delay in development after the stool sample is applied. Sensitivity will vary with the size of the polyp, with larger polyps having a greater propensity to bleed. It also depends on continuous bleeding from the polyp. Obviously a lesion will be missed if there is not active bleeding during the screening. Specificity is affected by nonsteroidal antiinflammatory drug (NSAID) use, diverticuli, hemorrhoids, and other sources of GI bleeding. It also can be affected by red meat and certain vegetables in the diet. Some of these obstacles to specificity can be overcome by having the patient avoid red meat and NSAIDs before testing. A recent review of the Minnesota Colon Cancer Study showed that there was a decreased number of CRCs in persons screened with annual or biennial FOBT. This is presumably because of the increased detection and removal of precancerous polyps. At this time, the American Cancer Society (ACS), the National Cancer Institute (NCI), and the U.S. Preventive Services Task Force (USPSTF) all recommend annual FOBT for those older than 50 years.

Flexible sigmoidoscopy examines up to 60 cm of the rectum and distal colon and can detect about 50% of CRC. Its advantages are that it can be performed in the primary care physician's office and that it has a specificity of nearly 100%. Its cost of $200 to $400 is the lowest of the visualization methods. Disadvantages

include discomfort associated with the bowel preparation and the procedure itself and the inability to visualize more proximal lesions.

Several trials of varying quality have found decreased CRC deaths with sigmoidoscopy. Flexible sigmoidoscopy is recommended in conjunction with FOBT by the ACS every 3 to 5 years.

Double-contrast barium enema (DCBE) is a radiologic method for detection of CRC and is the safest of the visualization methods. It does require a bowel preparation. Although its sensitivity has been reported as 70% to 90%, a recent blinded comparison of DCBE and colonoscopy found that in patients with a history of polyps, DCBE detected only 32% to 53% of colonoscopically detected polyps, with an increased sensitivity for polyps larger than 0.6 cm (*N Eng J Med* 2000;342:1766–1772). It also has the disadvantage like FOBT of needing endoscopy for biopsy of identified lesions. It usually costs between $150 and $200.

Colonoscopy is considered the gold standard for detection of CRC but is associated with a higher complication rate (20 per 10,000) and a higher cost ($1,500) than the other methods. In the previously mentioned trial, colonoscopy missed 26% of adenomas smaller than 0.6 cm seen by DCBE and only 16% of those larger than 0.6 cm. These results are comparable to those of other trials.

Most groups concerned with prevention recommend annual FOBT after age 50 years and flexible sigmoidoscopy every 5 years or colonoscopy every 10 years. They also recommend screening at an earlier age if risk factors such as a history of inflammatory bowel disease or genetic risk such as family members with CRC, or a known defect such as HNPCC or FAP.

VIII. **Epidemiology**

CRC is the third most common cancer after prostate and lung in men and breast and lung in women and accounts for about 15% of all cancers diagnosed in the United States. In the United States, there are approximately 94,000 new cases of colon cancer and 37,000 new cases of rectal cancer in 2000. CRC also ranks third in mortality with approximately 48,000 deaths from colon cancer and 8,600 deaths from rectal cancer in 2000. The incidence of CRC has been declining since 1985 for unclear reasons, although some have speculated about lifestyle changes such as increased vegetable and fiber intake or increased NSAID use. Screening also may play a role in the decline by facilitating removal of adenomatous polyps that can become malignant. The decline has been sharpest in white women and men. Now CRC is more common in African-Americans than whites, but this did not happen until the late 1980s for men and the late 1970s for women. This occurred because the incidence in African-Americans has declined more slowly than that in whites. American Indians, American Pacific Islanders, and Hispanics have lower incidence rates than do whites. Overall CRC is more common in men than in women. Regionally the risk is higher in the east and midwest and lower in the south and west. The incidence increases with age, with about 90% of cases diagnosed in those older than 50 years. Peak incidence occurs in the eighth decade of life. The lifetime risk for CRC is 6% in average-risk persons living in the United States.

The death rate from CRC also has been declining in all groups in the United States since the mid-1980s. The mortality rate in women has been declining since the 1950s but not for men until the 1980s. Black mortality from CRC increased through the 1970s and then began to decline in the middle to late 1980s. Speculated reasons for the decline in mortality rates include implementation of “no-touch” surgical technique and lower morbidity and mortality associated with the resections. Screening also can play a role in decreased mortality by detecting the cancer at an earlier stage. Overall about 20% of those older than 50 years were screened by FOBT in the last year, and 30% of those older than 50 years have had a sigmoidoscopy or proctoscopy during the previous 5 years. The percentage screened was very similar for African-Americans and whites.

Worldwide, the incidence of CRC is low in Africa and Japan and higher in Europe, North America, and Australia. The range of incidence rates vary from 3.4 cases per 100,000 in Nigeria to 43 cases per 100,000 in the Unites States.

Cancers are more common on the right side of the colon than the transverse colon, left side, or sigmoid colon. All sites had a decreased incidence except for the right side of the colon over the last several decades.

IX. **Risk factors**

A family history of CRC is critical because this is the most important risk factor for CRC. FAP is an autosomal dominant disease caused by a defect in the APC gene that will lead to colon cancer in 100% of patients by age 40 years if they are left untreated. Persons affected will have up to thousands of adenomatous polyps in their bowel that have malignant potential. Because of this, it is recommended that persons with FAP have a prophylactic subtotal colectomy in their teens. 0.5% of CRC are associated with FAP. Another inherited disease associated with CRC is hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. It also is inherited in an autosomal dominant manner and often leads to malignancies in the right side of the colon with a mucinous histology. It is caused by mutations in a group of genes that lead to faulty repair of DNA mismatches. DNA microsatellites are especially susceptible to mismatches, and new alleles occur when microsatellite mismatches are not repaired in persons with HNPCC. Generation of new alleles of microsatellites is referred to as microsatellite instability. HNPCC also is associated with cancers of the endometrium, ovary, stomach, and hepatobiliary system. Persons with this disease also are recommended to have a prophylactic subtotal colectomy. HNPCC is associated with approximately 5% of CRC cases seen.

Several other inherited syndromes are associated with an increased risk of CRC. These include Gardner syndrome, Turcot syndrome, Muir–Torre syndrome, and Peutz–Jeghers syndrome. Genetic testing is not yet diagnostic unless a complete family history and DNA samples are available.

Persons with a first-degree relative with a history of CRC also have an increased risk for CRC. This is especially true if the relative has had CRC before age 45 years. Data from the Nurses' Health Study and the Health Professional Follow-up study showed that those with a history of CRC in a first-degree relative have a 1.72 relative risk for the disease. If there was more than one relative with CRC, the relative risk was 2.75, and if the cancer occurred in a relative before age 45 years, the relative risk was 5.37.

Several other risk factors are associated with a clear increase in CRCs and, therefore, should be monitored carefully. These include persons with a history of ureterosigmoidostomies. These persons have an increased risk of malignancy at the site of the ostomy, such that in up to 29%, CRC will develop. Persons with inflammatory bowel disease, especially ulcerative colitis but also Crohn disease, are at increased risk. The risk is associated with the duration of the disease, especially active disease for longer than 10 years. Therefore the cumulative risks after 25 years have ranged from 9% to 42% in several studies.

Other diseases associated with an increased risk for CRC are a previous history of CRC. These persons have an increased risk (1.1% to 4.7%) of developing a metachronous tumor at a site different from the primary. Persons with a history of other malignancies such as breast cancer are also at increased risk of CRC. A history of radiation therapy to the abdomen or pelvis, such as with endometrial cancer, increases the CRC risk.

Increasing age, especially older than 50 years, is associated with an increased incidence of CRC. Those younger than 40 years represent less than 3% of cases, whereas those older than 50 years represent more than 85% of cases. The seventh and eighth decades are the most affected.

The role of diet in CRC is somewhat controversial. Dietary factors that have been associated with CRC include a low-fiber diet and a high-fat diet. The role of fiber in CRC was postulated by Burkitt in the 1960s after he observed the high-fiber diet of Africans and their low rate of CRC. This idea was reinforced by immigration studies that showed an increased risk of CRC when persons who came from low-risk countries adopted the Western diet of the United States. For example, Japanese immigrants to Hawaii have a 2.5-fold risk compared with those who remain in Japan. Several case–control studies done subsequently have shown varying relative risks of CRC with fiber intake. Recently, prospective trials done in the United States failed to show a relation, but there is still much controversy around this topic. Likewise, studies looking at fat intake have not shown a clear inverse relation on the relative risk of CRC.

Other dietary factors with a speculated role in CRC are calcium, vitamin D, folate, and alcohol. Calcium, vitamin D, and folate have been associated with a decreased relative risk, whereas alcohol in some studies is associated with an increased risk. Body mass index (BMI) and level of activity also have been hypothesized to have a role; the highest quintile of BMI and a sedentary lifestyle have an increased relative risk in some studies. These two factors affect the relative risk independent of one another.

Unlike most malignancies, CRC does not seem to be associated with smoking cigarettes. Some studies have suggested a role for pipe and cigar smoking in increasing the risk of CRC.

The risk of CRC has been shown to be inversely associated with use of aspirin and other NSAIDs in several prospective trials. In the Health Professionals Follow-Up Study, the relative risk of CRC was 0.68 in those who took aspirin at least 3 times a week. In those with FAP, the use of the NSAID sulindac or the COX-2 inhibitor celecoxib reduced the number of polyps, as compared with placebo.

The mechanism of action is thought to be through the specific inhibition of the cytokine-inducible COX-2, which leads to prostaglandin synthesis. Normal colonic epithelium does not express cyclooxygenase, but COX-2 and prostaglandin levels are elevated in most sporadic colon carcinomas and in many adenomas. Animal studies have shown that the offspring of COX-2 knockout mice bred to FAP model mice have significantly fewer polyps than those with just the FAP mutation.

How COX-2 expression or subsequent increases in prostaglandins causes CRC is unclear. Speculated methods include increases in angiogenesis or decreases in apoptosis. It also is possible that the decreases in CRC and polyps with NSAIDs is unrelated to cyclooxygenases.

X. **Pathogenesis**

Most CRCs are thought to arise from adenomatous polyps that line the colonic mucosa. Studies have shown that adenomatous polyps can become malignant over a 5- to 20-year period. The histology of a polyp is tubular, tubulovillous, or villous. Villous adenomas are most likely to become malignant. Other characteristics of a higher propensity for malignancy are size greater than 1 cm in diameter and a high grade of dysplasia. Adenomatous polyps are found in approximately 35% of persons in autopsy studies. Up to 5% of polyps are believed to become malignant over time.

More than 95% of CRCs are adenocarcinomas. Of these, more than 80% are moderately differentiated. Other histologic types seen are undifferentiated, squamous, carcinoid, leiomyosarcomas, and hematopoietic and lymphoid neoplasias. Poor prognosis is associated with colloid and signet-ring subtypes of adenocarcinoma, which together represent about 20% of tumors.

XI. **Molecular basis of colorectal cancer**

Vogelstein et al. proposed a model in which sequential mutations occur that ultimately lead to malignant transformation. These mutations lead to inactivation of tumor-suppressor genes and activation of oncogenes. In this model, genetic diseases associated with CRC have mutations on the pathway to malignancy. For example, in FAP, the causative mutation is in the APC gene located on the long arm of chromosome (5q). This gene product is a cytoplasmic protein that appears to bind b-catenin and prevent its translocation to the nucleus, where it activates transcription of growth-promoting genes such as c- *myc* and cyclin D1. The APC gene is a tumor suppressor that is autosomal dominant in inheritance. Similar to the retinoblastoma gene, it follows the two-hit pathway of tumor-suppression inactivation, in that a mutated form is inherited, and then a single somatic mutation leads to loss of tumor suppression. In a wild-type individual, two separate mutations must occur at this locus for loss of the APC tumor suppressor, but only one is needed in FAP.

Another inherited mutation associated with CRC is responsible for HNPCC. In this disorder, which also is inherited in an autosomal dominant fashion, there are mutations in a family of genes that are responsible for mismatch repair of DNA. This leads to amplification of microsatellites in DNA and then DNA instability. Microsatellites in the coding region of genes, such as transforming growth factor type 2 receptor and insulin growth factor 2 receptor, cause loss of function and increased tumorigenesis.

Other gene products that appear to be mutated in CRC are p53, K-*ras,* MCC (mutated in colon cancer), and DCC (deleted in colon cancer). Sequential mutations in several of these are believed to result in CRC.

XII. **Anal cancer**

A. **Presentation.** Patients with anal cancer present with bleeding 50% of the time. Other symptoms include pain, mass, constipation, diarrhea, and pruritus. Often the symptoms are ascribed to hemorrhoids, and delays in diagnosis occur. About 25% of people are asymptomatic when the cancer is discovered.

   Physical examination findings include an anal mass and lymphadenopathy. On palpation, an anal mass will often be firm and indurated. Note should be made of the location of the mass including its position relative to the dentate line. Anal cancers are divided into those of the anal margin and those of the anal canal. The line of demarcation is a zone approximately halfway between the dentate line and the anal verge. Anoscopy, proctoscopy, and transrectal ultrasound are used to visualize the mass. Diagnosis is made with incisional biopsy of the mass and any inguinal lymphadenopathy.

B. **Staging.** Staging is based on the TNM system.

C. T_{is}, carcinoma in situ
   T1, tumor is 2 cm or smaller
   T2, tumor is between 2 cm and 5 cm
   T3, tumor larger than 5 cm
   T4, tumor of any size that invades adjacent organs such as the vagina, urethra, or bladder
   N0, no regional lymph nodes involved
   N1, metastases in unilateral internal iliac or inguinal lymph node
   N3, metastases in perirectal and one inguinal lymph node and/or bilateral internal iliac or inguinal lymph nodes
   M0, no distant metastases present
   M1, distant metastases present
   Stage I, T1, N0, M0
   Stage II, T2, 3, N0, M0
   Stage IIIA, T1–3, N1, M0 or T4, N0, M0
   Stage IIIB, T4, N1, M0 or any T, N2–3, M0
   Stage IV, any T, any N, M1

D. **Prognosis.** Prognosis is based on staging. T1 and T2 tumors have a more than 80% 5-year survival, whereas T3 and T4 tumors have 5-year survivals of less than 20%. Inguinal lymphadenopathy and male sex also are related to a poorer prognosis. Tumors in the anal margin have a more favorable prognosis than do those in the canal.

E. **Treatment.** Very small tumors at the anal margin may be treated with wide local excision, but combined chemotherapy and radiation therapy has been the preferred treatment for locoregional disease. Treatment is with mitomycin C and 5-FU, with concurrent radiation. In several trials, 5-year survival varied between 64% and 83% with combined-modality therapy.

F. **Epidemiology and risk factors**

   1. **Epidemiology.** Anal cancer accounts for about 1% of all CRC in the United States. It is now more common in men than women, although in the past, the number of cases in women was 5 times that in men. Its incidence generally increases with age, with peak incidence in the sixth and seventh decades of life. The incidence is increasing in men younger than 40 years.

      Histologically 47% of anal cancers are squamous cell carcinomas. Transitional cell carcinomas and adenocarcinomas make up 42% of cases. More rare types are papillary adenocarcinoma, mucinous adenocarcinoma, and melanoma.

   2. **Risk factors.** The risk factor most commonly associated with anal cancer now is human papillomavirus (HPV) infection. HPV 16 and 18 have been linked to the disease. This is seen in both men and women. In women, increased anal cancers are seen with HPV-associated cervical cancer. In men, anal cancer is more frequently associated with receptive anal intercourse and HPV. As many as 70% of anal cancers are positive for HPV.

      Other risk factors include immunosuppression, such as that seen after renal transplant. Immunosuppression with acquired immunodeficiency syndrome (AIDS) also seems to be associated with an increased incidence. Current cigarette smoking also is a risk factor for anal cancer, with a relative risk of sevenfold to ninefold for smokers.

SUGGESTED READINGS

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CHAPTER 11. GYNECOLOGIC MALIGNANCIES

Matthew A. Powell and Janet S. Rader

Uterine neoplasia
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I. **Uterine neoplasia**

A. **Premalignant disease of the endometrium**

1. **Presentation.** Patients usually have abnormal or postmenopausal bleeding. Normal menstrual cycles occur every 28 days (range, 21 to 35 days) with a normal duration of 2 to 7 days and an average blood loss of less than 80 mL. Bleeding outside of these ranges or any postmenopausal bleeding should be evaluated. Any age group can be affected, but one should be especially concerned with abnormal bleeding in patients aged 35 years and older. Obesity, a history of irregular periods, and use of an exogenous estrogen without concurrent progestational agents are known risk factors.
2. **Workup and staging.** Typically the diagnosis can be made with an office endometrial (Pipelle) biopsy. If this is nondiagnostic or technically not feasible, a dilation and curettage (D&C), with or without hysteroscopy can be performed. Pathologic specimens demonstrating hyperplasias are classified by the International Society of Gynecological Pathologists (1984) into the following four groups: simple hyperplasia with and without atypia, and complex hyperplasia with and without atypia.
3. **Therapy and prognosis**
   a. **Simple and complex hyperplasias without atypia** are usually caused by anovulation. Treatment is usually conservative and depends on the fertility desires of the patient. If untreated and monitored, 1% of patients with simple hyperplasias and 3% of patients with complex hyperplasias without atypia would be expected to develop endometrial cancer over a 13- to 15-year period (Kurman, 1985).
      1. **Treatment for those considering pregnancy** is ovulation induction with clomiphene citrate. Give medroxyprogesterone acetate (Provera), 10 mg p.o. per day for 5 days (after a negative pregnancy test). Then begin clomiphene citrate, 50 mg p.o. on day 5 of bleeding (which ptusually begins 2 to 3 days after the completion of the medroxy-progesterone acetate) and continue for a total of 5 days. If patient does not menstruate within a month, repeat the pregnancy test, and if negative, give another 5 days of medroxyprogesterone acetate, 10 mg, and increase the clomiphene citrate by 50 mg per month until ovulation occurs. Limit use to no more than 6 to 12 months.
      2. **If pregnancy is currently not desired,** cycle the patient with medroxyprogesterone acetate, 10 mg p.o., for 10 days per month or any other progestational therapy (depo-medroxyprogesterone acetate, 100 to 150 mg intramuscular injection, every 1 month or combination oral contraceptives).
   b. **Atypical hyperplasia (simple or complex).** Patients with atypical hyperplasia should undergo a fractional D&C. There is a 17% to 25% incidence of concurrent endometrial cancer with atypical hyperplasia. If untreated and followed up for 11 years, 23% of patients would be expected to develop an endometrial cancer (*Cancer* 1985;56:403).
      1. **Patients who desire pregnancy.** Ovulation induction as described. Patients should be closely monitored and periodic biopsies taken (every 6 to 12 months).
      2. **Patients not desiring pregnancy. Medical treatment:** (approximately 90% to 95% success rate) medroxyprogesterone acetate, 40 mg p.o. per day in divided doses, or megestrol acetate (Megace), 20 to 40 mg p.o. twice daily. **Surgical treatment:** Extrafascial hysterectomy with gross inspection of the endometrium for evidence of endometrial cancer.
4. **Complications** are rare and related mainly to abnormal uterine bleeding.
5. **Follow-up.** Medically managed patients should be resampled after several months (4 to 6) of treatment. Those with normal histology can then either be taken off therapy or be cycled with progestational agents. Follow-up interval for patients after hysterectomy is not well established, but annual examinations should be adequate.
6. **Background.** Endometrial hyperplasias are proliferative disorders primarily of the endometrial glands, and to a lesser extent, the stroma. Unopposed estrogen (i.e., without progesterone or progesterone-like compounds) is thought to be the etiologic factor of endometrial hyperplasia. This often results from chronic anovulation (polycystic ovarian syndrome), obesity (high peripheral conversion of androstenedione to estrone), estrogen-producing ovarian neoplasms (granulosa cell tumor), or exogenous unopposed estrogen administration.
7. **Current focus.** The Gynecologic Oncology Group (GOG) is currently evaluating medical versus surgical management of atypical hyperplasias.

B. **Endometrial cancer**

1. **Presentation.** More than 90% of patients are first seen with abnormal uterine bleeding. Patients with either any amount of postmenopausal bleeding or abnormal pre- or perimenopausal bleeding deserve evaluation. Papanicolaou (Pap) smears with atypical glandular cells of undetermined significance (AGUS) in any age patients with a history of anovulation or women older than 35 years should be evaluated.
2. **Workup and staging.** An office endometrial biopsy (Pipelle) is more than 90% sensitive in detecting endometrial carcinoma. Patients with a nondiagnostic office biopsy, persistent bleeding abnormality despite a normal office biopsy, or those who are unable to undergo a biopsy in the office should undergo a fractional D&C, with or without hysteroscopy. All patients should be screened for other malignancies as appropriate for age and family history (Pap smear, mammogram, colorectal cancer screening). Cystoscopy, proctoscopy, and radiologic imaging may be necessary, as clinically indicated, if advanced stage is suspected. Surgical staging of endometrial carcinoma was adopted by the International Federation of Gynecologists and Obstetricians (FIGO) in 1988 and is summarized in Table 11.1. All patients who are medically able should undergo surgical exploration with appropriate staging. Extrafascial hysterectomy with bilateral salpingo-oophorectomy, collection of peritoneal cytology, pelvic and araaortic lymph node sampling, and biopsy of any suggestive areas are necessary for staging, except in well-differentiated tumors without myometrial invasion.

Stage/Grade	Description
IA G123	Tumor limited to endometrium
IB G123	Invasion to less than half of the myometrium
IC G123	Invasion to more than half of the myometrium
IIA G123	Endocervical glandular involvement only
IIB G123	Cervical stromal invasion
IIIA G123	Tumor invades serosa and/or adnexa, and/or positive peritoneal cytology
IIIB G123	Vaginal metastasis
IIIC G123	Metastasis of pelvic and/or paraaortic lymph nodes
IVA G123	Tumor invasion of bladder and/or bowel mucosa
IVB G123	Distant metastases including intraabdominal and/or inguinal lymph nodes

FIGO, International Federation of Gynecology and Obstetrics.

TABLE 11.1. FIGO SURGICAL STAGING OF ENDOMETRIAL CANCER, 1988

3. **Therapy and prognosis.** Adjuvant treatment after primary surgical management of endometrial cancer is controversial in many areas. Table 11.2 summarizes current treatment recommendations after surgery for endometrial cancer. **Hormonal** therapy is often used for patients with advanced/recurrent disease who test positive for estrogen and progesterone receptors. In the absence of receptor levels, usually only grade 1 and 2 tumors are treated in this manner. Grade 3 tumors are unlikely (fewer than 25%) to express hormone receptors. Response rate with either medroxyprogesterone acetate, 200 mg daily, or megestrol acetate, 160 mg daily, is approximately 20%. When indicated, **cytotoxic chemotherapy for endometrial cancer** includes the following agents (response rate): cisplatin (20% to 35%), carboplatin (30%), doxorubicin (Adriamycin; 20% to 35%), and epirubicin (25%). The current "standard" combination is doxorubicin, 60 mg/m ^{2} plus cisplatin 50 mg/m^2 every 3 weeks. A response rate of 66%, progression-free interval of 6.2 months, and median survival of 9 months was noted with this regimen in a randomized trial by the GOG (*Proc Am Soc Clin Oncol* 1993;12:261).

Condition	Possible Therapies to Consider
Stage IA or IB and grade 1 or 2	No further therapy or vaginal brachytherapy
Any stage I grade 3 or IC of any grade	No further therapy vs. whole-pelvic radiotherapy (RT) vs. vaginal brachytherapy
Stage II	Vaginal brachytherapy vs. pelvic RT
Stage IIIA (positive peritoneal cytology)	Treat based on uterine disease risk factors as above vs. progestins vs. intraperitoneal P-32
Stage IIIA (adnexal and/or serosal involvement)	Whole-pelvic RT vs. whole-abdominal RT
Stage IIIB (vaginal involvement)	Pelvic RT with vaginal boost
Stage IIIC (microscopic nodal involvement)	Pelvic RT with extended-field radiation to para-aortic region, if indicated
Stage IIIC (macroscopic nodal), stage IV, and recurrent disease (extrapelvic)	Whole-abdominal radiation vs. palliative radiation vs. systemic chemotherapy (see text) vs. hormonal therapy [see text] vs. combinations
Recurrent disease (pelvic)	Radiotherapy in the patient without prior RT vs. possible surgical resection (exenteration) vs. chemotherapy [see text]

TABLE 11.2. TREATMENT OF ENDOMETRIAL CANCER

4. **Complications.** Complications of staging surgery are generally minimal. Lymphocysts and lymphedema of the lower extremities are rare complications of lymphadenectomy. Immediate and late effects of radiation are usually related to bowel and bladder dysfunction.
5. **Follow-up.** Typically patients are evaluated with physical examination, Pap smear, and pelvic examination every 3 months for the first 2 years, and then every 6 months for 2 years, and then annually.
6. **Background.** Endometrial cancer is the most common gynecologic malignancy in the United States, with approximately 31,000 cases reported annually, and more than 6,000 of these women dying of disease. Risk factors include unopposed estrogenic stimulation (either estrogens or tamoxifen), chronic anovulation, obesity (especially truncal), diabetes mellitus, nulliparity, and late age of menopause (older than 52 years).
7. **Current focus.** Endometrial cancer tumorigenesis is rather poorly understood. The genetic and epigenetic factors responsible are slowly being elucidated. Current efforts include identification of tumor-suppressor genes, identification of epigenetic changes (DNA methylation), and better understanding of estrogen-driven tumorigenesis. Clinical studies relate to identification of more effective therapies for metastatic and recurrent endometrial cancers.

C. **Sarcomas**

1. **Presentation.** Similar to that of endometrial cancers.
2. **Workup and staging.** Uterine sarcomas are have been classified in many different ways, but most commonly they are subdivided into the following four types: (a) leiomyosarcomas, (b) endometrial stromal sarcomas, (c) malignant mixed mesodermal tumors (MMMTs) with homologous or heterologous elements (also called mixed Müllerian mesodermal tumors or carcinosarcomas), and (d) other uterine sarcomas. There is no accepted staging system for uterine sarcomas, but the FIGO system used for endometrial cancers is most commonly used (see Table 11.1). Patients should be treated primarily with surgical exploration with appropriate staging, as primary radiotherapy and chemotherapy have very disappointing results.
3. **Therapy and prognosis.** Although each histologic subtype of sarcoma behaves differently, in general, survival is poor, with more than half of patients dying of their disease. Adjuvant therapy for **stage I and II** disease in the form of radiation therapy often improves local recurrences but has little impact on long-term survival. Cytotoxic chemotherapy may have a role in the adjuvant setting, but currently there is no definitive proof of a survival benefit. Hormonal therapy with high-dose progestin therapy (megestrol acetate, 240 to 360 mg p.o. daily) has shown activity against endometrial stromal sarcomas. **Advanced stage** (III/IV) and **recurrent disease** have been treated with radiotherapy with minimal success. Chemotherapy is most often used in this setting. For the MMMTs, ifosfamide plus MESNA, with or without cisplatin, is most often used (ifosfamide, 1.2 to 1.5 g/m ^{2} i.v. qd × 5 days, or ifosfamide, 1.2 to 1.5 mg/m^2 i.v. qd × 4 days, with cisplatin, 20 mg/m^2/day i.v. × 4 days, repeated every 3 weeks (response rates, 30% to 50%). In a randomized GOG study, combination therapy produced higher response rates but greater toxicity and no survival advantage over single-agent ifosfamide (Sutton, 2000). Single agents doxorubicin (60 mg/m^2 i.v. q3 weeks) or ifosfamide (similar dosing as for MMMTs) have shown activity against leiomyosarcomas (approximate response rates, 25% and 20%, respectively.
4. **Complications.** See Section I.B.4.
5. **Follow-up.** See Section I.B.5.
6. **Background.** Two percent to 3% of uterine tumors are sarcomas with the following histologic subtypes: mixed müllerian mesodermal sarcomas (50%), leiomyosarcomas (40%), and endometrial stromal sarcomas (8%).
7. **Current focus.** Patients with optimally debulked MMMTs of any stage are being studied to evaluate whole abdominal radiation therapy versus chemotherapy with ifosfamide and cisplatin in a randomized fashion (GOG no. 150). Recent chemotherapy trials for advanced or recurrent leiomyosarcoma have included doxorubicin, 40 mg/m^2; mitomycin, 8 mg/m^2; and cisplatin, 60 mg/m^2 q3 weeks; results not yet available (GOG no. 87-I); liposomal doxorubicin (Doxil), 50 mg/m^2 i.v. q4 weeks (GOG no. 87-J), recently activated; and paclitaxel, 175 mg/m ^{2} i.v. over a 3-hour period q3 weeks, results not yet available (GOG no. 131-C).

D. **Gestational trophoblastic disease**

1. **Presentation.** Most cases of malignant/persistent gestational trophoblastic disease (GTD) are seen after a hydatidiform mole. Hydatidiform moles have vaginal bleeding and a positive pregnancy test. Nearly all hydatidiform moles are now diagnosed with ultrasound examination, demonstrating the

"snow-storm" appearance of the vesicle-filled intrauterine cavity. Occasionally patients will have symptoms of preeclampsia, hyperthyroidism, and/or severe hyperemesis. Physical examination demonstrates uterine size inconsistent with estimated gestational dates, bilateral enlarged ovaries (thecal lutein cysts), and usually an absence of fetal heart sounds. GTD also can occur after a normal pregnancy, abortion (spontaneous or induced), or ectopic pregnancy. It is this group of patients in which the diagnosis is often missed. These patients typically have persistent vaginal bleeding, signs and symptoms of pregnancy, a positive pregnancy test, and/or widely metastatic disease.

2. **Workup and staging:** After diagnosis of a molar pregnancy (usually by ultrasound), the patient should undergo chest radiograph (CXR; if positive, a metastatic workup should follow; see later), type and cross matching of blood, quantitative b-human chorionic gonadotropin (HCG), and a suction D&C, followed by sharp curettage. Intravenous (i.v.) oxytocin, 20 to 40 units/L or other oxytonic agents should be used shortly after the beginning of the procedure and continued for several hours to avoid excessive bleeding. Patients with Rh-negative blood should receive Rh immune globulin (RhoGAM), as indicated. Patients are followed up after surgery with quantitative pregnancy tests weekly until normal and then monthly for 1 year. Eighty percent of moles will resolve with D&C alone. **Persistent gestational trophoblastic neoplasia (GTN)** is diagnosed with any of the following conditions (note that histologic verification is **not** required): (a) after evacuation of a hydatidiform mole, the HCG level does not decrease appropriately (plateau or 2 consecutive weeks with an increasing titer); (b) metastatic disease is discovered; or (c) pathologic diagnosis of choriocarcinoma or placental-site trophoblastic tumor. Once the diagnosis of persistent GTN is made, a further metastatic workup should include a complete history and physical examination and computed tomography (CT) of the chest, abdomen, pelvis, and possibly head, if indicated. A pelvic ultrasound should be performed to rule out an early pregnancy in patients with possible inadequate contraception. Complete blood count (CBC) and metabolic panel (hepatic and renal) also are indicated. An anatomic staging system (FIGO, 1992) does exist but is seldom used. Prognosis and subsequent therapy are usually based on the World Health Organization (WHO) scoring system (not shown) or the National Institutes of Health (NIH) system used by most U.S. trophoblastic disease centers (Table 11.3).

I. Nonmetastatic disease
II. Metastatic disease
  A. Low risk
    1. Short duration since last pregnancy event (<4 mo)
    2. Low pretreatment HCG (<40,000 mIU/mL serum)
    3. No brain or liver metastasis
    4. No prior chemotherapy
    5. Pregnancy event is not a term delivery
  B. High risk
    1. Long duration since last pregnancy event (>4 mo)
    2. High pretreatment HCG (>40,000 mIU/mL serum)
    3. Brain or liver metastasis
    4. Prior chemotherapy failure
    5. Antecedent term pregnancy

NIH, National Institutes of Health; HCG, human chorionic gonadotropin.

TABLE 11.3. PROGNOSTIC CLASSIFICATION OF GESTATIONAL TROPHOBLASTIC NEOPLASIA (NIH)

3. **Therapy and prognosis.** Therapy is directed by the NIH class or the WHO score. Prognosis is generally excellent, and the key is to limit toxicity of the therapy as much as possible. Therapy should be started quickly, as delays can be devastating. **Treatment of nonmetastatic GTN** includes hysterectomy for those no longer desiring fertility and for all with placental-site trophoblastic tumors. Chemotherapy is recommended for all patients, even if hysterectomy is performed, and is usually given as single-agent chemotherapy. Table 11.4 summarizes the chemotherapy regimens used to treat GTN. **Low-risk metastatic GTN** is treated primarily with single-agent chemotherapy; both methotrexate and actinomycin D should be used before resorting to multiagent chemotherapy. **High-risk metastatic disease** is treated with multiagent chemotherapy with the addition of radiation if a brain metastasis is present and surgery to remove resistant foci in the uterus or chest, as needed. All patients receiving chemotherapy should be evaluated with appropriate laboratory studies (CBC, hepatic and/or renal panel) for the specific regimens plus a serum b-HCG every cycle. Treatment should continue until three consecutive normal HCG levels with at least two courses given after the first normal HCG.

Nonmetastatic and low-risk metastatic GTN
  Methotrexate, 0.4 mg/kg i.v./i.m. qd × 5 days, repeat every 2 weeks
  Methotrexate, 30–50 mg/m^2 i.m. qwk (preferred method, *Obstet Gynecol* 1988;72:43)
  Methotrexate, 1–1.5 mg/kg i.m., days (1, 3, 5, 7) + folinic acid, 0.1–0.15 mg/kg i.m., days (2, 4, 6, 8), repeat every 15–18 days
  Actinomycin D, 10–13 μg/kg i.v./day × 5 days, repeat every 14 days
  Actinomycin D, 1.25 mg/m^2 i.v. q14 days
High-risk metastatic GTN: EMA-CO regimen
  Day 1, etoposide, 100 mg/m^2 i.v. (over 30 min); actinomycin D, 0.5-mg i.v. push; methotrexate 100 mg/m^2 i.v. push, then 200 mg/m^2 i.v. infusion over 12 h
  Day 2, etoposide, 100 mg/m^2 i.v. over 30 min; actinomycin D, 0.15-mg i.v. push; folinic acid, 15 mg i.m. or p.o. q12 h × four doses
  Day 8, vincristine, 1 mg/m^2 i.v., plus cyclophosphamide, 600 mg/m^2 i.v.
  Repeat entire cycle every 2 weeks. Patients with CNS metastasis also should receive radiation therapy and intrathecal methotrexate (12.5 mg on day 8)
  (*Gynecol Oncol* 1989;31:439)

GTN, gestational trophoblastic neoplasia; CNS, central nervous system.

TABLE 11.4. CHEMOTHERAPY REGIMENS FOR PERSISTENT GTN

4. **Complications.** Complications are related mainly to the specific chemotherapy regimen used. Single-agent therapy is well tolerated with minimal side effects.
5. **Follow-up.** Patients should be monitored with serum HCG monthly for 1 year. Contraception is needed for a minimum of 6 months, but 12 months is preferred. If pregnancy should develop, an early ultrasound should be performed to document an intrauterine pregnancy.
6. **Background.** Abnormal growth of the human trophoblast is called GTD. The most common abnormality, the hydatidiform mole, has two pathologic varieties—complete and partial mole. The reported incidence of mole varies widely throughout the world, with 1:1,500 pregnancies affected in the United States. Invasive mole is a pathologic diagnosis of a benign tumor that invades the uterine myometrium or on occasion metastasizes. The incidence is estimated at 1:15,000 pregnancies. Choriocarcinoma is a malignant tumor that has a propensity for early metastasis and an aggressive course, arising in 1:40,000 pregnancies. Fifty percent of choriocarcinomas develop after a molar gestation, 25% after a term pregnancy, and 25% after an abortion or an ectopic pregnancy. Placental-site trophoblastic tumor is rarest variant, arising from the intermediate trophoblast, and is relatively chemotherapy resistant. The tumors often secrete human placental lactogen (HPL), which can be used as a tumor marker.
7. **Current focus.** Chemotherapy for low-risk GTN is currently being studied by the GOG (no. 174) in a randomized fashion with methotrexate (30 mg/m ^{2} i.m. q week—maximum, 60 mg) versus dactinomycin (1.25 mg/m^2 i.v. push q2 weeks—maximum, 2 mg). A trial for patients who failed prior methotrexate therapy using dactinomycin (same dosing as earlier) also is enrolling patients (GOG no.176).

II. **Ovarian cancer and fallopian tube cancers**
  A. **Presentation.** Women often have vague symptoms of abdominal bloating/distention, early satiety, anorexia, weight loss, constipation, and are often treated for gastrointestinal problems like gastritis, irritable bowel syndrome, and gallbladder disease. Unfortunately, given the vague nature of the symptoms, nearly 80% of these have advanced-stage (metastatic) disease.
  B. **Workup and staging.** Women found to have a mass on examination or with radiographic or ultrasonic imaging should be evaluated to assess the possible risk that the abnormality represents a malignancy. Appearance and size on ultrasound (complex cystic/solid components) or CT scan combined with patient age and family history are factors that help determine need for surgical evaluation. Benign-appearing and indeterminate lesions can be monitored for a brief period to evaluate for progression of disease. Serum CA 125 can occasionally be of aid in postmenopausal patients. No definitive tests are currently available, and definitive diagnosis is often possible only with surgical evaluation. Patients should undergo all age-appropriate cancer screening (Pap smear, mammogram, colorectal cancer screening) before surgery, as well as additional tests, depending on the clinical scenario (barium enema, colonoscopy, and/or cystoscopy). Laboratory assessment should include CBC, type and screen, electrolytes, renal/hepatic panel, electrocardiogram, and CXR. Additional studies depend on the patient's medical condition(s). Given the likelihood of large and small bowel involvement requiring resection, a thorough bowel preparation should be performed. Staging of ovarian cancer is surgical, and proper staging procedures should consist of the following: (a) midline abdominal incision; (b) evacuation of ascites or peritoneal washings for cytologic analysis; (c) resection of the primary ovarian tumor (i.e., total abdominal hysterectomy with bilateral salpingo-oophorectomy; (d) biopsies of omentum or omentectomy, biopsies of the pelvic and abdominal peritoneum, including pericolic gutters; and (e) retroperitoneal nodal sampling (pelvic and paraaortic), if indicated by lack of abdominal disease larger than 2 cm or if grossly involved with tumor (Table 11.5).

FIGO Stage	Tumor Characteristics
I	Growth limited to the ovaries
IA	Growth limited to one ovary; no ascites; no tumor on the external surface; capsule intact
IB	Growth limited to both ovaries; no ascites; no tumor on the external surfaces; capsule intact
IC	Tumor either stage IA or IB but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells; or with positive peritoneal washings
II	Growth involves one or both ovaries with pelvic extension
IIA	Extension or implantation to the uterus or tubes
IIB	Extension to other pelvic tissues
IIC	Tumor either stage IIA or IIB, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells; or with positive peritoneal washings
III	Tumor involves one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis but the histologically proven malignant extension to small bowel or omentum
IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none >2 cm in diameter; nodes are negative
IIIC	Abdominal implants >2 cm in diameter or positive retroperitoneal or inguinal nodes
IV	Growth involves one or both ovaries, with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equal stage IV

FIGO: International Federation of Gynecology and Obstetrics.

TABLE 11.5. FIGO OVARIAN CANCER STAGING

C. **Therapy and prognosis**

1. **Epithelial tumors of low malignant potential (LMP),** also called borderline tumors, represent approximately 10% to 15% of all epithelial ovarian tumors. The tumors are usually stage I (80% or more) and are characterized pathologically by epithelial cell stratification, increased mitoses, nuclear abnormalities, and atypical cells without stromal invasion. Surgical staging is recommended, but because these tumors tend to occur in younger patients, conservation of fertility is often possible. Treatment is simple surgical resection. Chemotherapy does not appear to have a role in treating these tumors. However, LMP tumors are on rare occasion found to have invasive implants (metastasis), in which case, the patient should be treated as if for frankly invasive disease (adjuvant chemotherapy; see Section II.C.4), although by convention, the tumor is still considered LMP, as the diagnosis is based on the primary tumor only. Recurrent disease is usually treated with repeated surgical debulking. The prognosis is excellent, with very few patients dying of disease. The average time to recurrence is 10 years. Patients are often monitored with annual serum cancer antigen (CA 125) determinations, but it is unclear whether this provides any survival benefit.
2. **Stage IA or IB, grade 1 or 2 ("low-risk") malignant epithelial ovarian cancers** have an excellent prognosis (90% or more 5-year survival). Surgical removal with staging followed by close follow-up is usually all that is required.
3. **Stage IC or II of any grade and stage IA or IB, grade 3 ("high-risk") malignant epithelial ovarian cancer** is usually treated with adjuvant chemotherapy, as this has been shown to increase disease-free survival and likely overall survival (*N Engl J Med* 1990;316:1435). Multiple regimens have been studied [intraperitoneal phosphorus 32 (^{32}P), melphalan, and platinum-based chemotherapy].
4. **Stage III and IV malignant epithelial ovarian cancer** is the most common, with more than 80% of patients first seen with advanced stage disease. Maximal efforts for surgical cytoreduction of the tumor before chemotherapy should be made, as studies have consistently demonstrated improved survival in those patients with an "optimal" cytoreduction. Optimal cytoreduction has been defined in a variety of ways in the literature. Currently the GOG defines optimal cytoreduction as no residual tumor nodules with a diameter of 1 cm or larger. Optimally patients after cytoreduction have a median progression-free (PFS) and overall survival (OA) of 22 and 50 months, respectively (GOG 158) versus patients after suboptimal cytoreduction, with an 18-month PFS and 38-month OA (GOG 111). Adjuvant therapy is recommended for all stage III and IV patients, and the combination of paclitaxel plus a platinum-containing compound is the current standard. Although the therapy is rarely used in the United States, patients with microscopic residual disease can be treated with whole abdominal radiation therapy. The current "standard" therapy is based on three recent clinical trials demonstrating similar efficacy of carboplatin/paclitaxel to that of cisplatin/paclitaxel, with less chemotherapy-related toxicity and a shorter administration time (Ozols, 1999; du Bois, 1999; Neijt, 2000). The regimen: **paclitaxel**, 175 mg/m^2 i.v., given over a 3-hour period, followed by **carboplatin** i.v., dosed with an area under the time–concentration curve (AUC) of 5 to 7.5 (Jeliffe formula to estimate creatinine clearance and Calvert formula to determine AUC) × six cycles (Ozols, 1994). Response rates [complete response (CR) + partial response (PR)] are nearly 80% with this combination. More than half of the patients will have a CR, with 30% demonstrating a complete pathologic response at second-look laparotomy. Sadly, even with these encouraging results, the cancer in the vast majority of patients will recur, and they must be monitored closely, usually with q1- to 3-month complete physical examinations with pelvic examination and serum CA 125 test. Patients found to progress with up-front therapy or with a recurrence should be offered additional treatments that we hope will allow control of their disease and maintain the best quality of life possible. One must realize that very few of these patients are ultimately cured of their disease. The usual first sign of recurrence is an increasing CA 125 level, which is usually followed by evidence of recurrence on examination (pelvic) or by a CT scan of the abdomen and pelvis. It is not clear whether early retreatment (before the onset of symptoms or radiographic evidence of disease) of a patient with an increasing CA 125 has any effect on disease control or overall survival. **Treatment of recurrent or persistent disease** is based on the timing and location of the recurrence. Radiation and or surgical resection has been successfully used to treat localized disease. Indications for repeated surgery (secondary debulking) are highly controversial, and decisions must be individualized. In general, if the progression-free interval is longer than 1 year and the mass appears isolated, or if it is symptomatic (obstruction of bowel or kidney), surgical resection can result in prolonged survival. "Platinum-sensitive" patients have recurrences more than 6 months from the time of their initial complete response. These patients can be successfully retreated with platinum-based regimens with reasonable responses (20% to 40%). Patients with recurrences before 6 months ("platinum resistant") can be treated with a variety of agents. Many authorities recommend that single-agent therapy be used in this setting to minimize toxicity and more easily to identify agents evoking no response. Given that there is no ideal second-line salvage agent(s), patients should be encouraged to participate in available study protocols. Second-line (salvage) agents will have an approximate response rate of 15% to 40%, depending on agent and number of prior chemotherapeutic treatments. Treatment is usually continued until the CA 125 normalizes, toxicity precludes further therapy, or disease progresses. Patients with progressive disease are then offered a different regimen, usually with a differing side-effect profile to minimize toxicity. A partial list of available agents include (in no specific order) the following.
    1. Topotecan, 1.25 mg/m^2 i.v., days 1 to 5 q3 weeks (Swisher, 1997).
    2. Liposomal doxorubicin, 40 to 50 mg/m^2 i.v., given over a 30-minute period, q3 to 4 weeks (Muggia FM, et al., 1997).
    3. Paclitaxel, 80 mg/m^2 i.v., over a 1-hour period every week (Abu-Rustum, 1997).
    4. Docetaxel, 100 mg/m^2 i.v., over a 1-hour period every 3 weeks (Verschraegen, 2000).
    5. Etoposide, 50 mg/m^2 orally on days 1 to 21 q28 days (Rose, 1998).
    6. Gemcitabine, 1,250 mg/m^2 over a 30-minute period on days 1, 8, and 15, q28 days (von Minckwitz, 1999). We prefer 800 to 1,000 mg/m^2 to limit toxicity.
    7. Hexamethylmelamine, 260 mg/m^2 daily × 14 days, repeated q4 weeks (Moore DH, 1993).
    8. Tamoxifen, 40 mg p.o. b.i.d. × 30 days, and then 20 mg p.o. b.i.d. (Ahlgren JD, 1993).
    9. Vinorelbine, 30 mg/m^2 i.v. bolus, given days 1 and 8, repeated q3 weeks (Sorensen P, 2001).
    10. Oxaliplatin, 130 mg/m^2 i.v. over a 2-hour period q3 weeks (Piccart M, 2000).
5. **Fallopian tube carcinoma** is a rare gynecologic malignancy that behaves biologically like serous epithelial ovarian carcinoma. Fallopian tube carcinoma is staged and treated in a manner similarly to those used with ovarian carcinoma. The classic presentation is intermittent, profuse, watery vaginal discharge (hydrops tubae profluens). The diagnosis is seldom made preoperatively but has been detected by Pap smear. Prognosis is related to stage of disease, with long-term survival of approximately 50% for stages I and II. As with ovarian carcinoma, long-term survival is rare with advanced disease.
6. **Germ cell ovarian cancers** typically occur in young women, are highly curable, and account for nearly 3% of ovarian cancers. The majority are first seen as early-stage lesions confined to one ovary, except for dysgerminomas, which are bilateral in 15% of cases. Dysgerminoma, endodermal sinus tumor (yolk-sac tumor), embryonal carcinoma, choriocarcinoma, immature (embryonal) teratoma, and malignant mixed germ cell tumors are the cell types seen. Fertility-sparing surgery is nearly always possible. Surgical cytoreduction appears to be important and is likely associated with increased survival. Most of these tumors will have a tumor marker available to monitor [HCG, a-fetoprotein (AFP), lactate dehydrogenase (LDH), CA 125, or neuron-specific enolase (NSE)]. After surgery, all tumors are treated with chemotherapy except some well-staged IA cancers. The bleomycin, etoposide, platinum (BEP) regimen, the most commonly used, is a 5-day regimen, although a 3-day regimen also has been studied (cisplatin, 20 mg/m ^{2} i.v. days 1 through 5; bleomycin, 30 units i.v. weekly; and etoposide, 100 mg/m^2 i.v., days 1 through 5, with the cycle repeated q3 weeks) (*N Engl J Med* 1987;316:1435).
7. **Stromal tumors of the ovary** are classified by the WHO into five main classes: (a) granulosa–stromal cell tumors (adult and juvenile granulosa cell tumor and tumors in the thecoma/fibroma group); (b) Sertoli–stromal cell tumors (Sertoli, Leydig, or Sertoli–Leydig cell tumor); (c) gynandroblastoma; (d) sex cord tumor with annular tubules; and (e) unclassified. These tumors are rare and are usually of early stage and low grade, which makes them readily curable with simple surgical resection. Primary metastatic or recurrent disease is usually treated with surgical cytoreduction followed by combination chemotherapy. The BEP regimen is most often used (see Section II.C.6).

D. **Complications** of therapy are related primarily to continued growth of the tumor (bowel obstruction) and toxicities of the chemotherapy. Bowel obstructions should initially be managed conservatively with intravenous fluids and gastric decompression. Studies such as abdominal plain films, small-bowel follow through, contrast enemas, and abdominal/pelvic CT may be necessary to evaluate further the cause of obstruction. Persistent obstructions can be managed with long-term decompression (g-tube) or surgical exploration in cases in which the imaging studies suggest a limited focus of obstruction. Toxicities of the

chemotherapy are related to the specific agents and are covered elsewhere in this text.

E. **Follow-up** for patients with ovarian cancers relies on careful physical examination, patient's symptoms, and serum tumor markers (CA 125). Patients need to be monitored closely for a prolonged period (more than 10 years), given that ovarian tumors have a propensity for late recurrences. Radiologic assessment is rarely necessary and is usually performed only for protocol or to evaluate further patient complaints or examination findings.

F. **Background.** Ovarian cancer is the most deadly of the gynecologic malignancies, with nearly 15,000 deaths in the United States annually and more than 25,000 cases. The majority of ovarian cancers appear to arise from the outer most epithelial (mesothelial) layer. Less common are the germ cell tumors, stromal cell tumors, and ovarian sarcomas. Risk factors for the development of epithelial ovarian cancer include hereditary factors (26% to 85% risk in BRCA1 mutation carriers), dietary (high fat), infertility, and a history of other cancers (especially breast cancer). Known protective factors include pregnancy, oral contraceptive use, and tubal ligation. Oral contraceptive use of 5 years or more can decrease a woman's risk of ovarian cancer by 40%. Screening of asymptomatic women with more than an annual pelvic examination (ultrasound, CA 125) has not been shown to be useful.

G. **Current focus.** A great deal of attention has been focused on identification of the genetic factors involved with ovarian cancer tumorigenesis with identification of potentially useful biomarkers. Early detection with screening using current technology has been disappointing. Identification of more specific tumor markers could potentially be used to identify disease at earlier, more treatable stages. Intraperitoneal (i.p.) chemotherapy would appear to have a theoretic advantage in treating ovarian carcinoma, allowing dose intensification without undue toxicity. Multiple studies have evaluated i.p. chemotherapy with promising results. However, the role of i.p. chemotherapy has yet to be clearly defined and remains investigational. Current clinical studies are examining new chemotherapeutic agents and novel combinations of known agents in efforts to improve survival from this devastating disease.

III. **Uterine cervix neoplasms: preinvasive lesions of the cervix.**

A. **Presentation.** Preinvasive lesions of the cervix are asymptomatic and are reliably detected only with cytology or biopsy. The American Cancer Society and the American College of Obstetrics and Gynecology recommendation for cytologic screening (Pap smear) is as follows: All women who are or have been sexually active or have reached age 18 years should undergo an annual Pap test and pelvic examination. After a woman has had three or more consecutive satisfactory annual examinations with normal findings, the Pap smear may be performed less frequently, at the discretion of her physician. At least an annual Pap smear is recommended for women at high risk. In 1988, the Bethesda system for the reporting of cervicovaginal cytologic results was developed in an effort to simplify and bring uniformity to the reporting of cytology results.

B. **Workup.** The following is a highly simplified approach to managing the abnormal Pap smear and will not apply to all situations. **For atypical squamous cells of undetermined significance (ASCUS),** the Pap smear can usually be repeated in 3 to 6 months. If the patient already has had a previously abnormal Pap or is considered “high risk,” then colposcopy is indicated. Follow-up evaluation of **AGUS** is more controversial. Colposcopy with endocervical curettage should be performed on all patients. Women older than 35 years or any women with a abnormal menstrual bleeding needs sampling of the endometrium. Pap smears with **low-grade (LGSIL) and high-grade (HGSIL) squamous intraepithelial lesion** need colposcopic examination. **Colposcopy** is performed with a colposcope that allows magnification of the cervix, which is treated with a 4% acetic acid solution. Biopsies are performed of abnormal areas, and a histologic diagnosis is made. Endocervical curettage is part of most routine colposcopic examinations. Diagnostic cervical conization (a large cervical biopsy performed with scalpel, laser, or electrosurgical device) may be necessary to evaluate the following further: inadequate colposcopy (lesion extends into the canal or the entire transformation zone is not seen), the endocervical curettage is positive for cervical intraepithelial neoplasia (CIN), there is a high-grade lesion on Pap smear not accounted for by colposcopy, a biopsy suggesting microinvasion, or adenocarcinoma *in situ* of the endocervix.

C. **Therapy and prognosis.** Treatment of CIN is dependent on biopsy results. **Cervical intraepithelial neoplasia I (CIN I)** can safely be monitored with screening Pap smear every 3 to 6 months in a compliant patient. More than 60% of these abnormalities will spontaneously resolve. Repeated colposcopy should be performed if high-grade lesions are suggested or after 1 year of LGSIL on Pap. Low-grade disease that persists may be treated (see treatments later) or continue to be closely monitored. All biopsies showing high-grade lesions should be treated. Treatment of cervical dysplasia consists of ablative (cryotherapy and laser) and resective techniques [loop electrosurgical excisional procedure (LEEP) and “cold” knife conization]. The LEEP procedure has gained widespread acceptance and use; it is a well-tolerated office procedure that results in a pathologic specimen (Herzog, 1995).

D. **Complications.** Cervical stenosis or incompetence as well as decreased fertility have been reported but generally affect fewer than 2% of patients. Hemorrhage after LEEP or cold-knife conization can occur in 3% to 5% of patients.

E. **Follow-up.** After treatment for CIN, patients should be monitored with Pap smears every 3 to 6 months. Repeated colposcopy is needed if recurrent CIN develops.

F. **Background.** More than 2.5 million women in the United States have Pap smear abnormalities, with more than 200,000 new cases of dysplasia diagnosed annually. Risk factors for the development of cervical dysplasia all relate to the likelihood of acquisition of human papillomavirus (HPV). HPV DNA has been detected in more than 90% of preinvasive and invasive carcinomas, and there is convincing evidence that HPV is the etiologic factor in the vast majority of dysplasias and cervical cancers. HPV subtypes 16, 18, 45, and 56 are consider high risk; 31, 33, 35, 51, 52, and 58 are of intermediate risk; and 6, 11, 42, 43, and 44 are of low risk for progression to cancer. The role of routine HPV testing for the evaluation of abnormal Pap smears or as a primary screening device has not yet been established. The number of lifetime sexual partners and smoking are the most often cited independent risk factors for the development of dysplasia and cervical cancer. Communities that implement cervical cancer screening programs reduce deaths from cervix cancer by approximately 90%, making it one of the most successful cancer screening programs. Most women in whom cervix cancer develops in the United States have been inadequately screened.

G. **Current focus.** New technologies for Pap smear collection (liquid-based methods), computer-aided evaluation, and molecular testing (HPV) are continuing to be developed. Vaccine and other immune-modulating medications directed at HPV are currently being developed and tested.

IV. **Cervix cancer: invasive disease**

A. **Presentation.** The majority of patients are first seen with abnormal vaginal bleeding or discharge, usually of a serosanguinous or yellow color, often foul smelling. Cancer detected by Pap smear screening is much less common. Visually, cervix cancer lesions are exophytic (most common), endophytic, or ulcerative. Lesions are usually very vascular and bleed easily. Biopsies should be performed on all lesions, with pathologic confirmation of disease before initiation of therapy.

B. **Workup and staging.** Women with biopsies suggesting microinvasive cervical cancer without a gross lesion on the cervix should undergo a large cone biopsy to evaluate and stage the cancer appropriately. FIGO staging of cervical cancer is clinical and determined mainly by physical examination, CXR, intravenous pyelography, cystoscopy, proctosigmoidoscopy, and results of the cone biopsy (if necessary). CT, magnetic resonance imaging (MRI), lymphangiography, and positron emission tomography (PET) scans are used to guide treatment of the patient with cervix cancer but cannot be used to change stage. Table 11.6 summarizes FIGO staging of cervix cancer, 1995.

Stage	Description
0	Carcinoma in situ, intraepithelial carcinoma
I	The carcinoma is confined to the cervix
IA	Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB
IA1	Measured invasion of stroma ≤3 mm in depth, and ≤7 mm width
IA2	Measured invasion of stroma >3 mm and ≤5 mm in depth, and ≤7 mm width
IB	Clinical lesion confined to the cervix or preclinical lesion greater than stage IA
IB1	Clinical lesions ≤4 cm
IB2	Clinical lesions >4 cm
II	The carcinoma extends beyond the cervix but has not extended to the pelvic wall. The carcinoma involves the vagina but not as far as the lower one third
IIA	No obvious parametrial involvement
IIB	Obvious parametrial involvement
III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer free space between the tumor and the pelvic wall. The tumor involves the lower one third of the vagina. All cases of hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to other causes
IIIA	No extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

FIGO, International Federation of Gynecology and Obstetrics.

TABLE 11.6. FIGO STAGING OF CERVIX CANCER, 1995

C. **Therapy and prognosis.** In general, all cancers of the cervix can be treated with radiation therapy. Specifics of therapy as well as the surgical alternative are as follows: **Stage IA1** may be treated with extrafascial hysterectomy or cervical cone biopsy alone in a patient strongly desirous to preserve her fertility. The risk of lymph node metastasis is very rare (0.2%), and prognosis is excellent, with very few deaths of disease. Lesions with lymph-vascular space involvement should be treated similar to stage IB cancers. **Stage IA2, IB1, and IIA** can be treated with either radical hysterectomy with pelvic lymphadenectomy or radiation therapy, both with similar efficacy. Although controversial, lesions larger than 4 cm should be managed with primary radiotherapy, except when on a study protocol or if a contraindication to radiat- ion therapy exists (adnexal mass, inflammatory bowel disease, or prior radiation therapy). Surgically managed patients with positive margins, positive lymph nodes, or other high-risk factors should be offered adjuvant radiation therapy. Other high-risk factors include lymphovascular space involvement plus one of the following: (a) deep-third penetration of tumor, (b) middle-third penetration and clinical tumor larger than 2 cm, or (c) superficial penetration and larger than 5 cm; *or* absence of lymph-vascular space involvement plus and middle- or deep-third invasion and clinical tumor larger than 4 cm (Sedlis, 1999). Sensitizing chemotherapy (cisplatin) also can be added for patients with positive margins or lymph nodes (Peters, 2000). **Stage IB2, IIB–IVA** lesions are treated primarily with radiation therapy, usually with whole-pelvis radiation with 5,040 cGy, given as 180- to 200-cGy daily fractions with one to three brachytherapy applications. Patients should be given weekly cisplatin chemotherapy as a radiation-sensitizing agent (Whitney, 1999 ; Morris, 1999; Rose, 1999; Keys, 1999). Our weekly regimen is cisplatin, 40 mg/m^2 i.v. given

every Monday during radiation therapy. A CBC with differential, basic metabolic panel (electrolytes and renal panel) and magnesium levels are usually obtained weekly before administration of the chemotherapy. **Stage IVB** is usually treated with palliative doses of radiation to minimize symptoms of pain or vaginal bleeding. Chemotherapy in this setting has been disappointing, and no agents or combinations have made a significant effect on survival. Recurrent disease is treated based on site of recurrence and previous therapies. Surgical resection (pelvic exenteration), radiation (if outside a previously radiated area), or chemotherapy can be used. The optimal chemotherapy regimen is not known. Single-agent cisplatin (50–70 mg/m ^{2} i.v. q3 weeks) has reported response rates of 20% to 30% and is currently the standard with which other agents/combinations are compared. Prognosis (5-year survival) by stage is as follows: IB, 85% to 90%; IIA, 73%; IIB, 65% to 68%; III, 35% to 44%; and IV, 15%. **Adenocarcinoma of the cervix** is treated in a similar manner as squamous cell carcinoma. **Other histologic variants (small cell: neuroendocrine, carcinoid, oat cell; verrucous carcinoma; sarcoma; lymphoma; and melanoma)** are very rare and are beyond the scope of this text—refer to Suggested Readings.

D. **Complications.** Surgical complications of radical hysterectomy are prolonged bladder dysfunction (4%), fistula formation (1% to 2%), lymphocyst requiring drainage (2% to 3%), pulmonary embolism (fewer than 1%), and operative mortality (fewer than 1%). Complications of radiation therapy include vaginal stenosis with sexual dysfunction (30% to 60%), serious small- and large-bowel injury (3% to 4%), and urinary fistula formation (2%).

E. **Follow-up.** In more than one third of patients, the cancer will recur, with more than 80% recurring in the first 2 years after therapy. Patients are seen every 3 months for the first 2 years. Special attention should be paid to weight loss, abdominal pain, leg pain, and lower extremity edema. Examination should include a complete physical examination with attention to the supraclavicular and inguinal lymph nodes. A pelvic examination with Pap smear and rectovaginal examination are performed. The presence of nodularity of the cervix, vagina, or rectum should prompt biopsies.

F. **Background.** Cervix cancer is the third most common gynecologic malignancy in the United States, with approximately 15,000 cases diagnosed annually with nearly 5,000 deaths. Worldwide it is the second most common cancer among women, with approximately 200,000 deaths annually. Areas of the world that have implemented screening and treatment programs for preinvasive cervical lesions have decreased the mortality by nearly 90%. Risk and etiologic factors are summarized in section on premalignant disease of the cervix.

G. **Current focus.** PET to assess for presence of metastatic disease and help guide radiation therapy is currently being studied. Neoadjuvant chemotherapy with cisplatin and vincristine for stage IB2 lesions followed by surgery is currently being studied by the GOG.

V. **Vulvar cancer**

A. **Presentation.** The vast majority of patients are first seen with complaints of vulvar pruritus. The presence of a mass, ulcer, bleeding, swelling, and pain with urination also are often noted.

B. **Workup and staging.** A biopsy should be taken of any gross lesion and especially any new lesion on the vulva. There are a wide variety of appearances of vulvar cancers: raised, ulcerative, exophytic, white, red, and pigmented. Application of 4% acetic acid solution or toluidine blue to the vulva can help define the extent of some lesions. Use of the colposcope is only rarely helpful. A biopsy is performed under local anesthesia, using a 3- to 5-mm Keyes punch biopsy to sample the worst-appearing areas. Hemostasis is obtained with direct pressure, silver nitrate, or suture ligature. More than 90% of vulvar cancers are squamous cell carcinomas, and the other cell types (melanoma, extramammary Paget disease, basal cell carcinoma, adenocarcinoma, verrucous carcinoma, and sarcoma) are all very rare and are beyond the scope of this text (see Suggested Readings). The trend for surgical management of all vulvar cancers has become more conservative over the last decade. The treatment for invasive vulvar cancer is radical vulvectomy with bilateral groin node dissection (usually through separate skin incisions). Two exceptions to this recommendation are (a) with biopsies demonstrating less than 1 mm of invasion, a radical (down to the level of the underlying fascia) excision with at least 1 cm margins should be performed. If the final pathology confirms only microinvasion, the groin lymph nodes need not be sampled; and (b) invasive lesions (larger than 1 mm) that are less than 2 cm in diameter and more than 2 cm from the midline may be staged with ipsilateral groin nodes dissection alone. FIGO staging is summarized in Table 11.7.

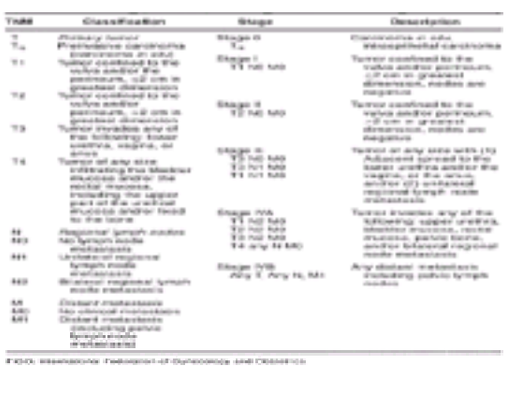

TABLE 11.7. FIGO STAGING OF VULVAR CARCINOMA WITH TNM CLASS

C. **Therapy and prognosis.** Surgical resection in patients with pathologically negative groin nodes is curative in more than 90% of patients. More than half of all patients with positive groin nodes will die of their disease. Currently it is recommended that patients with two or more positive groin nodes undergo inguinal and pelvic irradiation after primary surgery.

D. **Complications.** Wound infections with skin breakdown are very common after surgery, so proper wound care is critical. Lymphocysts and lymphedema also are quite common. Diligent surgical technique and the use of negative-pressure drains help minimize this complication.

E. **Follow-up.** The majority (70% to 80%) of recurrences occur in the first 2 years after the initial surgery. Patients should be examined every 3 to 6 months during this period, and biopsies should be liberally performed.

F. **Background.** Vulvar cancer is the fourth most common gynecologic malignancy, with fewer than 3,000 cases diagnosed annually in the United States. The average age at presentation is in the mid-60s, but there appears to be a bimodal age distribution. There is an increasing incidence of younger patients developing vulvar cancer, and this is thought to be HPV mediated. The etiology of vulvar cancer is not well understood. HPV infection, environmental/industrial toxins, chronic irritants, chronic infections, and vulvar nonneoplastic disorders (vulvar dystrophies) all may have an etiologic role. Knowledge of the anatomy of the vulva with special attention to the lymphatic drainage is vital to understanding disease progression.

G. **Current focus.** Current study is under way to investigate the role of chemotherapy (cisplatin) as a radiation-sensitizing agent combined with standard radiation therapy for patients requiring adjuvant radiation therapy (see Section IV.C. for specifics on chemoradiation with cisplatin).

VI. **Vaginal cancer**

A. **Presentation.** Vaginal bleeding, either spontaneous or after coitus, and vaginal discharge are most common. Patients also may have an abnormal Pap smear, pelvic pain, dyspareunia, and/or bowel and bladder complaints.

B. **Workup and staging.** Biopsies should be performed of gross lesions to confirm the diagnosis of invasive cancer. A patient with an abnormal Pap smear who has previously undergone hysterectomy or in whom evaluation of the cervix showed no disease should undergo colposcopy of the vagina with biopsies. It is important to realize that tumors of the vagina represent metastatic disease from other sites more often than primary vaginal cancer. Other gynecologic cancers or colorectal carcinomas are the most common tumors metastatic to the vagina. Staging of vaginal cancer (Table 11.8) is similar to that of cervix cancer in that it is a clinical staging system. Stage 0 or vaginal intraepithelial neoplasia (VAIN) is preinvasive disease and is graded in a manner similar to that of CIN, from I to III. Patients with invasive disease should be evaluated with a complete history and physical examination with special attention to supraclavicular and inguinal lymph nodes. CXR and intravenous pyelogram (IVP) are indicated as part of staging. Location and size of the tumor will dictate necessity of cystoscopy and proctosigmoidoscopy to complete staging.

Stage	Characteristics
0	Carcinoma *in situ* (intraepithelial carcinoma)
I	Carcinoma is limited to the vaginal mucosa
II	Carcinoma has involved the subvaginal tissue but has not extended into the pelvic wall
III	Carcinoma has extended into the pelvic wall
IV	Carcinoma extension with involvement of the mucosa of the bladder or rectum or extension beyond the true pelvis

FIGO, International Federation of Gynecology and Obstetrics.

TABLE 11.8. FIGO STAGING OF VAGINAL CANCER

C. **Therapy and prognosis. Squamous cell carcinoma** of the vagina is by far the most common primary vaginal cancer, and stage-based treatment is as follows: **Stage 0** (intraepithelial disease) lesions have an unclear malignant potential, and usually only VAIN III lesions are treated. The lesions are often multifocal, so the method of treatment should be tailored to the given lesion(s). Simple surgical excision and/or laser vaporization are most often used. Topical 5-fluorouracil (5-FU) also is used (5 g intravaginally at nighttimes for 5 days; repeated every 2 to 3 months) but can cause significant irritation and burning. All invasive lesions (**stage I to IV**) can be treated with some form of radiation therapy; specifics of therapy as well as possible exceptions are as follows: **stage I** lesions that are next to the cervix may be treated with radical hysterectomy, upper vaginectomy, and pelvic lymphadenectomy. Thus the patient can often avoid radiation and preserve ovarian function. Lesions of the lower one third of the vagina, although staged similarly to upper vaginal lesions, clinically behave more like vulvar carcinomas. For these lesions, bilateral inguinal–femoral lymphadenectomy is recommended to direct possible radiation therapy. Patients also may receive radiation therapy tailored to the specific lesion(s). Radiation therapy consists of brachytherapy alone (tandem and ovoids, intracavitary vaginal cylinder, or interstitial implants) or in conjunction with external-beam radiation to treat the pelvic and/or inguinal lymph nodes. **Stage II to IV** lesions are usually treated first with external-beam radiation (5,000 to 6,000 cGy) to treat the pelvic lymph nodes and to shrink the primary tumor, allowing easier application of brachytherapy. Brachytherapy with interstitial needles usually provides the best tumor dosing. **Long-term survival** in patients treated with definitive irradiation by stage at our institution is as follows: I, 75%; II, 49%; III, 32%; and IV, 10% (Perez, 1988). **Clear-cell adenocarcinomas, melanomas, rhabdomyosarcomas,** and **endodermal sinus tumors** are rare tumors of the vagina and are beyond the scope of this text—refer to Suggested Readings.
D. **Complications.** Major complications of therapy (primarily radiation) are seen in 10% to 15% of patients and are directly related to the dose of radiation. Vaginal stenosis, fistulas (large or small bowel, bladder, and ureteral), bowel and ureteral obstruction, and bowel perforation are not uncommon.
E. **Follow-up.** Patients are usually seen every 3 to 6 months for the first 2 years after therapy and are evaluated with pelvic examination with Pap smear. Recurrences can be treated successfully with pelvic exenteration.
F. **Background.** Vaginal cancers are very rare, only 1% to 2% of gynecologic malignancies. Squamous cell carcinoma is the most common primary tumor, but metastatic disease from other sites is more common. Squamous cancers are most often located on the anterior wall of the upper third of the vagina and are usually multifocal. The specific etiology is unclear, but as with cervical cancer, HPV appears to have a role.
G. **Current focus.** The combination of chemotherapy (cisplatin) with radiation, although not well studied in vaginal squamous cancer, will likely become the preferred method of treatment. (cisplatin, 40 mg/m^2 i.v. q week for six cycles given concurrent with radiation therapy—see Section IV.C.).

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CHAPTER 12. HEAD AND NECK CANCER

Matthew A. Arquette

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I. **Approach to the head and neck cancer patient**
   A. **General.** The poignancy of head and neck cancer is difficult to underestimate; in the face, we recognize an individual, and through speech, we communicate as humans. Although there are many similarities between the sites where head and neck cancer arise, there are particular differences in anatomy, natural histories, and function that present treatment challenges specific to each site. The population with head and neck cancer frequently has comorbid diseases related to the effects of tobacco and alcohol use that may further complicate treatment options.

II. **Lip and oral cavity**
   A. **Cancer of the lip and oral cavity** is the most common site of malignancy in the head and neck, representing 30% of the total. Sites include the lip, floor of the mouth, mobile tongue (anterior two thirds), buccal mucosa, gingiva, hard palate, and retromolar trigone.
   B. **The presentation** of lip and oral cavity cancer is often delayed despite the easy accessibility of this region to examination. As a result, many patients are first seen with advanced disease. Patients may present their dentists or family physicians with complaints that should prompt further evaluation of suggestive lesions.
      1. **Pertinent history** should include a history of tobacco use, including smokeless tobacco, cigarette, pipe, and cigar use, and marijuana and ethanol consumption or abuse. Comorbid diseases including heart disease, chronic obstructive pulmonary disease, and diabetes may complicate treatment and affect overall prognosis. Dental history and symptoms of chronic irritation may be noted. The time course of symptoms may yield clues to the aggressiveness of the disease. Symptoms of pain, trismus, “hot potato speech,” and weight loss should be included.
      2. **A thorough physical examination** includes assessment of performance status, complete evaluation of the nares, oral cavity, oropharynx, hypopharynx, and larynx with indirect or fiberoptic laryngoscopy, and neck. Evaluate for trismus (the mouth should permit entry of three fingers vertically) and tongue movement. Fixation of the tongue (ankyloglossia) may suggest a more advanced lesion. The extent of any mass lesion should be noted. Drawings of the primary lesion are often helpful. Palpation with a gloved finger should be used to inspect the tongue base, retromolar trigone, and floor of mouth. Carious dentition should be noted. Lymph nodes in the neck should be palpated, with measurements of palpable nodes, noting their size, level, and whether they are fixed to underlying tissue. Cranial nerve (CN) examination should include evaluation of extraocular movement, sensation in the trigeminal distribution, protrusion of the tongue or atrophy, and elevation of the palate. Absent shoulder shrug with atrophy of the trapezius muscle may indicate involvement of CN XI by disease in the neck.
      3. **Diagnosis and staging.** In addition to a thorough history and physical examination, the staging evaluation should include diagnostic imaging, triple endoscopy (laryngoscopy, bronchoscopy, and esophagoscopy), and biopsy of the lesion and evaluation for distant metastasis.
         a. **Radiographic imaging** includes computed tomography (CT) or magnetic resonance imaging (MRI) of the primary site and neck. CT scans may be preferred for patients with claustrophobia or difficulty lying supine for a long examination. Better detail of bone invasion may be noted on CT. MRI may be preferred in the patient with allergy to iodinated contrast dyes or for its multiplanar imaging capabilities. These two modalities may be complementary.
            1. **Evaluation for distant metastasis** should include chest radiograph or CT of the chest. Chest CT also may be useful in detecting synchronous primaries of the lung. Other sites of potential distant metastasis include bone and liver, and use of nuclear medicine imaging or CT of the abdomen may be helpful in evaluating patients with advanced locoregional disease at higher risk for distant metastasis.
         b. **Pathology. Squamous cell carcinoma** is the leading histology of cancers of the lip and oral cavity, representing more than 90%. Adverse pathologic features include increasing depth of invasion (which correlates with risk of nodal metastasis in tongue carcinoma), infiltrative borders, poorly differentiated tumors, and perineural and lymphovascular invasion. Sarcomatoid differentiation or basaloid features also may portend a worse prognosis. Less common histologies include adenoid cystic carcinoma and mucoepidermoid histology of minor salivary gland origin.
         c. **Staging.** The staging of head and neck cancer is defined by the size and extension of the primary and extent of nodal disease or distant metastasis (Table 12.1, Table 12.2, Table 12.3, Table 12.4, Table 12.5 and Table 12.6). The prognosis of the patient with head and neck cancer also is influenced by the overall health of the patient and the presence of comorbid disease.

TX Tumor (T)	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T_{is}	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4 (lip)	Tumor invades adjacent structures (e.g., though cortical bone, inferior alveolar nerve, floor of mouth, skin of face)
T4 (oral cavity)	Tumor invades adjacent structures [e.g., through cortical bone, into deep (extrinsic) muscle of tongue, maxillary sinus, skin. Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4]

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TABLE 12.1. AJCC STAGING OF LIP AND ORAL CAVITY CANCER: PRIMARY TUMOR (T)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, >3 cm but not ≤6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node >3 cm but not ≤6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node >6 cm in greatest dimension
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

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TABLE 12.2. AJCC STAGING OF LIP AND ORAL CAVITY CANCER, OROPHARYNX, HYPOPHARYNX, AND LARYNX: REGIONAL LYMPH NODES (N), DISTANT METASTASIS (M)

Stage 0	T_{is}	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1–T3	N1	M0
Stage IVA	T4	N0–N1	M0
	Any T	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

American Joint Committee on Cancer. *AJCC cancer staging manual*. 5th ed. Philadelphia: Lippincott-Raven, 1997, with permission.

TABLE 12.3. AJCC STAGE GROUPING: ORAL CAVITY AND LIP, OROPHARYNX, LARYNX, AND HYPOPHARYNX

TX tumor (T)	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T_{is}	Carcinoma *in situ*
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor invades adjacent structures [e.g., pterygoid muscle(s), mandible, hard palate, deep muscle of tongue, larynx]

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TABLE 12.4. AJCC STAGING OF OROPHARYNX CANCER: PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T_{is}	Carcinoma *in situ*
T1	Tumor limited to one subsite of hypopharynx and ≤2 cm in greatest dimension
T2	Tumor involves more than one subsite of hypopharynx or an adjacent site, or measures >2 cm but ≤4 cm in greatest dimension without fixation of hemilarynx
T3	Tumor measures >4 cm in greatest dimension or with fixation of hemilarynx
T4	Tumor invades adjacent structures [e.g., thyroid/cricoid cartilage, carotid artery, soft tissues of neck, prevertebral fascia/muscles, thyroid and/or esophagus]

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TABLE 12.5. AJCC STAGING HYPOPHARYNX CANCER: PRIMARY TUMOR (T)

TX Tumor (T)	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1 Supraglottis	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T1 Glottis	Tumor limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	– Tumor limited to one vocal cord
T1b	– Tumor involves both vocal cords
T1 Subglottis	Tumor limited to the subglottis
T2 Supraglottis	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T2 Glottis	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T2 Subglottis	Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Supraglottis	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues
T3 Glottis	Tumor limited to the larynx with vocal cord fixation
T3 Subglottis	Tumor limited to the larynx with vocal cord fixation
T4 Supraglottis	Tumor invades through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid, and/or esophagus
T4 Glottis	Tumor invades through the thyroid cartilage, and/or to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, pharynx)
T4 Subglottis	Tumor invades through cricoid or thyroid cartilage, and/or extends to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, esophagus)

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4. **Stage-directed approach to therapy**
   a. **Early stage disease** of the oral cavity and lip may be adequately treated with surgical resection or definitive radiation therapy. Advantages of surgery include a shorter treatment time and avoidance of radiation toxicity (xerostomia, dental caries, and mucositis). Radiation may be preferred in patients who are not able to tolerate a surgical procedure or where complete surgical resection would have an unacceptable effect on speech or swallowing. Patient preference also may be taken into account.
   b. **Advanced stage disease** commonly uses surgical resection and radiation therapy. Radiation to a dose of 60 to 70 Gy is especially used in patients with higher risk of recurrence after surgery (multiple involved lymph nodes, extracapsular extension through the lymph node capsule, or positive surgical margins). Whenever possible, surgical resection should be complete, achieving negative microscopic margins. Preoperative radiation therapy to 45 to 50 Gy may allow surgery on a marginally resectable tumor. Although it is associated with a high response rate in the neoadjuvant setting and reduces the incidence of distant metastases, trials of chemotherapy have not demonstrated a survival advantage in the treatment of resectable disease.
5. **Natural history of disease.** Squamous cell cancer of the head and neck is predominantly a locoregional disease with relatively late spread to distant sites in most patients. This is important for the success of the local modalities of surgery and radiation therapy in treating these patients.
   a. **Field cancerization** is an important concept in the natural history of head and neck cancer. Because the exposure of the mucosa to carcinogens in tobacco is diffuse across the aerodigestive tract, tumors may be surrounded by areas of dysplasia or carcinoma *in situ*. Patients with head and neck cancer are at increased risk of development of synchronous (diagnosed within 6 months of the index tumor) and metachronous (diagnosed more than 6 months after the index lesion) primaries, including new primary tumors in the head and neck, lung, and esophagus. Those who remain disease free after treatment of a head and neck cancer have a risk of developing second primary tumors of approximately 3% to 4% per year.
   b. **Leukoplakia and erythroleukoplakia** represent premalignant lesions of the mucosa, related to the epithelial injury due to tobacco and ethanol. Leukoplakia is a white patch of mucosa that cannot be scraped off and shows hyperkeratosis on biopsy. Erythroleukoplakia may appear red and velvety and may demonstrate dysplasia or carcinoma *in situ* on biopsy. The risk of malignant transformation increases with duration of observation and is higher with erythroleukoplakia.

      Treatment may include careful observation or surgical resection if the area involved makes this feasible. Retinoids such as isotretinoin (13 *cis*-retinoic acid) have shown promising results in the treatment of leukoplakia, but treatment is associated with cheilitis, skin irritation, dry eyes, and a risk of birth defects in patients who are of reproductive potential. In a trial, an isotretinoin dose of 1.5 mg/kg/day by mouth for 3 months followed by a maintenance dose of 0.5 mg/kg/day produced a response rate of 55%, with most responders maintaining their response over the course of 1 year.

III. **Oropharynx**
   A. **Cancer of the oropharynx** includes sites in the soft palate, tonsils, posterior and lateral oropharyngeal walls, and base of tongue. Its borders include the junction of the hard and soft palate, the tonsillar arch, and the circumvallate papillae on the tongue.
   B. **Many of the features** described earlier for cancers of the oral cavity also apply to cancers of the oropharynx.
      1. **Pertinent history** includes a history of tobacco and ethanol use and comorbid diseases. Bleeding from the mouth, alterations in speech, difficulty or pain with swallowing, and weight loss should noted.
      2. **The physical examination** includes assessment of performance status, complete evaluation of the nares, oral cavity, oropharynx, hypopharynx and larynx (with indirect or fiberoptic laryngoscopy), and neck. Assessment should include the cranial nerves. Evaluate for trismus, status of dentition, tongue movement, and atrophy. Palpation of the tongue base with a gloved finger is useful. Note the size and extent of tumors with appropriate drawings of the lesion. Lymph nodes in the neck should be palpated with measurements of palpable nodes, noting their size, level, and whether they are fixed to underlying tissue.
      3. **Diagnosis and staging.** Along with history and physical examination, the staging evaluation of patients with oropharynx cancers includes diagnostic imaging, triple endoscopy with biopsy of the lesion, and evaluation for distant metastasis and synchronous primaries. CT or MRI imaging of the primary site and neck and chest radiograph or CT should be included.
         a. **Pathology. Squamous cell carcinoma** is the histology in more than 90% of cancers of the oropharynx. Less common pathologies include lymphomas involving Waldeyer ring of lymphoid tissue (tonsils, lingual tonsils, and adenoids), mucosal melanomas, and tumors arising in the minor salivary glands that lie in the mucosa (including adenocarcinomas, adenoid cystic carcinomas, and mucoepidermoid carcinomas). Differentiation of squamous cell carcinomas from well-differentiated to poorly differentiated should be noted. Adverse pathologic features include increasing depth of invasion, infiltrative borders, poorly differentiated tumors, and perineural and lymphovascular invasion. Sarcomatoid differentiation or basaloid features also may portend a worse prognosis. Lymphoepithelioma represents a squamous cell carcinoma with extensive infiltration of lymphocytes that usually arises in Waldeyer ring or the nasopharynx and may be confused with non-Hodgkin lymphoma. Immunostaining for clonal lymphoid populations may be necessary for correct identification of these entities with critical treatment implications.
         b. **Staging.** The staging of oropharynx cancer is defined by the size and extension of the primary and extent of nodal disease or distant metastasis (Table 12.2, Table 12.3 and Table 12.4). The prognosis also is influenced by the overall health of the patient and comorbid diseases.
      4. **Stage-directed approach to therapy**
         a. **Early-stage disease** of the oropharynx may be adequately treated with surgical resection or definitive radiation therapy. Chemotherapy is not routinely used in this setting. Advantages of surgery include a shorter treatment time and avoidance of radiation toxicity. Radiation may be preferred in patients with tumors of the base of tongue, because of the risks of functional disability with swallowing and speech associated with larger resections. Tonsillar primaries tend to be very radiation sensitive, which may favor this approach. Patient ability to tolerate a surgical procedure or patient preference also may be taken into account.
         b. **Advanced-stage disease** typically requires a combined-modality approach. Resection of tumors of the base of tongue may be associated with particular disability, leading to difficulty with speech and swallowing. Contiguous spread or a subsequent risk of aspiration may require combined laryngectomy in the surgical approach. Resection should be complete, achieving negative microscopic margins. Larger tumors may require a mandibular splitting approach. Radiation therapy is used in the postoperative setting, especially in patients with multiple nodes, extracapsular extension in nodes, or microscopic positive margins. Brachytherapy may be useful in boosting the radiation dose to the primary lesion.

            Because of the morbidity associated with larger resections, tumors of the oropharynx are often considered for chemoradiation therapy. A multicenter, randomized phase III European trial in patients with stage III and IV oropharynx cancers compared standard radiation (70 Gy in 35 fractions) with a schema of standard radiation with three cycles of concurrent carboplatin and 5-fluorouracil (5-FU). Tonsil and base-of-tongue primary sites were the most frequent in this series. Concurrent chemoradiation was associated with higher rates of mucosal and hematologic toxicity. The 3-year overall actuarial survival and disease-free survival rates were 51% [95% confidence interval (CI), 39% to 68%) versus 31% (95% CI, 18% to 49%) and 42% (95% CI, 30% to 57%) versus 20% (95% CI, 10% to 33%) for patients treated with combined modality versus radiation therapy alone (p = 0.02 and 0.04, respectively). The locoregional control rate was improved in the chemoradiation arm (66%; 95% CI, 51% to 78%) versus radiation (42%; 95% CI, 31% to 56%; *J Natl Cancer Inst* 1999;91:2081). Although this trial did not address the advantages of a surgical approach, the improvement in overall survival that was seen supports the use of concomitant chemotherapy with radiotherapy in the management of patients in whom resection is not feasible in carcinoma of the oropharynx.
      5. **Natural history of disease.** Squamous cell cancer of the oropharynx is, like oral cavity cancer, predominantly a disease of locoregional control. Vertical growth may occur early where tissue planes permit, as in base of tongue and tonsil sites, and this may explain why tumors here represent a significant proportion of unknown primaries found on blind biopsies in patients with cervical metastases. The effects of tobacco and alcohol on the mucosa explain the risk of second primaries and field cancerization. Patients with advanced or recurrent disease are prone to poor lymphatic or venous drainage, and edema of the face and head may develop, worse after lying supine. The effects of prior treatment with neck dissection or radiation fibrosis in the neck may exacerbate this. Steroids may help some patients, and upright posture should be encouraged. These patients may be at risk for airway obstruction that may benefit from tracheostomy.

IV. **Larynx and hypopharynx**
   A. **Cancers of the larynx and hypopharynx** represent challenges in treatment because of their intimate involvement with speech and swallowing. As such, these sites have been associated with the most research on organ preservation, attempts to avoid laryngectomy while maintaining the best chance for cure. The boundaries of the hypopharynx are the level of the hyoid bone superiorly and the lower border of the cricoid inferiorly. Tumors in this area may be divided into those arising from the pyriform sinuses, the posterior wall of the hypopharynx, and the postcricoid area. Tumors of the larynx may be divided into those located predominantly above the true vocal cords (supraglottic), arising from the cords (glottic), or below the cords (subglottic).
   B. **The presentation** of cancers of the hypopharynx and larynx varies greatly with their primary site. Tumors of the supraglottic region or the pyriform sinus may be diagnosed only after cervical metastasis develop because of their greater access to rich lymphatics and vague symptoms of dysphagia that may not

become significant until the tumors are quite large. Conversely, glottic carcinomas are associated with symptoms of hoarseness, often despite a small size, and the tumors may remain localized until cartilage invasion takes place.

1. **Pertinent history** should include a history of tobacco and ethanol use, comorbid diseases, and symptoms of dysphagia, odynophagia, weight loss, dyspnea, and hoarseness. Unilateral paralysis of a vocal cord may result in speech that deteriorates with longer use of the voice and improves with rest. Patients may become dyspneic with speech. Symptoms of aspiration should be sought. The patient's use of the voice in his or her occupation and a history of gastroesophageal reflux should be noted. Symptoms of pain, trismus, altered speech, and weight loss should be included, along with the duration of symptoms.
2. **Physical examination** includes assessment of performance status, complete evaluation of the oral cavity, oropharynx, hypopharynx, and larynx with indirect or fiberoptic laryngoscopy, testing of cranial nerves, and palpation of the neck. Palpation and visualization of the tongue base should note whether there is extension of the tumor to this site. Pooling of saliva in the hypopharynx may interfere with the office examination and requires better visualization at the time of endoscopy and biopsy. Fixation of the true vocal cords should be noted, as this affects staging, and diagrams of the extent of the lesion are helpful.
3. **Diagnosis and staging.** The staging of cancers in the hypopharynx and larynx uses examination with laryngoscopic biopsy to determine the extent of the lesion and search for nodal disease and synchronous primaries. Triple endoscopy is usually done at the time of biopsy. CT or MRI imaging is included to look at the extension of the primary and cervical nodes. Chest radiograph or CT is used to assess for distant metastases and second primary tumors. The tendency of the thyroid cartilage to display irregular calcification should be noted, as it may result in overestimating cartilage invasion on staging.
    a. **Pathology. Squamous cell carcinoma,** or one of its variants, is the histologic description of more than 95% of tumors arising in the hypopharynx and larynx. Tumors of minor salivary gland histology (adenoid cystic, adenocarcinoma, and mucoepidermoid carcinoma) occur infrequently. The supraglottic larynx may be the site for neuroendocrine small-cell carcinomas and should be recognized because of their tendency to distant spread and sensitivity to chemotherapy and radiation.
    b. **Staging** of larynx and hypopharynx cancers uses a tumor, metastasis, node (TMN) system. In addition to using size criteria, many of the staging criteria for the primary (T stage) include whether adjacent subsites of the hypopharynx (pyriform sinus, pharyngeal wall, and postcricoid region) or supraglottic larynx (suprahyoid epiglottis, infrahyoid epiglottis, aryepiglottic folds, arytenoids, and false vocal cords) are involved (Table 12.2, Table 12.3, Table 12.5, and Table 12.6).
4. **Stage-directed approach to therapy**
    a. **Early-stage disease** is most likely to be encountered in laryngeal carcinomas. The primary approach may consist of surgical resection or radiation therapy with generally equivalent cure rates. In many cases, the patient may be able to undergo a larynx-conservation surgery, such as a supraglottic or hemilaryngectomy, in which one or both vocal cords are preserved to allow speech.
    b. **Advanced-stage disease.** Tumors of the pyriform sinus are usually advanced at the time of diagnosis. Tumors of the posterior pharyngeal wall may remain exophytic and superficial, allowing surgical resection if there is not invasion of the prevertebral fascia and muscle. The traditional approach to advanced tumors of larynx and hypopharynx has been surgical resection with laryngectomy or laryngopharyngectomy, as appropriate, to achieve a complete resection, with postoperative radiation therapy.
    c. **Interest in larynx conservation** has led to trials of chemotherapy and radiation in an attempt to avoid laryngectomy and preserve anatomy and function. The Veterans Administration Larynx Trial compared laryngectomy and postoperative radiation with initial chemotherapy with radiation therapy for those patients who responded (*N Engl J Med* 1991;324:1685). Cisplatin and 5-FU were administered every 3 weeks, with response assessed after the second cycle. Responding patients received a total of three cycles of chemotherapy followed by radiation, whereas patients who did not respond to chemotherapy or who had persistent disease after radiation underwent laryngectomy. This approach permitted equivalent survival compared with up-front surgery and allowed 64% of patients to retain their larynx.

        A European Organization for the Research and Treatment of Cancer (EORTC) trial in cancers of the pyriform sinus compared the results of surgical resection and postoperative radiation therapy with a similar experimental arm (*J Natl Cancer Inst* 1996;8:890). Patients were randomized between surgery and radiation or initial treatment with cisplatin and 5-FU. Responding patients received three cycles of chemotherapy followed by radiation with surgery used as salvage for nonresponders or persistent disease. As in the VA larynx trial, survival was equivalent between these two approaches, and functional larynx conservation at 3 years was achieved in 42% (95% CI, 31% to 53%) of patients on the chemoradiation arm.

        In a follow-up trial to the VA larynx trial, a Head and Neck Intergroup trial compared sequential chemoradiation, as given in the VA trial, with concurrent cisplatin during radiation versus radiation therapy alone. The concurrent cisplatin arm administered three cycles of cisplatin given every 21 days, during radiation therapy. Eligible patients included patients with stage III to IV laryngeal cancer who would require total laryngectomy for surgical management. Patients with T4 primaries were excluded if they had more than minimal cartilage invasion or more than 1-cm extension onto the base of tongue. Laryngectomy-free survival, the primary end point of the trial, was superior on the concurrent arm, with 2-year larynx preservation of 88% versus 74% in patients treated with sequential chemoradiation therapy or 69% after radiation therapy alone. The advantage of concurrent chemoradiation versus induction chemotherapy was statistically significant ($p = 0.0047$), whereas there was no difference in laryngectomy-free survival with the addition of induction chemotherapy to radiation alone ($p = 0.22$; *Proc Am Soc Clin Oncol* 2001;20:abst 4). Together, these trials demonstrate the feasibility of organ preservation in many advanced cancers of the larynx and hypopharynx while maintaining survival.
5. **Natural history of disease.** Locoregional control is the major challenge of treatment in patients with cancer of the hypopharynx and larynx, but these sites demonstrate the variable natural history of squamous cell cancer arising in adjacent structures. The lack of symptoms in early pyriform sinus cancers can be contrasted with those of the glottic larynx. The effect of anatomy with confinement of many laryngeal cancers to the primary site due to surrounding cartilage contrasts with the advanced disease typically seen in hypopharynx cancers to demonstrate these differences. Although most recurrences of head and neck cancers occur within the first 2 to 3 years after treatment, continued vigilance is warranted for the development of metachronous primaries, and all patients should be counseled about the benefits of smoking cessation.

V. **Nasopharynx cancer**

A. **The borders of the nasopharynx** include the choanae (anterior), the soft palate (inferior), and lateral walls, including the fossae of Rosenmuller and the eustachian tube orifices. Its sloping roof along the skull base (superior and posterior) lies in close proximity to the foramen lacerum and the carotid artery as it enters the cavernous sinus. Tumors may extend through the foramen ovale to access the middle cranial fossa and the cavernous sinus with access to the oculomotor (CN III), trochlear (CN IV), trigeminal (CN V), and abducens (CN VI) nerves. Optic nerve (CNII) and orbital invasion is possible in advanced cases. There is a rich lymphatic supply with retropharyngeal nodes, including the lateral retropharyngeal nodes (of Rouvière), representing an important route of spread.

B. **The presentation of nasopharyngeal cancer** has many unique features. Symptoms at diagnosis may be related to the primary site, disease in the neck, or distant metastases. The epidemiology of this cancer is different from that of other head and neck sites, with a separate set of risk factors.

1. **Pertinent history** may include genetic and environmental factors. The highest incidence of nasopharyngeal cancers is found in southern China and Southeast Asia. Places that have significant immigrant populations from these countries have a higher incidence, and a history of travel to these parts of the world may convey a higher risk of cancer among North American whites. This risk may be related to strains of Epstein–Barr virus (EBV), as viral titers for EBV are often elevated among patients with this disease. Genetic factors related to host response may explain the increased risk among people of Asian ancestry. Other risk factors have been implicated, including diet (consumption of salted fish, low intake of fresh fruits and vegetables) and smoking. Symptoms may include a painless neck mass, nasal obstruction, epistaxis, dysphagia, odynophagia, eustachian tube obstruction with otitis media, or cranial neuropathies. Trismus may indicate invasion of the pterygoid region. Other symptoms may include headache, referred pain to the ear or neck, and weight loss.
2. **A thorough physical examination** includes assessment of performance status, complete evaluation of the nares and oral cavity, and a thorough evaluation of the cranial nerves. Proptosis may indicate orbital invasion. Evaluation of the nasopharynx with fiberoptic endoscopy or examination under anesthesia with biopsy is appropriate. The status of dentition should be noted, as any needed restoration or extractions should precede the initiation of radiation therapy. Lymph nodes in the neck should be palpated, with measurements of palpable nodes.
3. **Diagnosis and staging.** Along with history and physical examination, the staging evaluation of patients with nasopharynx cancers includes diagnostic imaging, including MRI or CT from the skull base to clavicles, endoscopy, and chest radiograph or CT to look for distant metastases. Nuclear medicine bone scan should be considered in any patient with unexplained bone pain.
    a. **Pathology. Carcinomas represent 85% of nasopharynx tumors** (less common are lymphoma, adenocarcinoma, melanoma, plasmacytoma, rhabdomyosarcoma, and others). Nasopharyngeal carcinoma is classified according to a World Health Organization (WHO) schema. WHO-1 is squamous cell carcinoma. WHO-2 is nonkeratinizing carcinoma. WHO-3 is undifferentiated carcinoma, including lymphoepithelioma.
    b. **Staging.** The staging of nasopharynx cancer is shown in Table 12.7 and Table 12.8.

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T_{is}	Carcinoma in situ		
T1	Tumor confined to the nasopharynx		
T2	Tumor extends to soft tissues of oropharynx and/or nasal fossa		
T2a	Without parapharyngeal extension		
T2b	With parapharyngeal extension		
T3	Tumor invades bony structures and/or paranasal sinuses		
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Unilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa		
N2	Bilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa		
N3	Metastasis in a lymph node(s)		
N3a	Greater than 6 cm in dimension		
N3b	Extension to the supraclavicular fossa		
Distant metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		

American Joint Committee on Cancer. *AJCC cancer staging manual*. 5th ed. Philadelphia: Lippincott-Raven, 1997. With permission.

TABLE 12.7. STAGING OF NASOPHARYNX CANCER

Stage 0	T_{is}	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
Stage III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

American Joint Committee on Cancer. *AJCC cancer staging manual*. 5th ed., Philadelphia: Lippincott-Raven, 1997:35, with permission.

TABLE 12.8. AJCC STAGE GROUPING: NASOPHARYNX

4. **Stage-directed approach to therapy**
   a. **Early-stage disease** is rarely diagnosed because of lack of symptoms. EBV titers have been used in areas of high incidence to allow mass screenings. Radiation therapy, 60 to 74 Gy, is the typical treatment for early disease. Surgical resection or repeated irradiation with chemotherapy may be considered for local recurrence.
   b. **Advanced-stage disease** has traditionally been treated with radiation, but the results of a randomized North American Intergroup trial demonstrated a superior outcome with chemoradiation therapy. This study compared the results of standard radiation therapy (70 Gy) with a schema of the same radiation therapy with concurrent cisplatin given every 21 days during radiation therapy and three additional cycles of cisplatin and 5-FU given every 4 weeks after completion of radiation therapy. The 3-year progression-free survival was 24% versus 69% ($p < 0.001$) and 3-year survival was 47% versus 78% ($p = 0.005$) for radiation versus chemoradiation, respectively. Both local control and distant metastasis were improved in the combined-modality arm (*J Clin Oncol* 1998;16:1310).
5. **Natural history of disease.** Nasopharyngeal carcinoma is a disease with unique features unlike those of other head and neck cancers. There is a younger age at presentation compared with that for other sites and a higher incidence in endemic areas. Its greater radiation sensitivity leads to less need for neck dissection and a greater cure rate, despite advanced disease. Most patients are first seen with locally advanced disease, but the risk of distant metastasis is higher than with other sites. The role of genetic factors and EBV are well recognized but poorly understood. Viral titers, especially immunoglobulin A (IgA) viral capsid antigen and early antigen, may be helpful, as titers that remain elevated may identify a group at risk for distant recurrence.

VI. **Less common tumors of the head and neck**

A. **Salivary gland cancers** most commonly arise in the parotid gland, but may arise in the submandibular or minor salivary glands that line the mucosa of the upper aerodigestive tract.

1. The histology of salivary gland carcinoma is varied and affects prognosis and management. Perineural invasion and nodal metastases are adverse features.
   a. **Mucoepidermoid** cancers are the most common type arising in the parotid glands and are classified as low, intermediate, or high grade. Low-grade tumors respond well to surgical resection, whereas higher-grade lesions are associated with more aggressive local invasion, and nodal and distant metastases.
   b. **Adenoid cystic carcinoma** has the most frequent histology in the submandibular and minor salivary glands. Perineural invasion may lead to facial nerve (CN VII) paralysis and involvement of the skull base. It also is classified by grade and has a significant incidence of distant metastatic disease.
   c. **Malignant mixed tumors** (carcinoma ex-pleomorphic adenoma) arise from a preexisting benign mixed tumor (pleomorphic adenoma).
   d. **Adenocarcinomas** commonly arise from the minor salivary glands but also may arise in the major salivary glands. They have aggressive behavior and significant risk of distant metastasis. Low-grade polymorphous adenocarcinomas arise in the oral cavity and have an excellent prognosis with complete resection.
   e. **Acinic cell carcinomas** usually arise in the parotid glands. They are typically low-grade, slow-growing tumors, but may invade adjacent structures. Late recurrences and distant metastases may occur.
   f. **Squamous cell carcinomas** arising from the excretory duct of the salivary glands have an aggressive course with a poor prognosis despite aggressive therapy.
2. **Management of salivary gland cancers** is complete surgical resection. In the parotid, this may consist of total or superficial parotidectomy, depending on the location of the tumor. When possible, the facial nerve may be preserved. High-grade tumors benefit from adjuvant radiation therapy. Recurrent or metastatic tumors may be treated with chemotherapy, including cisplatin, doxorubicin, 5-FU, and cyclophosphamide combinations.

B. **Tumors of the nose and paranasal sinuses** also include a variety of tumors. These are rare malignancies. Risk factors may include occupational exposures to wood dust, shoe manufacture, nickel refining, and Thorotrast contrast media.

1. **Squamous cell carcinoma** is the most common type in the nose and paranasal sinuses, and the maxillary sinus is the most common primary site. Minor salivary gland histologies also may occur. Surgical resection and postoperative radiation therapy is the treatment.
2. **Esthesioneuroblastoma** (olfactory neuroblastoma) arises from the olfactory neuroepithelium. Complete surgical resection with radiation therapy is the treatment. There may be a limited benefit to the addition of chemotherapy in a combined-modality approach.
3. **Sinonasal undifferentiated carcinomas (SNUCs)** are high-grade epithelial malignancies that may occur with or without neuroendocrine differentiation. Treatment may include surgery, radiation, and chemo-therapy.

VII. **Unknown primary and management of the neck**

A. **The patient with a neck mass** may not have a primary site identified on inspection of the oral cavity and pharynx, despite careful examination.

1. **Fine-needle aspiration for cytology** of the neck mass should be pursued as the primary diagnostic procedure. Open biopsy should be pursued if a lymphoma is suggested. Evaluation should be performed of the thyroid, parotid, and any suggestive skin lesions. A mass in the supraclavicular fossa should prompt evaluation of possible primary sites below the clavicles.
2. **If squamous cell carcinoma is suggested by the cytology** obtained, endoscopy with blind biopsy of potential primary sites should include the nasopharynx, tonsils, base of tongue, and pyriform sinuses.
3. **If no primary site is found,** several approaches are considered. If the neck mass is unresectable, then primary radiation therapy with a nasopharyngeal port, which will include the likely potential primary sites, may be used. If a nasopharyngeal primary is suggested by the cytology, chemoradiation may be considered. Residual disease after radiation or neck masses larger than 6 cm should undergo subsequent neck dissection. If the neck mass is resectable, neck dissection may be pursued as primary therapy. If the pathology shows extracapsular extension or multiple nodes are involved, postoperative radiation therapy with a nasopharyngeal port is given. If the neck mass is solitary and small, then radiation therapy may be held off and the patient closely observed, with radiation used at the time of relapse.

B. **Management of the neck**

1. **Control of disease in the neck** is a major challenge in patients with head and neck cancer. Much of the morbidity and mortality of this disease is related to disease in regional nodes, and effective control of nodal metastases is important in overall control and cure.
2. **Patients with clinically negative** neck nodes that are at significant risk for occult disease may be treated effectively with elective neck dissection

(lymphadenectomy) or radiation therapy. Clinically involved nodes may require both modalities, especially if there is extracapsular extension, masses larger than 6 cm, or multiple nodes are involved.

3. **Anatomy of the lymphatic drainage** of the neck is divided into various groups. Level I nodes include the submental and submandibular nodes. Level II includes the upper jugular or jugulodigastric nodes. Level III includes the midjugular nodes. Level IV includes the lower jugular nodes. Level V includes the posterior triangle of the neck.
4. **Radical neck dissection** consists of removing all five lymph node groups on one side of the neck, as well as the sternocleidomastoid muscle, the internal jugular vein, and the spinal accessory nerve (CN XI). **Modified radical neck dissections** remove all five lymph node groups but may spare one or more of the latter structures. In a selective neck dissection, only lymph node groups at the highest risk are excised, and the sternocleidomastoid, jugular vein, and CN XI are preserved.

VIII. **Recurrent and metastatic disease**

A. **Patients with locoregional recurrence** should be evaluated for salvage surgery or radiation therapy. If salvage surgery is not possible, and radiation has previously been administered, concurrent chemotherapy with repeated irradiation may be effective in some patients. Tissue tolerance, the extent of prior radiation, and significant morbidity may limit this approach.

B. **Patients with metastatic disease** or locoregional recurrence who are not candidates for local therapies may be treated with chemotherapy. Median survival of such patients is 5 to 6 months in most series. Lung, bone, and liver are the most common sites of distant disease. Methotrexate has remained a mainstay of treatment, because it offers survival advantage equivalent to more aggressive regimens in randomized trials and low toxicity. Cisplatin and 5-FU offers a higher response rate of 30%, but more side effects. Other agents with significant activity include carboplatin, paclitaxel, docetaxel, ifosfamide, gemcitabine, and bleomycin.

IX. **Complications of disease**

A. **Aspiration** with risk of pneumonia should be considered in the patient with fever or cough. Weight loss or risk of aspiration may require placement of feeding gastrostomy tubes. Some patients will avoid aspiration with certain postures or food consistencies, and consultation with a speech pathologist is often helpful in rehabilitation. Shortness of breath should prompt evaluation of the airway and the potential need for tracheostomy.

B. **Fungating tumors** may ulcerate and bleed. Invasion of the carotid artery by tumor may be a terminal event and may be heralded by an episode of sentinel bleeding.

C. **Pain control.** Inability to swallow may limit narcotic analgesic choices. Transdermal fentanyl patches (25 µg/hour applied to skin q3d), or methadone elixir (30 mg q8h) may allow longer pain relief with concentrated narcotic elixirs (e.g., morphine sulfate, 20 mg/mL at 1 to 1.5 mL q2–4h) for breakthrough pain. Narcotic doses should be titrated to achieve pain control. Tumors invading nerves at the skull base may produce pain syndromes that are helped by coanalgesics such as amitriptyline or gabapentin.

D. **Paraneoplastic syndromes** may include hypercalcemia and symptom of inappropriate secretion of antidiuretic hormone.

X. **Complications of treatment**

A. **Complications of surgery** may affect cosmesis, intelligibility of speech, and ability to swallow. Reconstructive flap techniques and prosthetics may minimize this. Neck dissection may result in shoulder weakness with resection of CN XI. After laryngectomy, a tracheoesophageal puncture may allow speech by diverting expired air into the esophagus to vibrate the cricopharyngeus muscle as a “pseudo vocal cord.” An electrolarynx, a hand-held device that serves as a vibratory source for phonation, may be used to allow communication with the laryngectomy patient.

B. **Acute radiation toxicity** may include mucositis with pain and inability to swallow. Oral candidiasis complicating mucositis may be treated with topical agents (nystatin or clotrimazole) or systemic agents (e.g., fluconazole, ketoconazole). A cocktail of equal volumes of diphenhydramine suspension, nystatin, viscous lidocaine and aluminum hydroxide/magnesium hydroxide suspension may be used as a topical oral swish solution for mucositis. Some patients may prefer a solution of 1 teaspoon of baking soda and 1/2 teaspoon of salt in a quart of water for milder mucositis. Systemic narcotics are indicated for more severe pain. Skin toxicity should be treated with emollients (e.g., Aquaphor, Biafine) and wound dressings as appropriate.

C. **Late radiation effects include xerostomia,** which may be addressed by frequent access to water, or pilocarpine (5 to 10 mg, p.o. t.i.d.). Pilocarpine may cause uncomfortable sweats, especially at higher doses. Artificial saliva is available but poorly accepted by most patients. Dental caries is a chronic toxicity that may lead to tooth loss. Good dental care and use of fluoride preparations may minimize this. Osteoradionecrosis may be treated conservatively with antibiotics, surgical debridement, or hyperbaric oxygen therapy. Fibrosis of the neck tissues may result in trismus, lymphedema, and loss of range of motion. Exercises may be helpful in preventing trismus. Impaired swallowing due to weakness of pharyngeal constrictor muscles and aspiration may occur. Laryngeal edema may require tracheostomy for management and should prompt consideration of possible disease recurrence.

D. **Chemotherapy toxicities** vary according to the agents used. Used concurrent with radiation, they may increase the severity of mucositis. Methotrexate may cause mucositis and myelosuppression. Cisplatin is associated with significant nausea, nephrotoxicity, peripheral neuropathy, ototoxicity, and myelosuppression. 5-FU may cause myelosuppression and mucositis. Taxanes are associated with alopecia, myelosuppression, myalgias, and allergic reactions.

XI. **Background**

A. **Squamous cell cancer** of the head and neck is an example of the multistep process of carcinogenesis with accumulated genetic mutations that result in changes ranging from hyperplasia to dysplasia to carcinoma *in situ* to invasive cancer. A number of frequent genetic mutations have been identified, whereas others remain under investigation. Loss of tumor-suppressor genes, including p16, p53, and Rb, are frequent, and amplification of the protooncogene cyclin D1 has been demonstrated in many tumors.

B. **Risk factors.** For most patients, tobacco, often augmented by ethanol, is the source of carcinogens, which result in these mutations. The incidence of new cancers of the oral cavity, pharynx, and larynx is estimated at 40,000 in the United States in 2001, resulting in 11,800 deaths (*CA Cancer J Clin* 2001;51:15). These figures underscore the importance of educating patients about smoking cessation. The male-to-female ratio is approximately 3:1. Among nonsmokers, viruses, including human papilloma virus and EBV, are implicated.

XII. **Current focus of research**

A. **Areas of active investigation** include increasing use of combined-modality treatment, especially chemoradiation, to improve outcome. Recent trials demonstrated the feasibility of organ preservation of the larynx. Gene therapy, using modified adenoviruses that are injected directly into the tumor to produce cell death by cytolytic effect of the virus or by restoring p53 function to induce apoptosis, is showing promise. The overexpression of the epidermal growth factor receptor (EGFR) in 90% of head and neck cancers has been shown to be a factor that influences their growth. A monoclonal antibody, cetuximab, directed against the EGFR, is being tested in combination with cisplatin chemotherapy and radiation with apparent synergy with these modalities.

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CHAPTER 13. LUNG CANCER

Ali Al Shanquetti, Carol Kaplan, and Ramaswamy Govindan

Non–small cell lung cancer
Presentation
Workup and staging
Therapy and prognosis
Follow-up
Background
Research initiatives
Small cell lung cancer
Presentation
Workup and staging
Therapy and prognosis
Prognosis
Complications
Follow-up
Background
Current focus
Suggested Readings

I. Non–small cell lung cancer

A. Presentation

1. **Subjective.** Although non–small cell lung cancer (NSCLC) lung cancer can be asymptomatic and detected only by "routine" chest radiograph (CXR), most patients have symptoms secondary to a tumor in the lung, such as new or worsening cough, worsening or new dyspnea, chest wall pain, and fever, often secondary to postobstructive pneumonia. Hemoptysis, especially in the middle-aged or elderly smoker, should always raise the suspicion for lung cancer. Symptoms suggestive of regional spread may vary. Chest pain may signify chest-wall involvement, and dyspnea and hoarseness of the voice may indicate involvement of recurrent laryngeal nerve. Because of its long intrathoracic course, the left recurrent laryngeal nerve is more commonly affected than the right. Superior sulcus tumors can cause Pancoast syndrome; a triad of shoulder pain, lower brachial plexus palsy, and Horner syndrome. Swelling and engorgement of the face, upper trunk, and arms signal superior vena cava (SVC) syndrome, which is associated more with right-sided tumors. Patients with pleural effusions may have dyspnea and cough. Occasionally dysphagia may be one of the dominant presenting symptoms secondary to mediastinal lymph node involvement. Symptoms suggesting systemic spread are not specific and include weight loss, cachexia, and symptoms related to distant sites involved [e.g., bone pain or fractures from bone involvement, right upper quadrant abdominal pain with liver metastases, and neurologic symptoms associated with central nervous system (CNS) involvement]. Paraneoplastic syndromes associated with NSCLC include hypercalcemia (which can cause constipation, abdominal pain, and confusion) and hypertrophic pulmonary osteoarthropathy with marked clubbing and joint pains and swelling.
2. **Objective.** Assessment of the performance status and signs of recent significant weight loss carry a significant prognostic importance. The superficial lymph nodes, particularly the supraclavicular nodes, should be carefully examined, as enlargement of these nodes raises the high likelihood of metastatic involvement. Signs on examination of the chest can detect not only those sign related to pleural effusion, atelectasis, and postobstructive pneumonia, but also can help assess the severity of any underlying lung disease [e.g., chronic obstructive pulmonary disease (COPD)] that may influence subsequent management options. Careful abdominal examination may detect hepatomegaly suggesting metastatic disease. New focal neurologic signs may signify brain or spinal cord involvement.

B. Workup and staging

1. **Imaging.** Chest radiograph. A perfectly normal CXR does not necessarily exclude lung cancer, as conventional CXR may not always identify hilar or mediastinal lesions. Lung cancer can occur as a mass, peripheral nodule, hilar or mediastinal changes suggestive of lymphadenopathy, or pleural effusions. CXR may reveal areas of atelectasis suggesting endobronchial lesion, and pneumonic infiltrates may be seen in association with obstructing lesions.

   Computed tomography (CT) scan of the chest is the most effective noninvasive study to evaluate suspected lung cancer. Although its sensitivity to detect mediastinal metastases is variable, it has a high negative predictive value. It also can help identify local invasion (e.g., chest wall, bones, pleura). The upper abdomen is usually included in this study, and the liver and adrenal glands should be carefully inspected for evidence of metastases.

   Magnetic resonance imaging (MRI) of the chest is not routinely used in the staging workup of patients with lung cancer. It is particularly helpful in the setting of suspected spinal cord, vascular, or chest-wall involvement.

   Positron emission tomography (PET) scanning is a useful adjunct tool to complete the staging workup in patients with recently diagnosed NSCLC. The PET scan has been demonstrated to be superior to CT scans, particularly in identifying mediastinal lymph nodes that are involved by metastatic disease.

2. **Pathological diagnosis.** Sputum cytologic examination is simple, cheap, and effective. Up to 80% of central tumors can be diagnosed with three sputum samples compared with 20% of peripheral nodules larger than 3 cm. Squamous cell type is therefore more likely to be detected by this method.

   Flexible fiberoptic bronchoscopy can help determine extent of endobronchial lesions. It also can be used to obtain tissue for diagnosis (washings, brushings, bronchoalveolar lavage, transbronchial biopsy).

   Mediastinoscopy is very useful to determine status of mediastinal lymph nodes in patients who are considered to be candidates for surgical resection. Evaluation of mediastinal lymph nodes by mediastinoscopy is critical before surgical resection. Normal-appearing mediastinal lymph nodes may contain metastatic disease, and sometimes enlarged lymph nodes in the mediastinum may represent only hyperplastic lymph nodes from postobstructive pneumonia or may represent old granulomatous infection. Cervical mediastinoscopy is more accurate for staging superior mediastinal lymph nodes, whereas extended or anterior (Chamberlain) approach is better for anterior mediastinal lymph nodes. It is a safe procedure in experienced hands.

   Video-assisted thoracoscopic surgery (VATS) can be used to access peripheral nodules, suspected pleural disease, and effusions.

3. **Pathology.** Epithelial cancers are classified by the best-differentiated region but are graded by the most poorly differentiated region. There are two types: small cell lung cancer and NSCLC that comprises of three subtypes, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The distinction between NSCLC and small cell lung cancer (SCLC) is extremely important. SCLC accounts for 20% to 25% of all lung tumors and has a much worse prognosis because of frequent rapid spread. The bronchoalveolar subtype of NSCLC deserves special mention. Its incidence is increasing, particularly in women, and is not related to smoking.
4. **Staging.** The International Staging System (ISS) uses the TNM description system and is shown in Table 13.1. Stage-specific survival is outlined in Table 13.2.

TABLE 13.1. TNM DESCRIPTORS

Stage	TNM Subset	Average 5-year Survival
IA	T1 N0 M0	82%
IB	T2 N0 M0	68%
IIA	T1 N1 M0	52%
IIB	T2 N1 M0 T3 N0 M0	40%
IIIA	T3 N1 M0 T1–3 N2 M0	9%–15%, depending on subset
IIIB	T4 N0–2 M0 T1–4 N3 M0	≤5%
IV	Any T Any N M1	NA

NA, not applicable.

TABLE 13.2. EXPECTED 5-YEAR SURVIVAL (WITH TREATMENT)

C. **Therapy and prognosis**

1. **Overview of management of NSCLC**

   Stages I and II: surgical resection (or definitive radiotherapy if surgery is contraindicated)

   Stage IIIA: neoadjuvant therapy followed by surgery or definitive chemoradiation

   Stage IIIB (without pleural effusion): inoperable, chemoradiation

   Stage IIIB (with malignant pleural effusion): chemotherapy (best supportive care for those with poor performance status)

   Stage IV: chemotherapy [best supportive care (BSC) for those with poor performance status]

2. **Stages I and II.** T1 or T2 without extrapulmonary nodal disease (i.e., N2 or N3) is treated surgically whenever complete resection is possible. Preoperative assessment should determine stage (for resectability potential), cardiopulmonary reserve (whether intended resection is possible), and perioperative risk of intended procedure. Suitable surgical candidates are those with estimated forced expiratory volume in 1 second (FEV1) after pneumonectomy of more than 1.2 L, maximal O_2 consumption greater than 15 to 20 cc/kg/min, no hypercarbia (more than 50 mm Hg), and no cor pulmonale. Patients are instructed stop smoking at least 2 weeks before surgery. Stage of disease, patient's age, and extent of resection significantly affect mortality, which averages about 3% to 7%. Lobectomy is the most commonly used procedure and is equivalent to pneumonectomy when complete resection is achieved. Segmentectomy and wedge resection are associated with two- to threefold increased risk of local recurrence (*Ann Thorac Surg* 1995;60:615–623) and should be reserved for situations in which lobectomy cannot be done. Pneumonectomy is indicated if the tumor or lymph nodes involve the proximal bronchus or pulmonary artery or cross the major fissures. If chest wall is involved, then *en bloc* resection of tumor with the involved chest mass and minimum of 2 cm of normal chest wall in all directions beyond the tumor is recommended.

   Definitive radiation therapy (RT) is a good alternative for patients who are poor surgical candidates because of comorbid conditions. Selection of patients for RT is based largely on extent of the primary tumor and the prognostic factors. Survival after RT depends on PS (1 to 2), radiation dose (more than 60 Gy), and complete response by 6 months after completion of RT.

   Preoperative RT is not considered appropriate in early-stage lung cancer and postoperative RT (PORT) is not indicated in stage I disease. PORT meta-analysis revealed increased mortality (*Lancet* 1998;352:257–263). In patients with N1 or N2 disease, two studies by the Lung Cancer Study Group (LCSG) and BMRC concluded that PORT can improve local control but did not affect overall survival, possibly because of lack of effect on systemic disease (*N Engl J Med* 1986;315:1377–1381; *Br J Cancer* 1996;74:632–639). Patients with incompletely resected tumors or tumors with multiple nodal level involvement or bulky extracapsular extension, however, are generally treated with PORT.

   Adjuvant chemotherapy is not considered standard treatment in the management of either completely or incompletely resected NSCLC tumors. Three studies by LCSG and a recent study by the Eastern Cooperative Oncology Group (ECOG; *N Engl J Med* 2000;343:1217–1222) failed to show statistically significant benefit from adjuvant chemotherapy. Cancer and Leukemia Study Group (CALGB) is currently evaluating the role of adjuvant chemotherapy in patients with resected stage I NSCLC.

   Induction chemotherapy with paclitaxel and carboplatin followed by surgery has not been shown to increase postoperative morbidity or mortality (*J Thorac Cardiovasc Surg* 2000;119:429–439). The role of induction chemotherapy in resectable stage I and II NSCLC is being studied in an ongoing phase III study.

3. **Stage III.** Stage IIIA includes T3 N1 or N2 nodal disease with a significant difference in prognosis, with the latter being worse. Surgery for N2 disease is controversial, and many surgeons consider “bulky” N2 disease inoperable. A large intergroup study randomizing patients with N2 disease to chemotherapy and radiation followed by surgery or chemotherapy and radiation alone is currently under way. If patients are identified to have N2 disease before surgery, these patients should be considered for multimodality therapy. It has been our approach to consider surgical resection after induction chemotherapy for patients with single-station nonbulky N2 disease. We prefer to treat patients with multistation N2 disease or bulky N2 disease with a nonoperative approach using chemotherapy and radiation therapy.

   Patients with stage IIIB disease (except those with malignant pleural effusion) should be considered for combined-modality therapy with chemotherapy and radiation treatment (see later).

   The Radiation Therapy Oncology Group (RTOG) trial in 1987 established 60 Gy (in 30 daily fractions over a 6-week period) as the lowest optimal radiation dose for the treatment of lung cancer. Although a twice-daily fractionation regimen (total, 69.6 Gy) as well an accelerated fractionation regimen (54 Gy over a 2.5-week period) was found to have survival benefit at 2 years over the conventional regimen, the use is limited by increased esophagitis, pneumonitis, and logistic difficulties associated with twice-daily therapy. The use of three-dimensional or conformal radiotherapy may reduce the toxicity to the adjacent normal lung. Radiotherapy alone is not an optimal therapy in patients with unresectable stage III NSCLC and good performance status, as the 5-year survival rates are only 5%.

It has been proven now that addition of chemotherapy to radiation therapy improves survival in patients with stage III NSCLC over radiation therapy alone (ASCO Guidelines, 1997). Chemotherapy is administered either before the initiation of radiotherapy (sequential) or in conjunction with radiotherapy (concurrent). Two randomized studies reported some survival advantage for concurrent chemoradiation over the sequential chemoradiation approach in patients with stage III NSCLC (*Proc Am Soc Clin Oncol* 2000;19:484a; *Proc Am Soc Clin Oncol* 1999;18:458a). However, the concurrent chemoradiation approach has been associated with increased incidence of acute esophagitis and pneumonitis. It was recently shown that concurrent administration of cisplatin and etoposide with radiotherapy, followed by three cycles of docetaxel, is associated with an impressive median survival of 27 months, and 3-year survival of 40% in patients with stage IIIB NSCLC (*Proc Am Soc Clin Oncol* 2001;20:315a). Two large phase III studies are being conducted to confirm this promising result.

a. **Assessment of response.** Even though CT scans are commonly done nearly 2 months after the completion of radiotherapy, there is no clear correlation between the radiographic response (complete response, partial response, and stable disease) and survival, except for those who show evidence of progressive disease. There is no role for maintenance chemotherapy after the completion of chemoradiation in patients with stage III NSCLC.

4. **Stage IV**
   a. **Initial therapy.** Systemic chemotherapy for advanced NSCLC has been shown to improve the quality of life and survival. Some of the commonly used combination regimens in the treatment of NSCLC are listed in Table 13.3. It is important that both the patient and the physician realize that the goal of systemic chemotherapy is NOT to cure the disease but rather to achieve palliation of symptoms and prolongation of survival without unacceptable toxicity. Combination regimens incorporating newer agents (e.g., taxanes, vinorelbine, and gemcitabine) also have been studied and were shown to have higher response rates as well as higher median and 1-year survival than did the standard cisplatin–etoposide combination. A recent ECOG trial that compared four of the commonly used platinum-based chemotherapy regimens found no significant difference in overall response rate (18.5%), median survival (7.5 months), 1-year survival (33%), or median time to progression (3.6 months) (*Proc ASCO* 2000;abst 2). The treatment of stage IV disease should therefore be individualized and take into consideration the performance status of the patient and the comorbid conditions. Systemic chemotherapy should be given for approximately four to six cycles in the absence of progressive disease. There is no evidence to indicate that prolonged courses of chemotherapy result in improved survival. Patients are closely monitored on completion of the initial chemotherapy regimen and should be considered for salvage chemotherapy if they are found to have progressive disease.

Drug	Dose	Route	Day	Cycle
Paclitaxel–carboplatin				
Paclitaxel[a]	200 mg/m²	i.v. infused over 3-h period	Day 1	Every 21 days
followed by				
Carboplatin	Dose calculated by the Calvert formula to an AUC of 6 mg/mL/min	i.v. infused over 1–2 h	Day 1	
Premedications: Dexamethasone, 20 mg p.o., 12 and 6 h before paclitaxel; diphenhydramine, 50 mg i.v., and ranitidine, 50 mg i.v., both 30–60 min before paclitaxel[a]				
Cisplatin–vinorelbine[b]				
Cisplatin	120 mg/m²	i.v.	Day 1	Every 4 weeks
Vinorelbine	25 mg/m²	i.v.	Weekly	
Cisplatin–etoposide[c]				
Cisplatin	60 mg/m²	i.v.	Day 1	Every 21–28 days
Etoposide	120 mg/m²/d	i.v.	Days 1–3	
Cisplatin–gemcitabine[d]				
Cisplatin	100 mg/m²	i.v.	Day 1, 2, or 15	Every 28 days
Gemcitabine	1,000 mg/m²	i.v.	Days 1, 8, and 15	

NSCLC, non-small cell lung cancer; AUC, area under the time-concentration curve.
[a] [illegible]
[b] [illegible]
[c] [illegible]
[d] [illegible]

TABLE 13.3. COMBINATION REGIMENS USED IN THE TREATMENT OF NSCLC

   b. **Second-line therapy.** It has been shown that docetaxel improves the survival in patients for whom a platinum-containing chemotherapy regimen has failed. Docetaxel administered at a dose of 75 mg/m^2 every 3 weeks has been shown to improve survival over BSC, vinorelbine, or ifosfamide (*Semin Oncol* 2001;28(1 suppl 2):4–9).
   c. **Role of surgery or radiotherapy in stage IV NSCLC.** An isolated metastatic lesion (e.g., brain) can be surgically resected before systemic therapy. Surgical intervention also is indicated in certain situations (e.g., metastatic lesion in weight-bearing bones, stabilization of spine).

   RT is indicated for palliation of

   1. Atelectatic lobe, especially in COPD patients. Reexpansion is expected in 60% to 70% of patients if atelectasis has been present for less than 2 weeks.
   2. Hemoptysis, intractable cough, and pain.
   3. Metastatic disease. Bone: RT is used to alleviate pain and prevent impending fracture or compression syndrome. In case of pathologic fracture, RT is used in conjunction with orthopedic fixation to maintain function and activity. Brain: For solitary brain metastasis, better survival and function is seen when the lesion is resected before RT (see Chapter 8, sec. II.C.7).

D. **Follow-up**

The recommendations with regard to follow-up imaging for patients who have been treated for NSCLC is somewhat arbitrary. We generally monitor patients with periodic physical examinations, CXRs done at 3-month intervals for 3 to 5 years after they have had a curative resection.

For patients who have completed chemoradiation for stage III NSCLC, we perform physical examinations, CXRs every 2 months in the first 2 years and every 3 to 4 months in the next 2 years, and semiannually thereafter.

E. **Background**

Lung cancer is the second most common cancer in men and is the most common cause of cancer deaths in both men and women (32%). An estimated 169,400 new cases in 2002 will be diagnosed, accounting for 14% of cancer diagnoses. The incidence rate is declining significantly in men, from a high of 86.5 per 100,000 in 1984 to 70.0 in 1996. In the 1990s, the rate of increase among women began to slow. Although its incidence in women is less than that of breast cancer, it claims more lives (25% of cancer deaths in women vs. 16% caused by breast cancer).

1. **Risk factors**
   a. **Tobacco use.** Cigarette smoking is responsible for at least 80% of cases of lung cancer. The risk of dying of lung cancer is 22 times higher for male and 12 times higher for female smokers compared with that in those who have never smoked. The risk of developing lung cancer is directly related to duration of smoking. This risk for developing lung cancer persists for a long time, even after stopping smoking.
   b. Asbestos exposure increases the risk for the development of lung cancer, particularly in smokers.
   c. **Age.** Both the incidence and the percentage of patients with advanced-stage disease increase with age.
   d. **Genetic factors** (e.g., high metabolizers of debrisoquine, lack of class µ phenotype of glutathione transferase) probably contribute to the development of lung cancer in some patients.
   e. **Exposure** to arsenic, beryllium, chromium, hydrocarbons, mustard gas, and uranium in mining workers and, less clearly, silicosis in smokers.
2. **Screening.** The regular use of the CXR as a method of screening for lung cancer has not been shown to affect long-term survival in three large prospective population studies. Some high-risk patients may benefit from screening (e.g., heavy smokers, patients with head and neck cancer) with the spiral CT technique.

F. **Research initiatives**

We are evaluating the role of PET scan in staging of patients with resectable NSCLC. In addition, the role of reverse transcription–polymerase chain reaction (RT-PCR) to identify micrometastatic disease in the bone marrow of patients with resectable NSCLC is under evaluation. Optimizing radiotherapy administration, the use of three-dimensional treatment planning and of mucosal protectants is being studied to improve the outcome of patients with NSCLC. Specific therapies targeting epidermal growth factor–receptor tyrosine kinases (ZD 1839 or Iressa, OSI 774) are being investigated to improve the outcome of patients with metastatic NSCLC.

1. **Prognostic factors.** The most important prognostic factors are stage, performance status, and significant pretreatment weight loss (more than 5% to 10%). Women tend to do better than men. Age and race have no prognostic significance *per se*. The role of other biologic factors (e.g., p53 mutations, *ras* oncogene activation) is less clear.

II. Small cell lung cancer

A. Presentation

1. **Subjective.** Because of the primarily central endobronchial location of this tumor, presenting symptoms often include shortness of breath, wheezing, cough, hemoptysis, chest pain, and postobstructive phenomena such as pneumonitis. As the mediastinal lymph nodes are involved very commonly, patients can demonstrate SVC syndrome (10% of patients at time of diagnosis), hoarseness from recurrent laryngeal nerve involvement, and dysphagia. Thirty percent of patients at some point in their disease course will have brain metastasis; 90% of such patients will be symptomatic from brain metastases. However, bone metastasis only rarely results in pain or pathologic fractures.
2. **Objective.** The importance of a good physical examination in these patients cannot be emphasized enough, because more than two thirds of patients have obvious distant metastases, some of which can be recognized in the physical examination. This may include hepatomegaly, subcutaneous nodules, focal neurologic signs, palpable adenopathy, and bony tenderness. The most common sites of extrathoracic disease include bone (19% to 38% of all presenting patients), liver (17% to 34%), bone marrow (17% to 23%), and CNS (none to 14%).
3. **Laboratory.** Nearly 50% to 60% of patients with liver metastasis will have mildly abnormal liver function or hepatic enzyme laboratory tests; most of these patients will not have severely compromised liver function, however. When bone marrow is involved, it takes extensive involvement to lead to myelosuppression evident in the complete blood count. Seventy percent of patients will have mediastinal lymph node involvement. Paraneoplastic syndromes also are much more common in small cell than NSCLC, and in one large series, 11% of patients had syndrome of inappropriate secretion of antidiuretic hormone (SIADH; see sec. II.G.5).

   On radiographic examination, these tumors are found to cavitate very infrequently. In comparison to those with non–small cell tumors, CXRs of small cell patients more often demonstrate hilar and mediastinal adenopathy, pneumonitis, and atelectasis and do not as often exhibit pleural effusions or involvement of the chest wall.

B. Workup and staging

1. **Workup.** The physician should aim for a cost-effective workup that adequately stages the tumor for necessary therapeutic decisions. The key question is whether the patient has limited- or extensive-stage disease (defined later), because the therapy for patients with limited-stage disease includes thoracic radiation in addition to chemotherapy, whereas patients with extensive-stage disease would be treated with chemotherapy alone. Thus once metastasis has been documented with extensive-stage disease, there is no need to document any other metastatic locations unless they are symptomatic, requiring palliative therapy.

   Patients who do not have any evidence of overt metastatic disease should undergo CT of the chest and abdomen with contrast, a bone scan, and CT of the head with contrast to establish that disease is confined to one hemithorax (limited-stage disease). The role of a PET scan in staging workup of patients with SCLC remains investigational. Given the low yield associated with bone marrow biopsies, we do not advocate bone marrow biopsy in patients with SCLC for the purpose of staging.

2. **Staging.** The Veterans Administration Lung Group staging system currently in use in North America categorizes patients into limited-stage and extensive-stage disease. Limited stage is defined as tumor confined to one hemithorax and regional lymph nodes and is often subjectively defined by what can fit into one RT portal. Extensive stage is defined as any disease outside limited stage. Generally, 30% to 40% of patients will have limited-stage, and 60% to 70%, extensive-stage disease.

C. Therapy and prognosis

1. **Limited stage**
   a. **Therapy.** The current standard of care is combined-modality therapy with chemotherapy and RT.
      1. **Chemotherapy.** Even though patients with SCLC respond to chemotherapy initially, a vast majority relapse because of the emergence of drug-resistant clones. Combination chemotherapy results in higher response rates and longer survival than does single-agent chemotherapy. The overall response rate for limited stage is estimated to be 80% to 90%. The combination of cisplatin and etoposide (PE) has been repeatedly demonstrated to yield similar or improved results as compared with any other studied combination and is easily one of the most commonly used chemotherapy regimens for patients with SCLC. In addition, this combination is tolerated well when administered in conjunction with thoracic radiation. We typically administer PE for four to six cycles for those patients who have no evidence of progressive disease.
      2. **Radiation therapy.** Administration of thoracic RT in conjunction with systemic chemotherapy has been shown to improve survival. A meta-analysis of 13 trials including 2,140 patients with limited disease demonstrated a higher survival rate for combined-modality approach with the combination of chemotherapy and thoracic RT as compared with combination chemotherapy alone (3-year survival increased from 8.9% to 14.3%; *N Engl J Med* 1992;327:1618–1624). Another meta-analysis of 11 randomized trials confirmed this improvement in survival and demonstrated improved local tumor control with this regimen as well; however, this analysis also demonstrated a mild increase in therapy-related mortality when combined modality was used instead of chemotherapy alone (*J Clin Oncol* 1992;10:890–895). The schedule of RT and temporal coordination with chemotherapy may be of some importance. It is possible but not proven that radiation early in the treatment course may be advantageous because of its ability to eradicate tumor cells before they have a chance of acquiring chemotherapy drug resistance. Additionally, it has been shown that radiation administered twice a day concurrent with chemotherapy results in an increased 5-year survival rate and decreased local failure rate compared with the same chemotherapy regimen administered concurrent with daily radiation (*N Engl J Med* 1999;340:265–271).
      3. **Prophylactic cranial irradiation.** For those limited-stage patients who demonstrate a complete response to induction chemotherapy, prophylactic cranial irradiation (PCI) should be considered to reduce the incidence of brain metastasis and improve survival. The role of PCI in patients with SCLC has been debated for a while, because of initial randomized studies demonstrating no definite improvement in survival and because of concerns about effects on brain function. However, a recent meta-analysis of 987 patients demonstrated a 16% decrease in mortality, 5.4% increase in 3-year survival, decreased incidence of brain metastasis, and prolonged disease-free survival in limited-stage patients who received PCI after complete response to induction chemotherapy (*N Engl J Med* 1999;341:476–484). Recent studies also failed consistently to demonstrate cognitive deterioration after PCI.
      4. **Surgery.** Addition of surgical resection after chemoradiation has not been shown to improve survival in patients with SCLC (*Chest* 1994;106:320S–323S). If patients are found to have SCLC after resection and have no evidence of distant disease, they should be treated with chemotherapy and radiation.
2. **Extensive stage**
   a. **Therapy.** The current standard of care is combination chemotherapy. There is no role for thoracic irradiation in this stage except for palliation of symptoms. Chemotherapy improves survival in patients with extensive-stage disease; the overall response rate is 60% to 80%. Regimens used in this stage are similar to those used for limited-stage therapy. The combination PE is a commonly used regimen in patients with extensive-stage SCLC. It has demonstrated that the combination of carboplatin and etoposide (CE) is as efficacious as PE in offering improved survival in patients with SCLC (*Semin Oncol* 1994;21:23–30). Standard therapy should include four to six cycles of one of a number of different accepted regimens, including cyclophosphamide/doxorubicin/vincristine (CAV), cyclophosphamide/doxorubicin/vincristine /etoposide (CAVE), cyclophosphamide/doxorubicin/etoposide (CAE), or PE. Higher doses of PE, when compared with standard doses of CE, resulted only in increased toxicity without any increase in survival. *In vitro* drug-sensitivity testing on patients' pathologic samples has been evaluated in a prospective trial to determine if patient-specific chemotherapy is a possibility, because this could eliminate the problem of tumor resistance to therapy; however, the results of this trial revealed that this is of limited clinical utility, partly because of the time the testing takes (*J Natl Cancer Inst* 1990;82:117–124). Maintenance chemotherapy has not been shown to improve overall survival (*Proc Am Soc Clin Oncol* 2000;19:482a).

   Addition of paclitaxel to PE has been shown to result in improved response rates. Based on this observation, a large phase III randomized study has recently been completed to evaluate the role of paclitaxel in SCLC. It was recently reported from Japan that the combination of cisplatin and irinotecan is superior to PE in patients with extensive-stage SCLC (*Proc Am Soc Clin Oncol* 2000;19:483a). Two large confirmatory studies are under way in the United States to confirm the results of the Japanese study. Use for extensive-stage patients further supported this combination by demonstrating a very significant improvement in survival as compared with that with PE, with less myelosuppression as well.

1. **Relapsed small cell lung cancer.** In spite of a high response rate, most patients with SCLC eventually have relapse of the disease and die of progressive disease. There are two categories of relapsed SCLC: sensitive relapse, those who relapse 3 months after the completion of therapy, and resistant relapse, those who have progressive disease during initial chemotherapy or those who have relapse within 3 months of completion of therapy. Whereas the response rates for the subgroup of patients with sensitive relapse is approximately 20%, fewer than 5% of patients with resistant relapse respond to salvage therapy. A number of single agents have been shown to have some activity in this setting. They include topotecan, paclitaxel, gemcitabine, and vinorelbine. CALGB is currently evaluating the role of gemcitabine and irinotecan in relapsed SCLC. When

possible, patients with relapsed SCLC should be enrolled in clinical trials.

D. **Prognosis**

Unfavorable prognostic factors include extensive stage, poor performance status, older age, hyponatremia, male gender, and elevated serum lactate dehydrogenase (LDH) and alkaline phosphatase. Of these, stage and performance status are most powerfully associated with prognosis. The most important risk factor for treatment-related mortality, which can approach 5% in aggressive limited-stage therapy, is performance status. Additionally, amplification of the c-*myc* oncogene is linked with shorter survival.

The natural history of the progression of this disease is that of rapid growth and early dissemination. The median survival of patients with limited-stage SCLC is 10 to 16 months. The reported 5-year survival varies from 14% to 28%. One third of limited-stage patients who remain disease free for 2 years will still develop recurrent cancer. Median survival in extensive stage is 7 to 11 months, but only 2 to 4 months if untreated. From 50% to 80% of patients who survive longer than 2 years will have metastases to the brain. Only 10% to 15% of patients with extensive disease will survive to 2 years. An extremely small number of 5-year survivors (fewer than 1%) have been documented.

E. **Complications**

1. **Therapy related.** Therapy-related mortality overall is from none to 8%, greater in extensive-stage patients. The most common therapeutic complication is that of myelosuppression and associated neutropenia and thrombocytopenia.
   a. **Chemotherapy.** The chemotherapeutic regimens used in the treatment of this disease are very toxic. Oral etoposide has been associated with alopecia, nausea, and myelosuppression in a significant number of patients. CE has been demonstrated to produce less nausea, vomiting, neurotoxicity, and nephrotoxicity than PE (i.e., 18% of CE patients experienced neurotoxicity as compared with 53% of PE patients). Most of these side effects in PE therapy are attributed to the cisplatin component, which is well known to cause nephrotoxicity and neurotoxicity. Vincristine can lead to peripheral paresthesias in almost 40% of patients, which can resolve in some patients after discontinuation of chemotherapy. Furthermore, doxorubicin is associated with cardiotoxicity, cyclophosphamide is associated with hemorrhagic cystitis, and rarely patients will experience secondary acute myelocytic leukemia (AML), especially those who received prolonged therapy with nitrosoureas and procarbazine. Although chemotherapy initiation is associated with acute tumor-lysis syndrome for many cancers, SCLC is not often associated with this syndrome, and therefore routine use of allopurinol is not necessary. Finally, patients with ectopic Cushing syndrome are more prone to experience chemotherapeutic complications.
   b. **Radiation therapy.** Twice-daily RT has been associated with more severe esophagitis than once-daily therapy. Esophagitis can lead to dehydration from decreased oral intake, which often requires administration of intravenous fluids. Combined-modality pneumonitis, seen as cough, dyspnea, and/or infiltrates on CXR, can be treated with corticosteroids. Chemotherapy combined with radiation, especially in cases of concurrent administration, leads to significantly greater myelosuppression than does either modality alone. In one trial, 26% of patients required hospitalization for severe pulmonary toxicity related to combined-modality therapy.
   c. **Infection.** While undergoing chemotherapy, one third of patients will have a fever, but infection can be documented in only 5%. Anorectal infections, seen often as only perirectal pain or tenderness, are documented in 6% to 32% of patients; the major risk factor for anorectal infections is chemotherapy-induced neutropenia. Additionally, herpes zoster can be problematic in these patients; one study reported an incidence of 12% in patients undergoing the initial course of chemotherapy, whereas previous studies had reported a much lower incidence. Adrenocorticotropic hormone (ACTH)-producing tumors are associated with higher rates of infection. Granulocyte–colony-stimulating factor (G-CSF) administration during chemotherapy can decrease the incidence of culture-documented infections and neutropenic fever (decreased from 77% to 40% in one prospective trial). In randomized trials, PE therapy has demonstrated significantly less neutropenia and infections than the CAV regimen.
2. **Disease related**
   a. **Superior vena cava syndrome.** This neoplasm is often associated with SVC syndrome. Chemotherapy is adequate treatment for this if patients are not otherwise going to receive thoracic radiation; however, radiation is acceptable therapy for SVC syndrome in patients for whom thoracic radiation is already indicated.
   b. **Brain metastasis.** Of patients with SCLC, 30% will have metastasis to the CNS, and 90% of these patients will be symptomatic from this at some point. Symptoms can often be palliated with radiation therapy (using a higher dose than that used for PCI), but chemotherapy alone has also been shown to induce regression of these metastatic tumors. Some radiation oncologists also use steroids with radiation to help with symptom palliation. Unfortunately, symptom response duration is often short after palliative therapy for CNS metastasis.
   c. **Carcinomatous leptomeningitis.** Some 2.5% of patients at some point in their disease course will have carcinomatous leptomeningitis. Median survival after this diagnosis is made is less than 2 months. Treatment is often intrathecal methotrexate with or without irradiation. This will sterilize the cerebrospinal fluid (CSF) malignant cells in some cases, but such sterilization is not always associated with amelioration of neurologic derangements.

F. **Follow-up**

1. **Secondary malignancies.** These patients are at high risk of developing other malignancies related to smoking. The cumulative risk for a second malignancy 15 years after diagnosis of SCLC is 70%. Overall, in 20% of long-term survivors in one large analysis, secondary malignancies developed. The risk of having a second primary lung cancer increases with time (14.4% after 10 years). If a new lung mass develops in a long-term survivor, the physician must obtain a biopsy to rule out a new primary malignancy that may not be SCLC. Additionally, these patients are at increased risk for other tobacco-related malignancies like cancer of the upper aerodigestive tract (12.6% after 10 years).
2. **Smoking.** These patients should be strongly encouraged to stop smoking. Once a smoker quits, the risk of any type of lung cancer begins to decline, but it takes at least a decade for such patients to approach a risk equivalent to that of a nonsmoker.

G. **Background**

1. **Epidemiology.** SCLC is responsible for 18% of primary lung cancers. It is a disease of the elderly, with age peaks at 70 to 74 years in men and 60 to 69 years in women.
2. **Risk factors.** Almost all patients with this cancer have a history of tobacco abuse: only 2% of 500 patients treated at the National Cancer Institute in one series denied ever smoking. Exposure to radioactive radon in mining also may be a risk factor.
3. **Pathogenesis.** SCLC is thought to arise from peptide hormone–secreting basal neuroendocrine cells, which are much more common in fetal than in adult lung tissue. Often, but not always, these cells will stain positive with silver staining. Electron microscopy can demonstrate neurosecretory granules in these cells. Most small cell lines have upregulated expression of L-Dopa decarboxylase, gastrin-releasing peptide (GRP), and enolase, all of which point to the neuroendocrine origin of the cells. GRP is known to be both a bronchial epithelium and SCC growth factor and is therefore an autocrine growth factor. Antibodies to bombesin, a molecule analogous to GRP, can inhibit small cell line growth *in vitro*; unfortunately, this has not been found to be clinically effective as an antitumor agent.
4. **Pathology.** The classic “oat cell” type of small cell is represented by small round cells characterized by dark-staining nuclei, scant cytoplasm, and few to no nucleoli. Although other pathologic subtypes exist, as outlined by the 1981 World Health Organization (WHO) classification of oat cell, intermediate, and combined cell types, all subtypes demonstrate the classic “salt and pepper” chromatin distribution, cell size of 2 to 3 times that of a mature lymphocyte, nuclear molding, and numerous atypical mitoses. Additionally, these subtypes have not been found to demonstrate any significant difference in disease progression or response to treatment. Histologically, the distinction between SCLC and NSCLC can be difficult, and often a tumor is classified as combined, meaning it contains elements of both SCLC and NSCLC but should be clinically addressed as a small cell tumor.
5. **Paraneoplastic syndromes.** SCLC has a strong association with certain paraneoplastic syndromes that result from peptide hormone secretion from tumor cells. Syndromes that are fairly specifically associated with SCLC include ectopic ACTH secretion (leading to Cushing syndrome), SIADH, and Lambert–Eaton syndrome. The endocrinologic paraneoplastic syndromes can be relieved by chemotherapy; however, often the neurologic syndromes are not affected by antitumor therapy.

H. **Current focus**

1. **New chemotherapeutic regimens.** New chemotherapy drugs are currently being investigated including the taxanes (paclitaxel and docetaxel), which act to prevent intracellular microtubule depolymerization, thus impairing cellular mitotic function. Irinotecan is being evaluated in two large phase III studies. In addition the use of Gleevec (Imatinib STI 571) is being studied in SCLC.

SUGGESTED READINGS

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CHAPTER 14. LEUKEMIA

Randy Brown and Hanna Khoury

The acute leukemias
Epidemiology and etiology
Clinical presentation
Laboratory and radiographic features
Diagnosis and classification
Supportive care
Treatment and prognostic factors
New approaches to the treatment of acute leukemia
Acute promyelocytic leukemia
The chronic leukemias
Chronic myeloid leukemia
Chronic lymphocytic leukemia
Suggested Readings

I. The acute leukemias

A. Epidemiology and etiology

Acute leukemias are clonal malignant disorders characterized by the proliferation of abnormal (leukemic) blast cells and impaired production of normal blood cells. Approximately 10,000 new cases of acute leukemia are diagnosed annually in the United States, with the incidence of acute myelocytic leukemia (AML) being approximately 3.0/100,000 and of acute lymphoblastic leukemia (ALL), about 1.5/100,000 persons. Acute leukemia represents about 5% of all new cancer cases, but among persons younger than 35 years, acute leukemia is the most common cause of cancer death. The incidence of ALL peaks at around age 5 years, decreases to relatively low levels and then steadily increases at older than 50 years. About 75% of all cases of ALL occur in patients younger than 15 years. For AML, incidence increases steeply beyond 50 years, with the median age being approximately 60 years. AML represents about 80% of all new adult cases of acute leukemia.

Ionizing radiation and benzene are clearly associated with an increased risk of acute leukemia. The large majority of cases are AML, with an average latency of about 5 years and with most cases preceded by a myelodysplastic syndrome. AML that is secondary to radiation or benzene is associated with adverse cytogenetics and a very poor prognosis. With the exception of benzene, no nonmedicinal chemicals are clearly associated with an increased risk of acute leukemia. Two classes of chemotherapeutic agents are associated with an increased risk of acute leukemia (secondary leukemia). Alkylating agents are associated with AML similar to that described earlier for leukemia secondary to benzene or radiation. Topoisomerase II inhibitors such as etoposide or anthracyclines are associated with AML or mixed-lineage leukemia with a short (1- to 2-year) latency without a preceding hematologic disorder. The most common cytogenetic abnormalities involve the mixed-lineage leukemia (MLL) gene at 11q23 with a number of partner chromosomes. Treatment-related leukemia is associated with a very poor prognosis so that allogeneic transplantation in first complete response (CR) should be considered if a donor is available.

Acute leukemia occurs more frequently in family members than would be expected by chance. Full siblings have an approximately twofold increase in risk, whereas the concordance rate in identical twins may be as high as 25%, largely as a result of infantile leukemias. A number of families have been described in which multiple family members have had acute leukemia. In most of these cases, the molecular basis is unclear. However, a case in two kindreds in which thrombocytopenia developed around the time of birth, with affected individuals often progressing to AML, was recently described. Affected individuals demonstrated haploinsufficiency for the a subunit of the transcription factor, core-binding factor (see sec. I.G., New approaches to the treatment of acute leukemia).

With the exception of human T-lymphocyte leukemia virus (HTLV)-1 related leukemia, there is little evidence that known infectious agents are responsible for the development of acute leukemia. Congenital disorders that are associated with an increased risk of acute leukemia include Down syndrome, disorders associated with increased chromosomal fragility (Bloom syndrome and Fanconi anemia) and those associated with immunodeficiency (X-linked agammaglobulinemia and ataxia telangiectasia).

B. Clinical presentation

Acute leukemia is first seen with the recent onset of symptoms or signs related to pancytopenia or organ infiltration. The risk of infection is particularly high among patients whose absolute neutrophil count (ANC) is less than 100/µL. Common sites of infection include sinuses, perirectal area, skin, lungs, and oropharynx. Profound thrombocytopenia (platelets fewer than 10,000/µL) is associated with purpura, gingival bleeding, epistaxis, and retinal hemorrhage. Diffuse hemorrhage that does not respond to platelet transfusions suggests disseminated intravascular coagulation (DIC).

Lymphadenopathy, splenomegaly, and hepatomegaly each occurs in about half of all patients with ALL but are less common in AML. Similarly, although it is uncommon in AML, 5% to 10% of patients with ALL have symptomatic involvement of the central nervous system (CNS). Leukemic involvement of the skin (leukemia cutis) is most common in monocytic subtypes of AML and appears with multiple rose-colored or purple, nontender papules. Gingival hyperplasia due to infiltration by blasts occurs in up to 50% of patients with monocytic variants of AML and is not seen in ALL. Granulocytic sarcomas, also known as chloromas, are tumors composed of myeloid blasts that often involve the orbit, paranasal sinuses, or subcutaneous tissues, but can involve almost any organ. Granulocytic sarcomas may precede bone marrow involvement by AML.

In up to 50% of patients with AML and an absolute blast count [white blood cell count (WBC) × percent circulating blasts] exceeding 100,000/µL, respiratory compromise and/or CNS manifestations such as headache or confusion develop. This syndrome has been called “leukostasis” because it may result from vascular occlusion by blasts. Leukostasis can occur in AML with a blast count less than 100,000/µL but is rare in ALL. Emergency leukapheresis can be lifesaving. Transfusion of packed red cells may increase blood viscosity and should be minimized until leukapheresis can be performed.

C. Laboratory and radiographic features

Recommended testing for newly diagnosed patients is shown in Table 14.1. Approximately 60% of patients have an elevated white count, with blasts present in the peripheral blood in 90%. Most patients are thrombocytopenic and anemic, but only one third are first seen with a platelet count less than 25,000/µL. About one fourth of patients with monocytic leukemia have hypokalemia resulting from injury to the proximal tubule by lysozyme produced by blasts. Elevation of uric acid and phosphorus are common and indicate an increased risk of tumor lysis syndrome (see sec. I.E.). Hypocalcemia can accompany hyperphosphatemia related to tumor lysis syndrome. The large majority of patients with ALL and many with monocytic variants of AML have elevation of the lactate dehydrogenase (LDH). For these patients, the first evidence of relapse may be an increasing LDH level. Elevation of the LDH also can occur as a result of microangiopathic hemolytic anemia associated with DIC. Refractory lactic acidosis is an uncommon manifestation of AML, seen primarily among patients with advanced disease. Spurious laboratory values are associated with hyperleukocytosis (WBC greater than 100,000/µL) and can include falsely prolonged coagulation tests, hypoxemia, and hypoglycemia due to blast cell metabolism *in vitro* and pseudohyperkalemia. Spurious hypoxemia and hypoglycemia can be minimized by keeping samples on ice and processing them rapidly.

TABLE 14.1. APPROACH TO THE NEWLY DIAGNOSED PATIENT WITH ACUTE LEUKEMIA

Although it is most common in acute promyelocytic leukemia (APL), a small percentage of patients with monocytic leukemia or ALL have DIC. DIC is associated with microangiopathic hemolytic anemia, thrombocytopenia, hypofibrinogenemia, elevated fibrin split products, and prolongation of the prothrombin time. Patients with DIC should receive cryoprecipitate and fresh frozen plasma to manage the coagulopathy and platelets to maintain a count greater than 50,000/µL if bleeding is present. Treatment with heparin and antifibrinolytics remains controversial.

The presence of a mediastinal mass on chest radiograph is suggestive of T-cell ALL. Osteopenia or lytic lesions may be seen in up to 50% of patients with ALL, and these patients may have intractable bone pain.

D. Diagnosis and classification

The classification of acute leukemia is based on morphology, cytochemistry, flow cytometry, cytogenetics, and molecular markers. The French–American–British (FAB) classification relies on morphology and cytochemistry to provide diagnostic criteria for acute leukemia, to distinguish AML from ALL, and to define subtypes of AML (M1 through M6) and ALL (L1 through L3). Application of these criteria requires a thorough examination of the peripheral blood and bone marrow aspirate with enumeration of blasts. In normal bone marrow, blasts are undifferentiated hematopoietic progenitors and represent 5% or less of all nucleated cells. Blasts have a high nucleus/cytoplasm ratio with fine nuclear chromatin and one or more nucleoli. Leukemic blasts represent transformed hematopoietic progenitors and have a similar appearance. By FAB criteria, acute leukemia is diagnosed when a 200-cell differential reveals that 30% or more of all nucleated cells in the blood or bone marrow are blasts.

By the FAB criteria, the diagnosis of AML is made when 3% or more of blasts are positive by cytochemistry for myeloperoxidase (MPO) or Sudan Black B (SBB). Originally other cases were considered to represent ALL, although it is now known that a minority of MPO- or SBB-negative cases are myeloid. These include minimally differentiated (M0) and megakaryocytic (M7) leukemias that require flow cytometry for diagnosis. In addition, some minimally differentiated acute monocytic or erythroid leukemias are MPO and SBB negative.

Subtypes of AML and ALL as defined by the FAB are of limited prognostic or therapeutic importance. For ALL, clinically meaningful subtypes are defined by immunophenotype (B-progenitor, B cell, and T cell; see section I.F.2) as determined by flow cytometry. Early recognition of APL (FAB-M3) is important because optimal treatment includes all-*trans*-retinoic acid (ATRA; see section I.H). FAB-M2 AML (myeloid with maturation) represents about one third of all cases of AML, with the a translocation between chromosomes 8 and 21 [AML-ETO, t(8;21)] being present in about 30% to 40% of patients with abnormal cytogenetics. FAB-M4Eo is characterized by monocytosis, a myeloblastic/monocytic infiltration of the marrow, and abnormal eosinophils that have a monocytoid nucleus and a mixture of eosinophilic and large, atypical basophilic granules. Nearly all patients with FAB-M4Eo have either inversion 16 or a balanced translocation between the arms of both chromosomes 16. Because patients with t(8;21) or inv16 have a particularly favorable prognosis with chemotherapy alone (see later), recognition of these subtypes has prognostic and therapeutic importance. For the remaining patients with AML, the FAB subtype is of much less importance than cytogenetics. It must be emphasized that for both ALL and AML, cytogenetics provides the most important information regarding prognosis and optimal treatment. **Therefore obtaining cytogenetics on initial bone marrow and/or peripheral blood is absolutely critical.**

Molecular techniques [Southern blot, polymerase chain reaction (PCR)] can detect important chromosomal rearrangements that are not apparent by routine cytogenetics. Examples include Ph chromosome negative, Bcr-Abl positive ALL, and ALL with the TEL-AML1 rearrangement. These techniques will assume greater importance as additional molecular abnormalities are described that are not accompanied by abnormal cytogenetics. The application of molecular techniques to the detection of minimal residual leukemia is discussed later (see section I.B, New approaches to the treatment of acute leukemia).

E. Supportive care

Nearly all adults with acute leukemia require multiple platelet and red cell transfusions. In the absence of bleeding, transfusions can safely be withheld until the platelet count is 10,000/µL or lower. For patients with active bleeding and for those who are to undergo surgical intervention, the platelet count should be maintained at greater than 50,000/µL (more than 100,000/µL for CNS bleeding). This usually requires more than one transfusion daily. Our institutional policy at Washington University is to transfuse blood to maintain hemoglobin at greater than 8.0 g/dL. However, younger patients may tolerate lower levels, whereas older patients and those who are critically ill may require a higher threshold value for red cell transfusion. Hypofibrinogenemia, usually the result of DIC or treatment with L-asparaginase, should be treated with cryoprecipitate when the fibrinogen decreases to less than 100 mg/dL. To prevent transfusion-related graft-versus-host disease (GVHD), all blood products must be irradiated (2,850 cGy).

Poor responses to platelet transfusions are in part due to alloimmunization by leukocytes that contaminate blood products. Red cells are rendered “leukopoor” by filtration. Leukoreduction of platelets can be achieved by bedside filtration of concentrates (random donor) or by apheresis collection. Although the risk of platelet refractoriness may be reduced, the use of leukoreduced blood products has not been shown to reduce the risk of hemorrhage or to improve survival. Our current policy is to filter red cells before storage and to transfuse platelets that have been collected by apheresis.

Reactivation of cytomegalovirus (CMV) after allogeneic transplant can result in life-threatening or fatal disease. Because all but the oldest or most infirm patients with acute leukemia are potential candidates for allogeneic transplant, steps should be taken to prevent transfusion-related infection with CMV. For CMV-seronegative patients, an attempt should be made to transfuse only products that have been collected from seronegative donors. If this is not possible, then the risk of CMV transmission may be reduced by leukoreduction of platelet products. Patients who are CMV seropositive may receive blood products from seropositive or seronegative donors.

Patients with poor increments to platelet transfusions may benefit from human leukocyte antigen (HLA)-matched products, although fully matched platelets are rarely available. Family members, particularly siblings, are a potential source of HLA-matched products, but the use of products collected from related donors may increase the risk of rejecting a later sibling-donor allogeneic stem cell transplant. However, in the event of life-threatening hemorrhage in a patient with resistance to platelet transfusion, administration of platelets collected from siblings may be lifesaving.

Infection is the most common cause of death among patients with acute leukemia. The single most important risk factor is prolonged neutropenia, although others include indwelling catheters and compromised mucosal barriers (mucositis or enteritis from chemotherapy). The large majority of infections are the result of colonizing microbial flora rather than exogenous sources. Therefore, with the exception of good hand washing, rigorous isolation procedures are not necessary. Food-borne infection is very uncommon, so that we now prohibit only consumption of uncooked meat (steak tartare). Neutropenic patients with a history of cold sores or with herpes simplex seropositivity should receive prophylaxis with acyclovir (400 p.o. t.i.d. or 125 mg/m ^{2} i.v. b.i.d.). Patients with ALL should receive *Pneumocystis* prophylaxis with trimethoprim/sulfamethoxazole, 1 double strength (DS) b.i.d. on Monday and Thursday, commencing when complete remission is achieved. An alternative for sulfa-allergic patients is aerosolized pentamidine, 300 mg monthly. During periods of neutropenia, prophylaxis with nystatin (15 mL, swish and swallow 5 times a day) or clotrimazole troche (5 times daily) is recommended. The use of other antibiotics for infection prophylaxis is controversial. Oral fluoroquinolones reduce the risk of infection with gram-negative organisms, but are associated with an increased

risk of gram-positive bacteremia and fluoroquinolone-resistant *Pseudomonas aeruginosa*. Clinical trials have not demonstrated improved survival, so that routine prophylaxis with these agents is not recommended. Prophylaxis with fluconazole reduces the risk of thrush and invasive candidal infections, but may select for resistant fungi. Prophylaxis has not been shown to reduce the risk of treatment-related mortality, so that routine use of this agent during induction chemotherapy cannot be recommended.

We recommend that newly diagnosed patients with acute leukemia be managed in the inpatient setting until complete remission is achieved. However, patients in whom neutropenia develops as a consequence of postremission chemotherapy can probably be managed in the outpatient setting if they are able to return rapidly to the hospital in the event of fever. Such patients should be evaluated by their physician frequently, avoid crowds, wear a mask to the physician's office or when crowds are unavoidable, monitor temperature every 6 hours, and report immediately to the hospital for temperature greater than 38.3°C or for rigors.

Febrile (greater than 38.3°C), neutropenic patients (ANC, less than 500/μL) should be cultured (blood and urine) and promptly receive empiric broad-spectrum antibiotics (cefepime or ceftazidime, 1 g i.v.). Vancomycin should be added if an indwelling catheter is a suspected source. Patients with allergy to b-lactams may be desensitized or receive a fluoroquinolone with vancomycin. Febrile patients with hypotension or respiratory distress should receive at least one dose of an aminoglycoside antibiotic. When fevers persist for 3 to 5 days despite broad-spectrum antibiotics and with no apparent source, empiric amphotericin B (0.5 mg/kg/day) should be initiated. Patients with renal insufficiency should receive liposomal amphotericin B (5 mg/kg/day). Fluconazole can be substituted if cultures reveal a sensitive organism, such as *Candida albicans*. In cases of fungal sepsis, we have generally removed all indwelling catheters. Febrile patients with newly diagnosed or relapsed acute leukemia should receive empiric broad-spectrum antibiotics whether or not they are neutropenic.

Once antibiotics are begun, they are continued until neutrophil recovery (ANC greater than 500/μL), even if fever resolves. Patients with bacteremia should receive a 10- to 14-day course of antibiotics. Patients with a history of *Aspergillus* or *Mucor* sp. infection should receive prophylactic antifungal therapy during subsequent courses of chemotherapy if profound neutropenia is likely. This may consist of amphotericin B or itraconazole. Resection of isolated pulmonary aspergillomas should be considered before patients receive additional intensive chemotherapy or bone marrow transplantation (BMT).

Typhlitis (neutropenic enterocolitis) occurs in neutropenic patients with fever, abdominal pain, and tenderness that can mimic appendicitis. Bloody diarrhea may be present. Computed tomography (CT) scan reveals evidence of right-sided colonic inflammation. The etiology is unclear. Treatment is with broad-spectrum antibiotics, including anaerobic coverage and nasogastric suction. Surgical intervention is reserved for patients with bowel perforation or if bowel necrosis is suspected.

The use of myeloid growth factors in acute leukemia remains controversial despite multiple randomized trials. Treatment with granulocyte (G) or granulocyte–macrophage colony-stimulating factor (GM-CSF) after induction chemotherapy shortens the duration of ANC less than 500/μL by 3 to 6 days with a smaller effect on the duration of ANC less than 100/μL. Because the duration of hospital stay and antibiotic use is often determined by the duration of ANC at less than 500/μL, it is not surprising that these parameters also are shortened by treatment with growth factors. However, most evidence indicates that growth factors do not improve the likelihood of CR or long-term survival, although there is no evidence that these agents increase the risk of resistant disease. One approach is to reserve growth factors for older patients (older than 60 years) or for those with life-threatening infection. Relatively few studies have addressed the role of myeloid growth factors after intensive consolidation chemotherapy. Although the duration of antibiotic use was shortened in one recent study, this did not translate into a difference in risk of infection or treatment-related death.

All patients with acute leukemia should undergo placement of a central venous catheter. Although tunneled catheters are preferred because of a lower risk of infection, the presence of fever, coagulopathy, or poor increments with platelet transfusion represent relative contraindications to placement of this type of access. Temporary catheters, such as the Hohn catheter, generally allow access throughout induction chemotherapy and are associated with a lower risk of hemorrhage.

Tumor lysis syndrome is a complication of rapid tumor breakdown after chemotherapy. Clinically it is marked by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute, often oliguric renal failure. Patients with B-cell ALL are at greatest risk, with other risk factors including a WBC greater than 50,000/μL, LDH greater than 1,000 IU/L, renal dysfunction, or elevation of the uric acid or phosphorus before treatment. All patients with newly diagnosed acute leukemia should be adequately hydrated before chemotherapy, and volume status should be closely monitored. If the patient's renal function is normal, allopurinol, 600 mg, is given the day before chemotherapy, followed by 300 mg daily until the WBC is less than 1,000/μL. Patients at high risk for tumor lysis syndrome should receive half-normal saline with 2 ampoules of $NaHCO_3$/L at 200 to 250 mL/hour with concurrent diuresis to maintain euvolemia. For these patients, electrolytes, calcium, magnesium, and phosphorus should be monitored 2 to 3 times daily for the first 2 to 3 days.

F. Treatment and prognostic factors

Until 1947 there was no specific treatment for acute leukemia, and the median survival of newly diagnosed patients was 2 to 4 months. Acute leukemia was one of the first neoplasms to be cured by chemotherapy, and many basic therapeutic principles have been developed through clinical trials in this disease. All newly diagnosed patients receive induction chemotherapy, with the goal being CR, which is a prerequisite for cure. CR is defined as normalization of blood counts (ANC more than 1,500/μL, platelet more than 100,000/μL) for at least 4 weeks, with bone marrow aspirate/biopsy demonstrating more than 20% cellularity with fewer than 5% blasts and with no evidence of leukemia outside the marrow. Once CR is achieved, therapeutic options include additional chemotherapy or stem cell transplantation. Chemotherapy given during CR can include consolidation (intensity similar to that for induction) and maintenance (reduced intensity administered for 18 to 36 months)

1. **Acute myeloid leukemia.** For more than 20 years, standard remission induction chemotherapy for AML has included treatment with cytosine arabinoside and an anthracycline. The most common regimen combines 7 days of cytosine arabinoside with 3 days of daunorubicin (“7 and 3”). A bone marrow examination is repeated 14 days after starting treatment, and patients with bone marrow cellularity 20% or greater and more than 5% blasts are considered to have residual disease and generally receive an abbreviated course of cytosine arabinoside and daunorubicin (“5 and 2”). Of patients who achieve CR, about 75% do so after the first cycle of 7 and 3 with neutrophil (ANC greater than 500/μL) and platelet recovery (more than 20,000/μL) occurring an average of 21 to 25 days from the start of chemotherapy. Substituting idarubicin, 12 mg/m^2/day × 3 for daunorubicin may improve the likelihood of CR, although higher doses of daunorubicin are probably equally effective.

   Failure to achieve CR with induction chemotherapy can result from resistant leukemia or from death during posttreatment neutropenia. CR is achieved in 65% to 75% of patients with AML younger than 60 years and approximately 50% of those older than 60 years. The reduced likelihood of CR among older patients is the result of an increased risk of resistant disease as well as an increased risk of death from complications of pancytopenia. Other factors associated with a lower rate of CR after induction chemotherapy include the presence of a preceding hematologic disorder of at least 2- to 3-months' duration, adverse cytogenetics (see later), and poor performance status at diagnosis.

   Patients who receive no additional therapy after achieving CR invariably relapse, usually within 1 year. When patients in CR receive one to two cycles of consolidation with regimens similar to 7 and 3, approximately 25% remain in CR 3 to 5 years after diagnosis. Early phase I trials indicated that the cytosine arabinoside dose could be escalated 30-fold above the usual induction dose, with cerebellar toxicity being dose limiting. Treatment with high-dose cytosine arabinoside (HDAC; Table 14.2) produces CR in about 40% of patients with resistant leukemia, indicating the ability of this regimen to kill leukemic cells that are resistant to conventional doses of cytosine arabinoside. On this basis, trials of HDAC consolidation for AML in first CR (CR1) were carried out and demonstrated 5-year leukemia-free survival approaching 50% among patients younger than 45 years. The value of HDAC consolidation in AML was subsequently demonstrated in a randomized trial carried out by Cancer and Leukemia Group B. In that trial, 596 patients in CR1 were randomized to consolidation with four cycles of conventional dose (100 mg/m^2/day × 5 days), intermediate dose (400 mg/m^2/day × 5 days), or high dose (3.0 g/m^2, total of six doses over 5 days) cytosine arabinoside. Among patients 60 years and younger, 4-year progression-free survival among those consolidated with HDAC was 44% versus 24% among those who received conventional-dose cytosine arabinoside. However, patients older than 60 years did poorly regardless of the type of consolidation they received, with fewer than 20% achieving durable remission, although only about one third of patients in this age group received all four courses of HDAC, primarily as a result of CNS toxicity.

7 and 3 chemotherapy regimen for newly diagnosed AML[a]
Ara-C, 100 mg/m^2/day, as a continuous infusion for 7 days
Daunorubicin, 45 mg/m^2/day × 3 on days 1, 2, 3 of ara-C
Administration of additional chemotherapy. Perform bone marrow on day 14 of chemotherapy. If cellularity is >20% and blasts are >5%, administer second cycle of chemotherapy (5 and 2): same doses as above with 5 days of ara-C and 2 days of daunorubicin.
High-dose ara-C consolidation regimen[b]
Cytosine arabinoside: 3.0 g/m^2 in 500-mL D5W infused i.v. over 3-h period every 12 h twice daily, days 1, 3, 5 (total, six doses)
Before each dose, patients must be evaluated for cerebellar dysfunction. If present, stop drug and do not resume. One way to monitor cerebellar function is to have patients sign name on sheet of paper before each dose. For significant change in signature, physician should evaluate patient before any further therapy is given.
To avoid chemical keratitis, administer dexamethasone eye drops, 0.1% 2 drops OU q6 h starting 1 h before first dose and continued until 48 h after last dose
Use of gemtuzumab (Mylotarg)
Dose is 9 mg/m^2. A second dose is usually given ~14 days later. Each dose is given as a 2-h i.v. infusion. Fever, which may be delayed, is the most common immediate reaction.
Premedication: acetaminophen (Tylenol) grains X and diphenhydramine (Benadryl), 50 mg, are given p.o. 1 h before. Repeat Tylenol 4 and 8 h later. Observe for a minimum of 4 h after dose

AML, acute myelogenous leukemia; ara-C, cytosine arabinoside.
[a]From *Blood* 1981;58:1203–1212, with permission.
[b]From *N Engl J Med* 1994;331:896, with permission.

TABLE 14.2. CHEMOTHERAPY REGIMENS

The critical role of cytogenetics in predicting the outcome of consolidation therapy for AML is indicated by subgroup analysis of this trial. The estimated likelihood of cure among patients with favorable cytogenetics [t(8;21) and inv16] who received HDAC was 84% versus less than 25% for patients with unfavorable cytogenetics [all except normal and t(15;17)].

As discussed earlier, HDAC can produce cerebellar toxicity and less commonly somnolence or confusion. Cerebellar function should be assessed before each dose so that the drug can be stopped immediately if this occurs. This can be done by asking the patient to sign his or her name on a signature record before each dose. HDAC also can cause keratitis, which can be prevented by administration of dexamethasone eyedrops, 0.1%, two drops OU every 6 hours around the clock, from the time treatment is started until 48 hours after HDAC ends. Other toxicities of HDAC may include an erythematous rash, often worse on the palms and soles, and hepatic dysfunction.

Several randomized trials examined the role of allogeneic or autologous transplantation versus conventional chemotherapy for patients with AML in first CR. These have been restricted to patients younger than 55 to 60 years with allogeneic transplant being assigned to patients with matched sibling donors and others randomized to chemotherapy versus autologous transplant. In these studies, transplantation was associated with improved leukemia-free survival compared with chemotherapy, but overall survival was not significantly improved, probably because transplantation salvaged some patients who relapsed after consolidation chemotherapy. These trials also showed that cytogenetic risk group was the major determinant of survival, regardless of whether consolidation was with chemotherapy or transplantation. Other factors independently associated with improved survival in some, but not all studies, included achieving CR by day 14 to 21 of induction chemotherapy, younger age, lower WBC, and the absence of a preceding myelodysplastic syndrome.

Data from these large randomized trials of transplant versus conventional chemotherapy also allowed further definition of cytogenetic risk groups. Patients with high-risk cytogenetics included those with a complex karyotype (three or more clonal abnormalities), monosomy 7 or 5, deletion of 5q, and abnormalities of 3q. The intermediate-risk group included patients with normal cytogenetics and all other changes not associated with the favorable or high-risk groups. The favorable group included translocation (8;21) and inversion 16 [or t(16;16), del(16q)], regardless of whether these abnormalities occurred alone or with other cytogenetic changes. The prognostic impact of 7q- and 11q23 differed somewhat between reports with the Medical Research Council (MRC) trial classifying both in the intermediate-risk group, whereas the South Western Oncology Group (SWOG) trial classified both in the adverse-risk group. The frequency of these cytogenetic subgroups depended on the age of the population, with unfavorable changes being more common in older patients. Among patients 55 years or younger, about 50% are in the intermediate-risk category, 20% in the favorable, and 30% in the unfavorable risk group.

By examining survival stratified by treatment and cytogenetics, therapeutic recommendations are possible for some groups. Approximately 60% to 70% of patients with AML and favorable cytogenetics achieve 3-year survival with intensive consolidation that includes HDAC. Therefore chemotherapy is the treatment of choice for this group. However, patients with adverse cytogenetics have a very poor outcome with conventional chemotherapy, so that allogeneic transplant is the treatment of choice if a matched sibling or matched unrelated donor can be identified. For patients with adverse cytogenetics who do not have a histocompatible donor and for those whose health problems represent a contraindication to unrelated donor transplant, autologous transplant is an option. Optimal treatment for patients with intermediate-risk cytogenetics is not clear.

When patients with AML relapse after conventional chemotherapy, they generally do so within 3 years, with the risk of relapse more than 5 years after diagnosis being 5% or less. For patients with relapsed AML and for those who do not achieve CR despite optimal induction chemotherapy, the only treatment option with curative potential is stem cell transplantation. For patients with an HLA-identical sibling, allogeneic transplant is the treatment of choice among those younger than 60 years. Recent results with reduced intensity (“minitransplant”) regimens suggest that, in the absence of major medical problems, older patients can safely undergo allogeneic transplant. However, relapse is common, with only 20% to 30% of those transplanted in second CR (CR2) being cured. Disease status at transplant (CR2 vs. relapse) and the presence or absence of GVHD are the most important prognostic factors. For relapsed patients (younger than 50 years) who lack an HLA-identical sibling, matched unrelated donor (MUD) transplant is the treatment of choice. However, durable remission occurs in fewer than 10% of patients who undergo MUD transplant in overt relapse with circulating blasts.

In patients with resistant AML, we have generally attempted to achieve CR before transplant. Commonly used regimens for treatment of resistant disease include HDAC with or without an anthracycline, etoposide with mitoxantrone, or etoposide with cyclophosphamide.

Gemtuzumab ozogamicin (Mylotarg) is a recombinant, humanized anti-CD33 antibody conjugated to the cytotoxic agent calicheamycin. CD33 is present on leukemic blasts in more than 80% of patients with AML and also is expressed by committed hematopoietic progenitors but not stem cells. Binding of the antibody leads to internalization of calicheamycin and cell death. Mylotarg has been approved for the treatment of resistant AML in patients 60 years or older, based on data from three single-arm, multicenter trials that included 142 patients with AML in first relapse. Mylotarg was given as a 2-hour infusion at a dose of 9 mg/m^2, with most patients receiving at least two doses given 14 to 28 days apart. The overall response rate was 30%, with 16% of patients achieving CR and 14% achieving CR with platelet transfusion independence, but with a platelet count less than 100,000/µL. Most patients went on to receive additional chemotherapy or stem cell transplant. Median relapse-free survival was 7 months. In about 90% of patients, an infusion-related symptom complex developed that included chills, fever, nausea, and vomiting. Anaphylaxis rarely occurred. Because of these side effects, patients should routinely be premedicated with acetaminophen and diphenhydramine (Benadryl) with careful observation and frequent vital signs taken for at least 4 hours after the infusion begins. In more than 95% of patients treated with Mylotarg, grade 3 or 4 neutropenia or thrombocytopenia developed, with the median time to ANC greater than 500/µL and platelet greater than 25,000/µL being approximately 40 days from the first dose.

Although Mylotarg lacks chemotherapy-related side effects such as stomatitis and enteritis, this agent produces severe pancytopenia, which is similar to that produced by intensive chemotherapy. Patients must be followed carefully for infectious complications. The role of Mylotarg in remission consolidation and in front-line therapy is being explored in a number of ongoing trials.

2. **Acute lymphoblastic leukemia.** Accurate subtyping of ALL is essential for appropriate treatment. Approximately 70% to 75% of patients have B-precursor, 20% to 25% have T-cell, and about 5% have mature B-cell ALL. Mature B-cell ALL expresses surface-membrane immunoglobulin and is characterized by the t(8;14), which results in fusion of the *myc* oncogene with part of the immunoglobulin heavy-chain gene. Variant translocations involve *myc* and light-chain genes [t(2;8), t(8;22)]. B-cell ALL is the leukemic equivalent of Burkitt lymphoma and is arbitrarily defined by the presence of more than 25% blasts in the bone marrow. B-cell ALL/Burkitt is the most rapidly proliferating neoplasm, and treatment is often complicated by tumor lysis syndrome. Treatment for B-cell ALL differs from that for other types of ALL in that intensive chemotherapy is given over a relatively short period (2 to 8 months) without maintenance chemotherapy. Important parts of this therapy include high total doses of cyclophosphamide and/or ifosfamide given in fractions over several days along with HDAC and high-dose methotrexate. Without adequate prophylaxis, CNS relapse is common, so that treatment programs for B-cell ALL usually include intrathecal therapy. With this aggressive combination of chemotherapy and intrathecal therapy, approximately 50% of patients appear to be cured.

Treatment of B-progenitor and T-cell ALL in adults was adapted from regimens developed for high-risk childhood ALL. Combinations of vincristine, prednisone, L-asparaginase and an anthracycline result in CR rates of approximately 75%. Inclusion of cyclophosphamide and cytosine arabinoside appears to increase CR rate and remission duration, particularly among patients with T-cell ALL. Standard consolidation therapy includes treatment with several cycles of chemotherapy that include agents used during remission induction along with antimetabolites such as 6-mercaptopurine and methotrexate. Recent trials have examined the role of intensive consolidation including HDAC and high-dose methotrexate, but the benefit of this approach is unclear.

Whereas CNS relapse is very uncommon in AML, in the absence of CNS prophylaxis, the risk of CNS relapse in ALL exceeds 10%; therefore consolidation therapy has usually included intrathecal chemotherapy and cranial radiation. However, cranial radiation may be associated with long-term neurologic sequelae including impaired cognition. Recent studies in children indicate that the combination of intrathecal prophylaxis and CNS-penetrating chemotherapy is associated with a risk of CNS relapse similar to that achieved with intrathecal prophylaxis and cranial radiotherapy. This approach is now being evaluated in adults and may eliminate the need for cranial radiotherapy.

For patients with B-progenitor and T-cell ALL, induction and consolidation usually occupy the first 6 months after diagnosis. Patients then go on to receive maintenance chemotherapy. The most commonly used regimen includes daily oral 6-mercaptopurine, weekly oral methotrexate, a single intravenous dose of vincristine monthly, and 5 days of prednisone per month. This is continued until 24 to 36 months after diagnosis. With this approach, the likelihood of 5-year disease-free survival is about 25% to 50%.

As in AML, cytogenetics is the most important prognostic factor in ALL. Traditional adverse prognostic factors such as advancing age and higher presenting white count can now, at least in part, be understood on the basis of their association with cytogenetic abnormalities. For example, Ph chromosome–positive ALL is associated with a very poor prognosis. Whereas approximately 25% of adults with ALL are Ph chromosome positive, fewer than 5% of children have this cytogenetic abnormality. Similarly, the t(12;21) has recently been described in nearly 25% of cases of childhood ALL and is associated with a particularly good prognosis. However, the t(12;21) is found in less than 5% of adult ALL.

Despite the importance of cytogenetics in determining the outcome of ALL, presenting white count and age retain independent prognostic significance in multivariate models. Another important factor is the rate of clearance of blast cells, so that patients who achieve CR more rapidly are more likely to achieve durable remission. Based on data from Cancer and Leukemia Group B, adult B-progenitor and T-cell ALL can be divided into three prognostic groups. Good-risk patients are characterized by all of the following: absence of adverse cytogenetics; age younger than 30 years; presenting WBC less than 30,000/μL; and remission achieved within 6 weeks of diagnosis. These patients have a 50% to 75% likelihood of 3-year disease-free survival with chemotherapy, so that transplant is reserved for relapse. Poor-risk patients are characterized by any of the following: adverse cytogenetics; for B-progenitor, presenting WBC greater than 100,000/μL; more than 6 weeks to achieve CR; age older than 60 years. For these patients, 3-year disease-free survival is 0 to 20% with conventional chemotherapy, so that allogeneic transplant is the treatment of choice for patients younger than 60 years with histocompatible donors. Older patients may be candidates if they are in good health. The remaining intermediate-risk patients represent about one third of all cases of ALL and primarily include patients younger than 60 years with B-progenitor ALL. For these patients, chemotherapy appears to be the treatment of choice, because transplantation has not been proven to improve survival. The intermediate-risk group is clearly heterogeneous, and advances in molecular genetics will allow a more precise assignment of risk.

Patients with acute leukemia in whom CNS symptoms or signs develop should undergo CT or magnetic resonance imaging (MRI) of the head and, in the absence of a mass lesion, proceed to lumbar puncture with glucose, protein, routine cultures, Gram stain, cryptococcal antigen, and cell count with cytocentrifuge differential. In the absence of contamination with peripheral blood, patients with blasts in the cerebrospinal fluid (CSF) should receive cranial radiotherapy and intrathecal chemotherapy, preferably through an Ommaya reservoir. Intrathecal therapy can include methotrexate, 15 mg alone, or alternating with cytosine arabinoside, 50 mg. Drugs must be preservative free and sterile. A Gram stain and bacterial culture, and cell count with cytospin differential should be repeated with each intrathecal treatment until blasts have cleared. Intrathecal therapy is given twice weekly until blasts have cleared and then monthly for 6 to 12 months. The sudden onset of unexplained cranial nerve palsy in a patient with acute leukemia is usually due to CNS leukemia, regardless of whether the CSF shows blasts. Such patients should be treated as described earlier. Isolated extramedullary relapse of CNS leukemia is generally followed soon thereafter by systemic relapse, so that we have usually administered salvage chemotherapy followed by allogeneic transplant if a compatible donor can be identified.

G. **New approaches to the treatment of acute leukemia**

P-glycoprotein (P-gp) is a 170-kDa, adenosine triphosphate (ATP)-dependent transmembrane drug-efflux pump that expels vinca alkaloids, anthracyclines, and epipodophyllotoxins, along with other natural products, from the intracellular space. Expression of P-gp by tumor cells results in a multidrug resistant (mdr-1) phenotype. Depending on the technique used, about one third of younger and three fourths of older, previously untreated patients with AML demonstrate phenotypic and functional expression of P-gp. In multivariate analysis, expression of P-gp is an independent adverse prognostic factor in *de novo* AML. Based on this, a number of clinical trials have been carried out to assess the therapeutic potential of chemotherapy combined with inhibitors of P-gp such as cyclosporine (CSA) or PSC 833. The latter agent is a CSA analogue that is much less nephrotoxic and that is a more potent inhibitor of P-gp than is CSA. List et al. treated 226 patients with resistant AML with HDAC and continuous-infusion daunorubicin. Patients randomized to CSA had substantial improvement in disease-free and overall survival compared with controls. However, because of inhibition of P-gp–mediated biliary efflux, daunorubicin levels were significantly higher among patients who received CSA; therefore CSA may have improved outcome by changing daunorubicin pharmacokinetics rather than by inhibition of leukemia cell P-gp. One way to address this issue is to determine equitoxic doses of drugs given with or without an MDR inhibitor. These dose levels can then be compared in a randomized trial. This approach is being explored in a CALGB trial that includes newly diagnosed patients with AML who are younger than 60 years.

After remission induction, most patients with acute leukemia receive several additional courses of aggressive chemotherapy with the goal of eliminating subclinical leukemia. A sensitive and specific technique for detection of minimal residual disease (MRD) would provide important prognostic information and could allow rational decisions regarding the duration of treatment. An example of the potential utility of this approach is the detection of *Bcr-Abl* transcripts by PCR after allogeneic transplant. In that situation, a persistent positive result for *Bcr-Abl* by PCR or an increasing titer detected by quantitative PCR is highly predictive of relapse. Monitoring MRD in AML is difficult because molecular rearrangements amenable to PCR have been found in a relatively small proportion of patients. Monitoring MRD in ALL is facilitated by the presence of clonotypic T cell–receptor gene or immunoglobulin heavy-chain gene rearrangement. A large multicenter study recently reported that the risk of relapse among children with ALL in first CR was 15-fold higher among those who had a positive PCR after consolidation. However, in another study among children with ALL in CR1, 15 of 17 patients who remained in remission 2 to 35 months after completion of therapy had a persistent positive PCR, raising the interesting possibility that complete eradication of disease may not be necessary to cure ALL. In this same study, the level of transcript, as determined by a semiquantitative PCR, did correlate with relapse risk. Problems with current PCR technology include the potential for contamination, the lack of reproducibility of results when small numbers of transcripts are present, the risk of RNA degradation, and inefficiency during conversion of messenger RNA (mRNA) to complementary DNA (cDNA). Ongoing studies of MRD using automated PCR techniques such as “real time” PCR may answer the question as to whether a threshold level of leukemia can be defined, above which the probability of relapse is high enough to be clinically useful.

Recent advances in our understanding of molecular genetics promise to transform the way that acute leukemia is treated. Elucidation of the possible mechanism for leukemia in core-binding factor (CBF)-related leukemia is a good example of this. CBF is a heterodimeric transcription factor that plays an important role in the activation of genes that are important in hematopoietic development, including interleukin 3 (IL-3), GM-CSF, and the M-CSF receptor. Both the a and b subunits are involved in translocations that are associated with acute leukemia. The gene for the a subunit resides at 21q22, which is the breakpoint in t(8;21) and in t(12;21), whereas the b subunit at 16q21 is involved in inversion 16. All three translocations result in a molecule that acts as a dominant negative inhibitor of wild-type CBF through recruitment of a nuclear co-repressor complex, which includes histone deacetylase. This complex may lead to leukemia by downregulation of genes that play a key role in cell differentiation. Therefore, CBF-related acute leukemia appears to be associated with a common mechanism of leukemogenesis, and this may explain the observation that patients with these translocations have a favorable prognosis. Based on this paradigm, treatment targeted at the nuclear co-repressor complex, such as inhibition of histone deacetylase, could be effective in a subgroup of patients with acute leukemia. Such trials are under way.

Other potentially promising agents under evaluation in clinical trials include angiogenesis inhibitors, hypomethylating agents such as decitabine, bcl-2 antisense, farnesyl transferase inhibitors, and IL-2.

H. Acute promyelocytic leukemia

APL is a distinct clinical and pathologic subtype of AML, characterized by a reciprocal translocation between the long arms of chromosomes 15 and 17. The breakpoint on chromosome 17 disrupts a gene that encodes a nuclear receptor for retinoic acid (RAR-a), and its translocation, most commonly to chromosome 15, results in a fusion protein, the PML-RAR-a. PML-RAR-a retains the retinoic acid ligand-binding domain, thus suggesting that this protein may not only mediate leukemogenesis, but also account for the unique sensitivity of APL to differentiation by ATRA. Other reciprocal translocations fusing RAR-a to genes other than PML have been identified in patients with APL. However, it is now apparent that the nature of the fusion partner has a significant bearing on ATRA responsiveness, and hence the optimal treatment of these disease entities. Detection of PML-RAR-a is associated with a good prognosis. Indeed, patients with APL who achieve complete remission have better long-term survival than do other patients with AML.

1. **Diagnosis of APL.** Given its unique response to specific therapy, rapid and accurate diagnosis is crucial. It is now commonly accepted that molecular evidence of the PML/RAR-a rearrangement is the hallmark of this disease, as it may be found in the absence of t(15,17). Even in cases with apparently normal metaphases, detection of the PML-RARa confers sensitivity to ATRA. Advantages and pitfalls of diagnostic tools commonly used in the diagnosis of APL are summarized in Table 14.3.

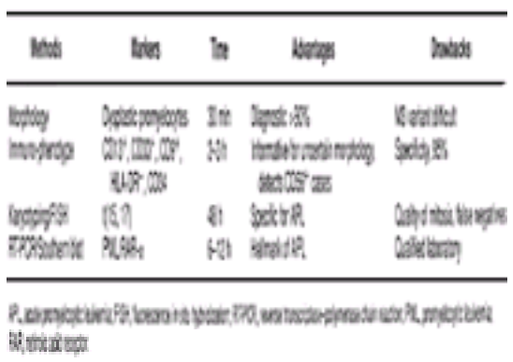

TABLE 14.3. ADVANTAGES AND PITFALLS OF DIAGNOSTIC TOOLS COMMONLY USED IN THE DIAGNOSIS OF APL

2. **Front-line therapy.** The advantage of including ATRA in the front line therapy for APL has now been clearly established in several randomized trials, with CR rates ranging from 72% to 95%, and a 3- to 4-year disease-free survival of 62% to 75%. These studies also defined the optimal combination of ATRA and chemotherapy by demonstrating improved disease-free survival in patients given ATRA simultaneous with chemotherapy. Furthermore, the addition of maintenance therapy with ATRA and/or chemotherapy after two cycles of intensive postremission consolidation also is associated with improved disease-free and overall survival. However, many questions remain unanswered. In some studies, ara-C was omitted inconsequently from induction and/or consolidation regimens. Given the lack of randomized trials, long-term results of these trials are needed to clarify the role ara-C plays in the management of APL. Additionally, the optimal maintenance regimen is still unknown. In one study, the combination of ATRA (45 mg/m ^{2}/day, 15 days every 3 months) with 6-mercaptopurine (90 mg/m^2/ day, orally) and methotrexate (15 mg/m^2/week, orally) was associated with the lowest relapse rates, especially for APL patients with a high WBC.
3. **Prognostic factors.** The two most important factors affecting CR rates and survival in patients with APL are age and the WBC at diagnosis. Younger age (younger than 30 years) and lower WBC (less than 5,000 to 10,000/mm ^{3}) are favorable prognostic factors. In contrast, several other biologic features such as the type of PML-RARa isoform, additional karyotypic abnormalities, and expression of the reciprocal RARa-PML transcript do not appear to influence outcome. Recent data suggest that the expression of CD56 antigen on promyelocytes is associated with an increased risk for relapse.
4. **Therapeutic considerations for elderly patients with APL.** Before the advent of ATRA, elderly patients with APL had a dismal prognosis, similar to that of age-matched patients with other AML subtypes. The introduction of ATRA into front-line therapy has considerably improved the prognosis of elderly patients. In one study, induction therapy for patients older than 65 years consisted of single-agent ATRA given until achievement of hematologic remission or for a maximum of 90 days, followed by a combination of anthracycline and Ara-C. The CR rate, 2-year event-free, and overall survival were 90%, 67%, and 69%, respectively. Tolerance to consolidation chemotherapy remains a significant problem in this age subset. The current approach for the treatment of patients with newly diagnosed APL at Washington University is summarized in the algorithm in Fig. 14.1.

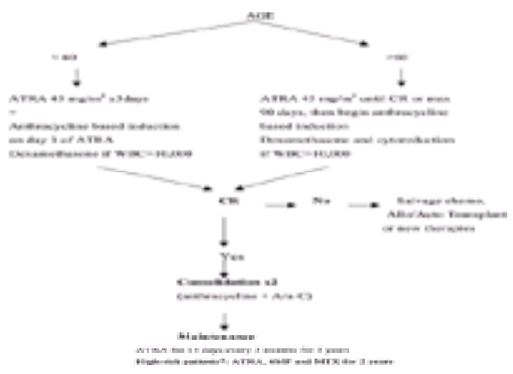

FIG. 14.1. Proposed algorithm for patients with newly diagnosed acute promyelocytic leukemia. *High-risk, presenting white blood cell count greater than 10,000, CD56$^+$.

5. **The ATRA syndrome.** Although ATRA is usually well tolerated, some patients develop a unique complication called retinoic acid syndrome (RAS). RAS occurs usually early after initiation of ATRA (7 to 12 days) and is diagnosed on clinical grounds. It is characterized by unexplained fever (80%), weight gain (50%), respiratory distress (90%), lung infiltrates (80%), pleural (50%) or pericardial effusion (20%), hypotension (10%), and renal failure (40%). RAS is the most serious toxicity of ATRA and is often, but not always, associated with the development of hyperleukocytosis. Its incidence varies from 6% to 25%, and mortality from RAS is variable (7% to 27%). The best approach to predict, prevent, or treat this syndrome has not been established. Early institution of corticosteroids (dexamethasone, 10 mg i.v. twice daily) simultaneous with cytoreduction (induction chemotherapy or hydroxyurea) is associated with rapid resolution of the syndrome in most patients. Discontinuation of ATRA is common practice after onset of RAS. Finally, RAS has not been observed when ATRA was given as maintenance therapy.
6. **Acute promyelocytic leukemia–associated coagulopathy.** Patients with APL usually have severe coagulopathy that is often exacerbated by cytoreductive chemotherapy. Therefore, monitoring DIC with twice-daily serum fibrinogen levels and aggressive replacement with cryoprecipitates (5 to 10 units for fibrinogen less than 100 mg/dL) is common clinical practice during the first 2 weeks of treatment of APL. The pathogenesis of APL-associated coagulopathy is complex and involves several mechanisms such as activation of coagulation, fibrinolysis, and nonspecific proteolysis. The differentiation process associated with ATRA therapy was shown to reduce the expression of procoagulant activity from APL blasts, which may partially explain the improvement of clinical and laboratory parameters. However, at the clinical level, the impact of ATRA in reducing early hemorrhagic death is still uncertain, as up to 10% of fatal hemorrhagic events were observed in both arms of randomized trials comparing ATRA ± chemotherapy with chemotherapy alone.
7. **Therapy for relapsed acute promyelocytic leukemia.** Approximately 10% to 25% of patients treated with ATRA-based therapy ultimately relapse. The duration of first CR and the achievement of a second PCR-negative remission after reinduction have been shown to be prognostic determinants. Options for salvage therapy include the use of new drugs such as the synthetic retinoid compound Am80 or arsenic trioxide (AsO_3), and hematopoietic stem cell transplantation (HSCT). When used as a single agent for APL in relapse after ATRA induction, Am80 produced a second remission in the majority of patients. Investigators from China first reported successful remission induction, including molecular remissions, in 80% of patients with relapsed APL treated with AsO_3. Subsequent trials have confirmed that treatment with AsO_3 is effective salvage therapy for relapsed and refractory APL, has a relatively low toxicity profile, and is associated with cytodifferentiation and induction of apoptosis. Further confirmatory studies and longer follow-up of patients treated with AsO_3 are ongoing and should serve as basis for the inclusion of AsO_3 in first-line therapy for APL. Patients with APL who receive autologous HSCT while in second remission have a 30% 7-year leukemia-free survival. However, after stratification according to PCR status of the grafted marrow, it appears that patients transplanted with PML-RARa–negative marrow cells are more likely to have prolonged clinical and molecular remissions. In

contrast, relapse after autologous HSCT is inevitable in patients with persistently positive PCR after reinduction and consolidation therapy. Allogeneic HSCT may be the preferable treatment modality in this setting.

8. **Role of molecular monitoring for minimal residual disease in acute promyelocytic leukemia.** Similar to chronic myeloid leukemia (CML), APL offers the opportunity to monitor for MRD by using a specific molecular marker (i.e., PML-RARa). The prognostic value of detecting MRD during clinical remission was recently recognized. However, a positive PCR assay (sensitivity, 10^{-4}) detected during remission is not always predictive of clinical relapse; neither is a negative PCR test always associated with prolonged remissions or cure. Monitoring for MRD earlier in the treatment course of APL (at any stage after induction or during consolidation therapy) and assessment by the rate of clearance of disease-related transcripts by using RT-PCR PML-RARa assay, was recently found to be an independent prognostic factor for relapse. Indeed, detection of transcripts after the third course of chemotherapy predicts a significantly higher risk of relapse (57% vs. 25%; $p = 0.004$) and is associated with a poorer 3-year overall survival (57% vs. 89%; $p = 0.02$) in comparison with that in patients with no evidence of MRD. Additionally, conversion to PCR positivity for PML-RARa during molecular remission is highly predictive of subsequent hematologic relapse. Detection of molecular relapse in these cases would allow earlier administration of salvage therapy, a strategy that may be advantageous in some patients with APL.
9. **Concluding remarks.** Important discoveries in the early 1990s paved the way for the significant improvement in the outcome of patients with acute leukemia, and in particular APL. Indeed, the survival of APL patients treated with a regimen including ATRA is very similar to the one seen in childhood ALL. Research now is focusing on improving survival by anticipating relapse in patients showing disease recurrence at the molecular level, identifying patients that may benefit from more intensive therapy after remission induction, and evaluating the promising role of AsO_3.

Acute leukemias in adults remain, however, a fatal disease for the majority of adult patients. Cytogenetics confers valuable prognostic information that helps in planning the management of patients. Improvement in the safety profile of allogeneic transplantation and the availability of immunotherapy may improve outcomes.

II. The chronic leukemias

A. Chronic myeloid leukemia

1. **Introduction.** CML is a clonal myeloproliferative disorder that is seen clinically with leukocytosis, splenomegaly, and an inexorable progression to a fatal blast crisis. Historically, CML was the first disease in which a specific chromosomal abnormality was linked to the pathogenesis of the disease. The discovery of the Ph chromosome and subsequently the *Bcr-Abl* fusion gene in almost all patients with CML contributed dramatically to the understanding of this disease in particular and to carcinogenesis in general. CML accounts for 7% to 15% of all leukemias in adults. Median age at presentation is the fifth decade. The etiology is unclear; no correlation in monozygotic twins was observed. A significantly higher incidence of CML occurred in survivors of the atomic disasters at Nagasaki and Hiroshima. Chemicals have not been associated with increased risk for CML.
2. **Clinical and laboratory features.** In most patients, CML is diagnosed incidentally. When symptomatic, patients have fatigue, weight loss, early satiety and sensation of abdominal fullness, and bleeding or bruising. Leukocytosis with a myeloid shift is universal. Importantly, and in contrast to cases of acute leukemia in which an arrest in maturation is the rule, granulocytes at all stages of maturation are observed on the peripheral smear. Basophilia (greater than 7%) occurs in only 10% to 15%. Anemia and thrombocytosis are common. Leukocyte alkaline phosphatase (LAP) activity is usually reduced, but can be increased with infections, stress, on achievement of remission, or on progression to blastic phase. The diagnosis is suspected when a constellation of splenomegaly, leukocytosis with a left shift, and thrombocytosis are found, and is confirmed by the detection of a reciprocal translocation between the long arms of the chromosomes 9 and 22 (Ph chromosome) or the *bcr-abl* fusion gene. *Bcr-Abl* can be detected in approximately 30% of clinical cases resembling CML but with no detectable Ph chromosome. Patients with Ph chromosome–negative *bcr-abl*–positive CML have similar response to therapy and outcome as is found in Ph-positive CML.
3. **Natural history.** CML has usually a biphasic clinical course, but can occasionally be triphasic. In the 2 years after the diagnosis of CML, 5% to 15% of patients will enter blast crisis, an incurable acute leukemia that is fatal within 3 to 6 months. In subsequent years, the annual rate of progression increases to 20% to 25%. Before blast crisis, 40% to 70% of patients pass through a transient accelerated phase that lasts a median of 4 to 6 months. The definition of accelerated-phase CML relies on several clinical and laboratory features. Criteria commonly used in clinical practice include the following: marrow or peripheral blasts greater than 10% and less than 30%, peripheral blasts and promyelocytes greater than 30%, peripheral basophilia (greater than 20%), thrombocytopenia (less than 100,000) unrelated to therapy, progressive splenomegaly, and cytogenetic clonal evolution. Once either accelerated-phase or blast crisis occurs, the success of any therapy declines dramatically. Several prognostic models (Sokal score, MD Anderson Cancer Center staging system) were developed to stratify patients into groups with different average survival, using variables such as age, spleen size, platelet count, percentage of peripheral blood blast count, hematocrit, cytogenetic clonal evolution, and sex to derive a hazard ratio for death. These scoring systems are certainly predictive at the level of the population; however, the predictive value for the individual patient is yet to be defined.
4. **Treatment of chronic myeloid leukemia: nontransplant options**
   a. **Conventional chemotherapy.** Until 1980, hydroxyurea and busulfan were the two most effective anti-CML agents. Busulfan is effective in hematologic control but is associated with unpredictable prolonged myelosuppression. When compared with busulfan, hydroxyurea is associated with longer duration of chronic phase (47 vs. 37 months), improved overall survival (58 vs. 45 months), and a better toxicity profile. However, the uniform transformation to the acute phase of the disease was unchanged, and no significant reduction in the percentage of cells bearing the Ph chromosome was observed with either agent.
   b. **Interferon a.** Studies involving interferon a (IFN-a) demonstrated that hematologic control can be achieved in the majority of patients, that Ph chromosome–negative hematopoiesis can be restored in some patients, and that regimens that involved IFN-a produced a statistically better survival than those involving either hydroxyurea or busulfan alone. The 5-year survival rates were 57% with IFN-a and 42% with chemotherapy, with an absolute difference of 15% (SD, 3%; $p < 0.00001$). It is not yet clear what the optimal dosage of IFNa should be; the dose used in most studies documenting a significant response is 5×10^6 U/m^2 daily.

      The median time to cytogenetic response with IFN-a is 12 months, with major cytogenetic responses (Ph chromosome suppression to less than 35%) observed in approximately 20% to 30% of patients. Most transplant series reported a better overall survival if allogeneic transplantation was performed within 1 year of the diagnosis. Thus a trial of IFN may worsen the outcome of patients who eventually go on to transplant by delaying the procedure beyond the first year after diagnosis. Models were developed to predict who would respond to IFN-a, in an attempt to identify and allow earlier pursuit of transplantation for those patients who are not destined to attain complete cytogenetic response with IFN-a. Based on these models, discontinuation of IFN-a should be considered 3 months after initiation of IFN-a in the absence of hematologic response and presence of pretreatment splenomegaly and thrombocytosis (less than $700{,}000 \times 10^9$/L), and 6 to 12 months after initiation of IFN-a in the absence of hematologic response, or in case of achievement of complete hematologic response but with persistence of the Ph chromosome and presence of pretreatment splenomegaly and thrombocytosis (more than $700{,}000 \times 10^9$/L).

      Although treatment with IFN-a prolongs survival throughout the first 5 years by delaying death from progression to blast crisis, it is not a curative option. The survival benefit seems to be lost beyond 5 years. A very small subset of patients will do extremely well with IFN-a, with the *bcr-abl* gene rearrangement becoming undetectable by RT-PCR. The duration of these molecular remissions and the outcome of these patients remain unknown. Long-term follow-up of the Italian randomized trial of IFN-a versus conventional chemotherapy recently reported a 30% 10-year survival for the IFN-a–treated patients. However, all the long-term survivors were in the low-risk Sokal score group.

      IFN-a initially causes flu-like symptoms, but these usually subside. Other more persistent side effects include anorexia, weight loss, depression, autoimmune disorders, thrombocytopenia, alopecia, rashes, and neuropathies. Toxicity leads to discontinuation in about a fifth of patients. A better tolerance can be achieved with gradual increase in the doses of IFN-a (start at 3 MU/day for 7 days, and then increase to 5 MU/day for 7 days, and then 5 MU/m^2/day) and the use of acetaminophen for premedication.

      The combination of ara-C and IFN-a is associated with higher complete hematologic remission rates and better cytogenetic response rates (41% vs. 24% in the IFN-a group) as compared with IFN-a alone. Furthermore, the survival rates at 3 years favor the combination of IFN-a with cytarabine (86% vs. 79%). However, the addition of ara-C to IFN-a increases treatment-related toxicity (thrombocytopenia, nausea, vomiting, diarrhea, and mucositis), leading to discontinuation of the drug in one of every four treated patients.

   c. **STI-571.** The signal-transduction inhibitor STI-571 (Imatinib, Gleevec) is a phenylaminopyrimidine that has been identified as a result of a precise understanding of the molecular pathology of CML and promises to be an important therapeutic advance in the management of this leukemia. With the discovery of the *Bcr-Abl* gene on the Ph chromosome, and the observation that transduction of murine stem cells with retroviral vectors containing this chimeric fusion gene caused a disease closely resembling CML, research efforts were directed toward the blockade of the *Bcr-Abl* gene product. One target was the normal protooncogene *Abl* located on the chromosome 9 that contains a tyrosine kinase (TK) domain and whose activity is greatly enhanced by the juxtaposition with Bcr. STI571 was designated to block the *Abl*-coded kinase activity by competing with ATP-binding site of the enzyme. *In vitro,* STI571 specifically inhibited the proliferation of CML-derived cell lines and clonal growth of myeloid cells from CML patients. It also

eradicated CML cell proliferation in nude mice. Clinical studies with STI571 started in 1998. The drug was given orally to patients with IFN-resistant chronic phase at a dose of 300 mg daily or more, and all went into hematologic remission. Preliminary results suggest that approximately half of the treated patients show cytogenetic responses when assessed 6 months after initiation of STI-571. STI-571 is well tolerated, with nausea (40%) and mild myelosuppression (20%) being the most commonly observed side effects. These preliminary results appear very encouraging and better than those achievable with any other agent in the management of CML.

d. **Homoharringtonine (HHT).** HHT is a plant alkaloid with activity in CML. Hematologic and cytogenetic responses were observed with single-agent HHT in patients with IFN-resistant CML, and preliminary investigations testing the combinations of HHT with IFN-a or ara-C are encouraging. The toxicity profile of HHT is low; dose-related myelosuppression and diarrhea are the most commonly reported side effects.

5. **Treatment of chronic myelogenous leukemia: transplant options**
   a. **Allogeneic bone marrow transplantation.** Allogeneic BMT from either related or unrelated donors is the only known curative therapy for CML. Transplantation from a matched sibling donor during chronic phase is associated with a 10-year survival of approximately 50% to 70%. Results of transplantation from unrelated donors are somewhat less impressive, but are improving with better matching strategies and supportive care. The objective of BMT is cure of CML by eradication of the leukemic clone with myeloablative chemoradiotherapy, and restoration of hematopoiesis by transplantation of normal donor-derived stem cells. In addition, the donor-derived allogeneic immune cells confer an important graft-versus-leukemia (GVL) effect, which acts to prevent recurrence of disease. GVL has been closely associated with the presence of GVHD. GVHD does not develop in patients receiving transplants from identical twin donors. These patients have at least twice the risk of relapse of CML, compared with transplant recipients from HLA-identical siblings.

      The best results occur when patients are transplanted while in chronic phase, with a 50% to 70% chance of cure. Long-term survival after BMT in accelerated phase is only 20% to 40%, whereas survival after transplants performed in blast phase further declines to none to 20%. The highest rates of survival for related and unrelated donor transplantation are documented in patients transplanted within 1 year of diagnosis. The effect of pretransplant IFN-a on the success of related and unrelated transplants was analyzed in multiple retrospective studies, and the results have been inconsistent. One study in unrelated donor transplantation showed that exposure to IFN-a for longer than 6 months before transplant adversely affected survival because of an increased risk of severe acute GVHD. Most studies in related-donor transplantation have shown little or no adverse effect of IFN-a before transplantation.

      One third of patients will have a histocompatible donor, and 50% of the population will locate a suitable unrelated donor (70% for whites and 15% for blacks and other minorities in the United States). Age of older than 50 to 60 years has been found to constitute a significant hurdle for transplant success, especially in the unrelated-donor transplant setting. The median age at diagnosis of CML is 67 years, according to Surveillance, Epidemiology, and End Results (SEER) data. Approximately 76% of patients are older than 60 years at the time of diagnosis, and 64% are older than 60 years. Therefore, when donor availability and age are considered, allogeneic transplantation is an option for only a minority of patients. Attenuated-intensity conditioning regimens [lower doses of total body irradiation (TBI), nonmyeloablative conditionings] are currently under investigation and may offer this curative therapy to older and ineligible patients for conventional transplantation.

      Most transplanted CML patients are cured of their disease, although transplant-related morbidity and mortality remain a significant problem. The cumulative incidence of severe GVHD is approximately 20% to 35% in matched-sibling transplantation and 40% to 55% in recipients of transplants from unrelated donors. Infection is a major cause of nonrelapse mortality in allogeneic transplantation. GVHD and immunosuppression are predisposing factors for infectious complications.

6. **Treatment of blast-phase chronic myelogenous leukemia.** Treatment of blast-phase (BP) CML is disappointing, as these patients respond very poorly to chemotherapy. BP-CML can present with myeloid (50%), lymphoid (25%), or undifferentiated (25%) features. Patients with lymphoid blast crisis treated with an ALL-like therapy have a somewhat better median survival (9 months) when compared with those with myeloid or undifferentiated BP. Preliminary results of treatment of myeloid transformation with STI-571 are promising, as normal blood counts with disappearance of excess blast cells occurred in approximately half of patients. Lymphoid transformation also responded; however, responses were short lived. STI-571 may offer a window of opportunity to proceed with allogeneic stem cell transplantation by restoring a transient second chronic phase or, in some cases, a remission.
7. **Initial treatment for patients with newly diagnosed chronic myelogenous leukemia.** The choice of initial therapy for patients with newly diagnosed CML is complex. To choose IFN-a as first-line therapy risks progression to blast crisis and inferior transplant results caused by a delay in transplantation. Electing allogeneic transplantation as initial therapy means that a patient quickly faces a risky procedure with a prolonged recovery period and long-term complications. Weighing the likelihood of surviving transplantation and responding to IFN-a may help in guiding the selection of initial therapy. Obviously many extenuating circumstances, coexisting medical conditions, and personal values must be a part of the ultimate decision. How should STI-571 be factored into this complex equation? STI-571 is very effective in controlling the hematologic manifestations of CML; however, little is known about the duration of its benefit, and nothing is known about its long-term toxicity. No patient has received STI-571 for more than 2 years as of October 2000. These points notwithstanding, hematologists seem to have an important new agent that might, alone or with combination with other agents, contribute to long-term control, or conceivably, cure of CML. As more information about this drug is gathered, younger patients with a fully matched donor still must be advised that allogeneic transplantation remains the only curative modality for CML.

B. **Chronic lymphocytic leukemia**
   1. **Introduction.** Chronic lymphocytic leukemia (CLL) is a clonal lymphoproliferative disorder seen clinically with an accumulation of mature neoplastic lymphocytes in the blood, bone marrow, lymph nodes, and spleen. CLL accounts for approximately 30% of all leukemias and is the most common adult leukemia in Western countries. Median age at presentation is the sixth decade, with only 10% to 15% of patients first seen at younger than 50 years. The etiology is unclear. This leukemia is not associated with exposure to ionizing radiation, drugs, or chemicals. There is epidemiologic evidence for a genetic susceptibility: CLL is uncommon in people from the Far East and in Japanese immigrants to America, when compared with people of white and African descent. A familial tendency also has been documented. Leukemic cells of affected family members sometimes express the same immunoglobulin heavy-chain variable region gene; however, different immunoglobulin gene rearrangements have been detected, suggesting that distinct somatic events are involved at the origin of this leukemia. B-CLL is a disease of dysregulated programmed cell death or apoptosis. The accumulation of lymphocytes is not attributable to an accelerated division rate, but rather to abnormally prolonged survival. The genetic mechanisms underlying this phenomenon remain largely unknown.
   2. **Clinical and laboratory features.** In most patients, CLL is diagnosed incidentally. When symptomatic, patients have fatigue, weight loss, recurrent infections, or bleeding. Because of the advanced age of the affected population, patients sometimes are seen with exacerbation of other underlying medical conditions, such as pulmonary, cerebrovascular, or coronary artery disease. Lymphadenopathies are usually generalized and nontender, but can be bulky and create symptoms from organ compression. Splenomegaly can cause early satiety, abdominal fullness, or hypersplenism.

      The hallmark of CLL is an increased white-cell count with predominance of mature small lymphocytes of B-cell lineage that have a characteristic immunophenotype: expression of relatively low levels of surface-membrane immunoglobulin, coexpression of B-lymphocyte markers (CD19, CD20) with an aberrant T-cell marker (CD5) and CD23. Immunophenotypic features of malignant conditions affecting mature B lymphocytes are summarized in Table 14.4. A bone marrow aspirate and biopsy are generally not required for the diagnosis of CLL; nevertheless, the pattern of marrow infiltration by the lymphocytes has prognostic significance, with nodular infiltration offering a better prognosis.

Disorder	Common Immunophenotype
CLL	DR$^+$, CD19$^+$, CD20$^+$, CD5$^+$, CD22$^-$, CD23$^+$, CD10$^-$, weak sIg
Prolymphocytic leukemia	DR$^+$, CD19$^+$, CD20$^+$, CD5$^-$, CD22^{++}, CD23$^-$, CD10$^-$, bright sIg
Mantle cell lymphoma	DR$^+$, CD19$^+$, CD20$^+$, CD5$^+$, CD22^{++}, CD23$^-$, CD10$^-$, moderate sIg
Follicular lymphoma	DR$^+$, CD19$^+$, CD20$^+$, CD5$^-$, CD22^{++}, CD23$^-$, CD10$^+$, bright sIg
Hairy cell leukemia	DR$^+$, CD19$^+$, CD20$^+$, CD5$^-$, CD22^{++}, CD23$^-$, CD103$^+$, CD11c$^+$, bright sIg

CLL, chronic lymphocytic leukemia; sIg, surface immunoglobulin.

TABLE 14.4. IMMUNOPHENOTYPIC FEATURES OF MALIGNANT CONDITIONS AFFECTING MATURE B LYMPHOCYTES

About 50% of patients with CLL have cytogenetic abnormalities, particularly trisomy 12, abnormalities of the chromosome 13, 14, 6, or 11. These abnormalities are better detected by fluorescence *in situ* hybridization than by conventional cytogenetic testing. Karyotypic abnormalities prevail in advanced stages of the disease, and clonal evolution (15% to 40%) is usually associated with disease progression.

a. **Natural history.** A distinctive feature of the natural history of CLL is that neoplastic B cells accumulate over time. Therefore in patients who are asymptomatic at diagnosis, lymphadenopathy, splenomegaly, and hepatomegaly will eventually develop. Likewise, the WBC will increase, and anemia and thrombocytopenia will become apparent as a result of progressive marrow infiltration, hypersplenism, or autoimmunity. The natural history of CLL is variable. Approximately a third of patients will not require therapy and die of causes unrelated to CLL; another third will have progressive disease after an initial indolent phase, and the remaining third will have aggressive disease at diagnosis and require immediate therapy. Outcomes of patients with CLL are predicted by the clinical stage, bone marrow findings, blood lymphocyte doubling time, and cytogenetic abnormalities. In addition, serum concentrations of LDH and b_2-microglobulin have been found to have prognostic values in some studies. Finally, response to therapy is associated with longer survival. The prognostic significance of clinical staging systems (Table 14.5) has been widely validated, but does not provide information on the likelihood of progression in a given patient. Other variables (pattern of lymphocytic infiltration of the bone marrow and the lymphocyte doubling time) may provide useful prognostic information. Recent data suggest that deletions of the chromosome 11q6 or somatic mutations in the immunoglobulin heavy-chain genes are good predictors of rapid progression and survival.

Staging System	Presentation	Median Survival (yr)	Patients
Rai			
0	Lymphocytosis	>10	30%
I	LN	9	35%
II	Splenomegaly	7	25%
III	Anemia	5	7%
IV	Thrombocytopenia	5	3%
Binet			
A	Lymphocytosis, <3 areas of LN	>10	65%
B	Lymphocytosis, >3 areas of LN	7	30%
C	Anemia, thrombocytopenia, or both	5	5%

CLL, chronic lymphocytic leukemia; LN, lymph node enlargement.

TABLE 14.5. CLL STAGING SYSTEMS

3. **Complications associated with chronic lymphocytic leukemia.** Complications that may occur during the course of the disease are listed in Table 14.6.

Complication	Patients Affected (%)
Autoimmune	
Hemolytic anemia	10–25
Thrombocytopenia	2
Neutropenia	0.5
Pure red cell aplasia	0.5
Hypogammaglobulinemia	20–60
Infections	
Streptococcus, Staphylococcus sp.	
Haemophilus sp.	
Candida, Aspergillus sp.	
Varicella zoster	
Legionella, Pneumocystis, Listeria sp.	
Toxoplasma sp.	
Disease transformation	
Prolymphocytic leukemia	10
Richter transformation	3–5
Second cancers (lung, skin, GI)	5–15

CLL, chronic lymphocytic leukemia; GI, gastrointestinal.

TABLE 14.6. COMPLICATIONS ASSOCIATED WITH CLL

Corticosteroids (prednisone, 1 mg/kg) are commonly used in the management of autoimmune complications; the addition of cyclosporine is effective to treat pure red cell aplasia. Hypogammaglobulinemia is common in patients with CLL and contributes significantly to the increased risk for infections. Prophylactic transfusion of high-dose immunoglobulin (400 mg/kg every 3 weeks) reduces the risk of infections without affecting survival. Vaccinations produce only suboptimal responses because of the impaired immune system in patients with CLL. Patients treated with fludarabine have an increased incidence of opportunistic infections. CLL can evolve into an aggressive high-grade large cell non-Hodgkin lymphoma (Richter transformation) or a prolymphocytic transformation. Richter transformation occurs in a minority of patients with CLL (fewer than 5%) at a median time of 2 years from diagnosis. Patients have systemic symptoms and bulky lymph nodes. The diagnosis is confirmed by a lymph node biopsy. Richter transformation has a very poor prognostic implication, with a median survival of 5 months from diagnosis despite aggressive treatment with large cell lymphoma–type combination chemotherapy. In nearly 15% of patients with CLL, the population of leukemic cells consists of a mixture of mature lymphocytes and prolymphocytes. Prolymphocytic transformation is seen with a progressive increase in circulating prolymphocytes with characteristic immunophenotypic changes (Table 14.6) and splenic enlargement. This transformation responds poorly to chemotherapy, and the prognosis is poor. Finally, patients with CLL appear to have an increased incidence of development of solid tumors.

4. **Treatment of chronic lymphocytic leukemia**
   a. **When to initiate therapy.** Treatment of CLL has been historically mainly palliative, because of the long natural history of the disease and to the lack of effective agents. The diagnosis of CLL does not imply the need for therapy. A number of indications justify treatment in CLL, including constitutional symptoms, bulky lymphadenopathies, symptomatic splenomegaly, cytopenias, and blood lymphocyte doubling time of less than 6 months. It is now well demonstrated that therapy with chlorambucil can be deferred inconsequently in patients in a low-risk group (Binet stage A). Moreover, deferring therapy until progression of the disease does not appear to compromise survival.
   b. **What treatment should patients receive?** Chlorambucil is a well-tolerated, relatively inexpensive oral therapy. Chlorambucil is administered at doses ranging from 0.1 to 0.2 mg/kg daily for 6 weeks and then tapered by 2 mg/day as tolerated; or 15 to 30 mg/m ^{2} once every 14 to 21 days. Fludarabine is an intravenous purine analogue with activity against CLL and is administered at 25 to 30 mg/m ^{2} daily for 5 days every 4 weeks. Fludarabine causes significant myelo- and immunosuppression. Although treatment of newly diagnosed, previously untreated patients with CLL with fludarabine is associated with higher response rates and longer periods of remission and progression-free survival when compared with treatment with chlorambucil, neither agent prolongs survival. Similar survival results were observed in a meta-analysis of 10 randomized trials comparing chlorambucil with combination chemotherapy, in which improvements in response rates never translated into improved survival. The addition of prednisone (mini-CHOP) to the combination chemotherapy with cyclophosphamide, doxorubicin, vincristine (CAP) improved response rates and progression-free survival but yielded results similar to those with fludarabine given as a single agent.

Current studies are evaluating the role of monoclonal antibodies (CAMPATH-1B or anti-CD52; rituxamab or anti-CD20) and novel agents for the management of CLL. Monoclonal antibodies offer a more targeted approach, and the best responses are observed when the disease does not involve nodal sites. Infusion related toxicities (anti-CD20) and marked immunosuppression and myelosuppression (anti-CD52) are common with these monoclonal antibodies. Protein kinase C modulators (UCN-01, bryostatin), and cyclin-dependent kinase inhibitors (flavopiridol) have shown promising results in phase I trials and are currently being tested in phase II trials. Other agents being investigated include GW506, a derivative of ara-G, and arsenic trioxide.

Conventional allogeneic hematopoietic stem cell transplantation may offer a chance for a cure in CLL but can be applicable to only a minority of patients. Allografting using a decreased intensity or a nonmyeloablative conditioning may increase the number of potentially eligible patients and is an option currently being investigated.

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CHAPTER 15. LYMPHOMA

Nina D. Wagner and Nancy L. Bartlett

Hodgkin disease
Presentation
Workup and staging
Therapy and prognosis
Complications
Follow-up
Background
Current focus
Non-Hodgkin Lymphoma
Presentation
Work-up and staging
Therapy and prognosis
Complications
Follow-up
Background
Current focus of research
Suggested Readings

I. Hodgkin disease

A. Presentation

1. **Subjective.** Hodgkin disease (HD) or Hodgkin lymphoma usually is first seen in young adults as painless lymphadenopathy in the cervical and/or supraclavicular regions. Isolated subdiaphragmatic lymphadenopathy or organ involvement is rare. Although staging studies reveal mediastinal adenopathy in more than 85% of patients, symptoms of cough, chest pain, dyspnea, and superior vena cava (SVC) syndrome are uncommon, even in patients with bulky mediastinal disease. Systemic symptoms or “B” symptoms, including fevers (temperature greater than 38°C), drenching night sweats, or weight loss (more than 10% of baseline body weight in the preceding 6 months) occur in 30% to 40% of patients with stage III or IV disease, but in fewer than 10% of patients with stage I or II disease. In most series, the presence of B symptoms portends a worse prognosis. Generalized, severe pruritus occurs in approximately 25% of patients with HD, often precedes the diagnosis by months, can be a presenting symptom of both early and advanced-stage disease, and has no known prognostic significance. Alcohol-induced pain in involved lymph nodes is a rare symptom of HD (less than 1%). B symptoms and pruritus usually subside within a few days of initiating therapy.

   Patients with HD older than 50 years or with human immunodeficiency virus (HIV) disease are more likely to have symptoms secondary to extensive intraabdominal disease; extranodal involvement including lung, bone marrow, liver, or bone; and marked B symptoms. HD, as well as non-Hodgkin lymphoma (NHL) should always be considered in the differential diagnosis of fever of unknown origin in an older patient, even without evidence of adenopathy. Nodular lymphocyte–predominant HD (LPHD), which represents about 5% of cases of HD in the United States and Europe, often is first seen as a solitary cervical, axillary, or inguinal lymph node. In LPHD, the mediastinum is generally spared, and in contrast to the contiguous pattern of lymph node involvement in classic HD, there is no consistent pattern of spread.

2. **Objective.** Although computed tomography (CT) scans and occasionally even positron emission tomography (PET) scans have replaced the physical examination in staging, thorough examination of all lymph node–bearing areas in patients with HD remains pertinent. Occasionally small supraclavicular and infraclavicular nodes can be missed on neck and chest CT scans. In addition, chest CT scans do not always include the entire axillae, especially in larger patients. Physiologic uptake in the sternocleidomastoid muscles on PET scan may decrease the sensitivity of this test in the cervical and supraclavicular regions. Identification of all involved nodal areas is especially important in early-stage patients who receive limited chemotherapy and “involved field” radiotherapy (RT).

B. Workup and staging

HD is nearly always diagnosed by an excisional lymph node biopsy, although rarely, biopsy of an extranodal site may be the source of diagnostic tissue. Diagnosis requires the presence of Hodgkin or Reed–Sternberg cells (HRS) within an appropriate cellular background of inflammatory cells. The most recent classification system proposed by the World Health Organization (WHO) classifies HD as either “classic” HD or nodular LPHD. This distinction is essential, because LPHD and classic HD have different natural histories, prognoses, and treatments. Immunohistochemical studies accurately distinguish LPHD from classic HD and should be performed if histology is equivocal. In classic HD, the large atypical cells are $CD15^{+}$ and $CD30^{+}$, whereas other T- and B-cell–associated antigens are usually negative. In contrast, the tumor cells of LPHD are $CD20^{+}$ (a pan–B-cell antigen), $CD45^{+}$ (leukocyte common antigen), $CD15^{-}$, and variably reactive for CD30, an immunophenotype often seen in B-cell NHL.

Pathologists continue to describe four patterns of classic HD, including nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depletion. Nodular sclerosis HD (NSHD) is the most common type (60% to 80%), accounting for most cases of HD in young adults and those with mediastinal involvement. Mixed-cellularity HD exhibits diffuse nodal effacement without sclerosis. Mixed-cellularity HD constitutes 15% to 30% of cases in most series. Lymphocyte-rich HD is characterized by the presence of RS cells in a lymphocyte-rich background, and without immunophenotyping, can be confused with nodular LPHD. Lymphocyte-depleted HD, characterized by large numbers of RS cells and diffuse fibrosis and necrosis, represents less than 1% of HD, occurs almost exclusively in older patients, and is usually advanced at the time of diagnosis.

Additional workup after a diagnostic lymph node biopsy includes a history and physical examination, laboratory evaluations, radiographic studies, and in some cases, a bone marrow biopsy. Necessary laboratory tests include a complete blood count (CBC), alkaline phosphatase, lactate dehydrogenase (LDH), calcium, albumin, and erythrocyte sedimentation rate (optional). A significant minority of patients have a mild leukocytosis, neutrophilia, lymphopenia, and rarely eosinophilia. Elevated alkaline phosphatase is common and does not necessarily signify liver or bone involvement. Anemia and decreased albumin are usually seen only in patients with B symptoms and stage III or IV disease.

The Ann Arbor staging system for HD is detailed in Table 15.1. The designation E applies to extranodal involvement, which is limited in extent and contiguous with lymph node disease. Since the classification system's inception in 1971, subtle modifications have been suggested but never universally adopted. Proper staging requires CT scans of the chest, abdomen, and pelvis. CT scans of the neck are optional and probably add little to a thorough physical examination. The mediastinal mass ratio (MMR), defined as the ratio of the maximal transverse diameter of the mediastinal mass to the maximal transverse intrathoracic diameter, is an important prognostic factor and should be calculated in all patients with significant mediastinal adenopathy. An MMR greater than 0.33 by chest radiograph (CXR) or 0.35 by CT portends a worse prognosis and may influence treatment recommendations. Small preliminary studies of PET for staging HD indicate that PET is “at least as good” as CT. In two small studies, PET resulted in changes in treatment strategy in 14% and 30% of patients, respectively. Whereas in at least two other small studies, PET was not superior but equal to CT in the detection of disease sites. Larger studies are needed to confirm the potential impact of PET on therapeutic management. Currently, PET scans should be considered primarily in patients with equivocal CT findings and in patients with B symptoms who appear to have localized disease by CT. Bilateral bone marrow biopsies are recommended in patients with B symptoms, known stage III or IV disease, or a subdiaphragmatic presentation of stage I or II disease.

Stage	Description
Stage I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic organ or site (IIE) or spleen (IIS) or both (IIISE)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement

TABLE 15.1. ANN ARBOR STAGING SYSTEM

Gallium scans are hampered by normal uptake in the liver, intestine, and spleen and do not appear to add to the accuracy of staging HD. Bipedal lymphangiography is no longer used to stage HD because of the lack of technical expertise in performing and interpreting the examination, as well as the improved sensitivity of CT and PET in evaluating abdominal and pelvic adenopathy. Based on randomized trials showing no difference in outcome for patients staged with laparotomy and splenectomy compared with those staged clinically, surgical staging is no longer indicated. Moreover, the recent addition of chemotherapy to standard treatment regimens for many patients with early-stage HD decreases the need to identify microscopic disease outside the radiation port.

C. **Therapy and prognosis**

The treatment of HD has been a true success story, with nearly 80% of all patients having durable remissions. However, reports of long-term complications and late deaths related to therapy continue to accumulate in the literature. Consequently, treatment recommendations, especially for low-risk, early-stage patients, are under intense scrutiny. Efforts are under way to design treatment programs that maintain efficacy but minimize late toxicities.

1. **Stage I/II classic Hodgkin disease: low risk.** Early-stage HD is usually considered “favorable” or low-risk if there are no B symptoms and no sites of bulky disease, with bulk commonly defined as a MMR greater than 0.33 or a nodal mass greater than 10 cm. Historically, treatment of favorable, early-stage HD consisted of extended-field RT. Growing numbers of reports of second malignancies and increased cardiac deaths related to previous RT have led to recent changes in treatment. Current trials of combined-modality therapy, with a limited number of cycles of chemotherapy (three to four) followed by **involved-field** radiotherapy (IFRT) are designed to reduce long-term complications of both chemotherapy and radiotherapy. A randomized trial of four cycles of ABVD [doxorubicin, bleomycin, vinblastine, dacarbazine (DTIC) (Table 15.2)] followed by either IFRT or subtotal lymphoid irradiation resulted in identical 7-year disease-free survivals of 94% and 97%, respectively, the first advance in limiting radiotherapy fields in early-stage patients (*Proc Am Soc Clin Oncol* 2001;20:281). Trials also are ongoing to determine if lower doses of radiation (20 Gy) in combination with chemotherapy are equivalent to currently prescribed doses of 35 to 40 Gy. The impact of these changes on the frequency of serious long-term complications will not be realized for at least two decades.

ABVD			
Doxorubicin	25	mg/m² i.v.	d1, 15
Bleomycin	10	mg/m² i.v.	d1, 15
Vinblastine	6	mg/m² i.v.	d1, 15
Dacarbazine	375	mg/m² i.v.	d1, 15
Cycles are repeated every 28 days			
Stanford V			
Mechlorethamine	6	mg/m² i.v.	wk 1, 5, 9
Doxorubicin (Adriamycin)	25	mg/m² i.v.	wk 1, 3, 5, 7, 9, 11
Vinblastine	6	mg/m² i.v.	wk 1, 3, 5, 7, 9, 11
Vincristine	1.4	mg/m² i.v.	wk 2, 4, 6, 8, 10, 12 (max, 2 mg)
Bleomycin	5	mg/m² i.v.	wk 2, 4, 6, 8, 10, 12
Etoposide	60 × 2	mg/m² i.v.	wk 3, 7, 11
Prednisone	40	mg/m² p.o.	wk 1–10 qod, taper wk 11, 12
G-CSF		s.c.	Dose reductions or delay
Cycles are repeated every 21 days			
Escalated BEACOPP			
Bleomycin	10	mg/m² i.v.	d8
Etoposide	200	mg/m² i.v.	d1–3
Doxorubicin (Adriamycin)	25	mg/m² i.v.	d1
Cyclophosphamide	1,250	mg/m² i.v.	d1
Vincristine	1.4	mg/m² i.v.	d1 (max, 2 mg)
Procarbazine	100	mg/m² p.o.	d1–7
Prednisone	40	mg/m² p.o.	d1–14
G-CSF		s.c.	d8+
Cycles are repeated every 21 days			

G-CSF, granulocyte colony-stimulating factor.

TABLE 15.2. CHEMOTHERAPY REGIMENS

Another approach to early-stage patients has been to eliminate RT altogether. This approach is particularly appealing in women aged 15 to 30 years, a subgroup particularly susceptible to second breast cancers after mediastinal and axillary radiation. Currently, data on using chemotherapy alone in early-stage HD is quite limited. A small study of six cycles of ABVD for stage I/II HD reported overall (OS) and progression-free survival (PFS) rates at 42 months of 95% and 84%, respectively. We hope that ongoing trials for early-stage HD will identify the minimal amount of chemotherapy with or without limited RT required to cure most patients with low-risk disease. While awaiting these results, most patients should be treated with three to four cycles of ABVD followed by IFRT, with consideration of six cycles of ABVD alone in young women.

2. **Stage I/II classic Hodgkin disease: high risk.** Patients with less favorable limited-stage disease, including those with B symptoms or bulky disease, should receive combined-modality therapy. At least 75% of patients are cured with this approach. Standard therapy is four to six cycles of ABVD followed by IFRT. Because most of these patients have bulky mediastinal disease, there is at least a theoretical concern about the overlapping cardiopulmonary toxicities of RT, doxorubicin, and bleomycin with this approach. Consequently, regimens that limit the cumulative doses of doxorubicin and bleomycin are under study in this subset of patients. For example, excellent preliminary results have been reported with the Stanford V regimen plus IFRT (*J Clin Oncol* 2002;20:630–637). Chemotherapy is administered weekly for 12 weeks, alternating myelosuppressive and nonmyelosuppressive drugs, including doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone (Table 15.2). The cumulative doses of doxorubicin and bleomycin, respectively, in the Stanford V regimen, are 50% and 25% of those in six cycles of ABVD. The 5-year failure-free survival (FFS) rate with Stanford V chemotherapy and IFRT was 96% for stage II patients with bulky mediastinal disease. Currently, a large cooperative group trial for bulky stage I or II HD and good prognosis stage III or IV HD is comparing ABVD with the Stanford V regimen. Currently, either is an appropriate choice for this group of patients.
3. **Stage III/IV classic HD.** Approximately 60% to 70% of patients with advanced-stage HD can be cured with six cycles of ABVD chemotherapy, the current standard of care. The older MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) chemotherapy regimen is inferior to ABVD, whereas the seven- to eight-drug regimens such as MOPP/ABV and MOPP/ABVD are equally efficacious but more toxic (*N Engl J Med* 1992;327:1478–1484).

   The International Prognostic Factors Project on Advanced HD identified seven independent prognostic factors in 1,618 patients with advanced-stage HD (*N Engl J Med* 1998;329;1506–1514). These included serum albumin less than 4 g/dL, hemoglobin less than 10.5 g/dL, male sex, age 45 years or older, stage IV disease, leukocytosis (WBC greater than 15,000/mm^3), and lymphocytopenia (lymphocyte count less than 600/mm^3 and/or lymphocyte count less than 8% of the WBC). The HD prognostic score showed that patients at the lowest risk with zero to two high-risk features had a 67% to 84% freedom from progression (FFP) at five years, whereas those at highest risk with four to seven adverse risk factors had a 42% to 51% FFP. Efforts to minimize toxicity in low-risk patients and improve outcomes in high-risk patients are under way.

   The German Hodgkin's Study Group also reported encouraging results of a more intense regimen, dose-escalated BEACOPP [bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine, procarbazine, and prednisone] for patients with advanced-stage HD (Table 15.2). In a randomized trial, dose-escalated BEACOPP resulted in a 2-year FFS rate of 89% compared with 70% for standard COPP/ABVD chemotherapy. Compared with ABVD, dose-escalated BEACOPP results in sterility in nearly all patients and is associated with a higher incidence of secondary acute leukemia. These added toxicities may be acceptable in the highest risk patients if improved cure rates can be confirmed.

4. **Lymphocyte-predominant Hodgkin disease.** Nodular LPHD is characterized by its indolent nature and favorable prognosis with 5- and 10-year OS rates of approximately 88% and 80%, respectively. Although nearly 20% of patients with LPHD eventually relapse, the prognosis after recurrence does not change greatly, with nearly 80% and 70% OS rates at 5 and 10 years, respectively. At least half of all deaths in patients with LPHD are potentially treatment related, primarily cardiac disease and second malignancies. Unlike classic HD, LPHD does not have a contiguous pattern of spread. This, in combination with long-term complications, rules out any role for extended-field or even “regional” (involved field plus contiguous sites) RT in this disease. Most physicians currently recommend IFRT alone for treatment of early-stage LPHD. Because most patients are first seen with stage I disease in the neck, axilla, or groin, exposure of normal tissues would be quite limited with IFRT. Treatment for the rare patient with stage III to IV disease continues to be ABVD chemotherapy.
5. **Recurrent Hodgkin disease.** All patients younger than 70 years who relapse after chemotherapy or combined-modality therapy should be considered for autologous hematopoietic cell transplant (HCT). Initially patients should receive one of several effective salvage regimens for two to four cycles to reduce tumor burden. Non–cross-resistant regimens such as ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin) and ICE (ifosfamide, cisplatin, etoposide) are most commonly used, with response rates of 73% to 88% in relapsed HD. Those patients who respond to salvage chemotherapy have a better prognosis with HCT, but even nonresponders should be considered for high-dose therapy. In contrast to NHL, several studies have shown that at least 20% to 30% of patients with chemorefractory HD will achieve long-term remission with HCT.

   Overall, high-dose chemotherapy with HCT is associated with PFS rates of 50%. Salvage therapy is most likely to be successful in patients whose initial remission is longer than 12 months, whose relapse is confined to limited sites, and who are without constitutional symptoms. Minimal disease before transplant, complete remission duration more than 12 months, no bone marrow or pulmonary involvement at relapse, and no B symptoms at relapse all predict improved outcome with transplant. The best approach for patients with favorable early-stage disease, treated with chemotherapy alone, who relapse in initial sites of disease still must be determined. Radiotherapy or standard-dose salvage chemotherapy followed by RT may be adequate.

   Patients who are ineligible for HCT or relapse after transplant are candidates for investigational drugs. Palliation for months or years is often possible with sequential use of single-agent chemotherapy after failure of HCT, especially in those relapsing more than 6 months after transplant. Vinblastine, chlorambucil, oral etoposide, and newer agents, such as vinorelbine and gemcitabine, have all shown activity in this setting.

D. **Complications**

1. **Acute complications of therapy.** ABVD chemotherapy can cause nausea, vomiting, pulmonary toxicity, fever, neutropenia, peripheral neuropathy (secondary to vinca alkaloids), hair loss, occasionally chemical phlebitis related to DTIC, and very rarely acute cardiac toxicity due to doxorubicin. All cycles require premedication with a serotonin antagonist, antiemetic, and dexamethasone. Central venous access for drug administration is occasionally needed because of marked pain during DTIC infusion through a peripheral vein. Bleomycin can cause acute lung injury, manifested by shortness of breath and a cough. A CXR and pulmonary-function tests should be obtained for any pulmonary symptoms developing while receiving therapy. Bleomycin should be discontinued immediately if there are new pulmonary parenchymal abnormalities or a significant decrease in the carbon dioxide diffusion in the lung (DLCO). Severe or life-threatening infections are rare with ABVD, occurring in approximately 2% of patients. Consequently, there is no role for prophylactic growth factors with this regimen. A significant minority of patients will have dose delays due to inadequate counts on day 1 of each cycle. Use of growth factors in this setting to maintain dose intensity is common practice, but not of proven clinical benefit. Acute toxicities related to RT usually include mild esophagitis, dry mouth, nausea if abdominal field is radiated, fatigue, and occasionally radiation pneumonitis occurring 2 to 6 months after treatment.
2. **Late complications of therapy.** As described in the treatment section of this chapter, the devastating late complications of HD therapy, including second cancers and life-threatening cardiovascular disease, have led to reconsideration of our approach to this disease. After 15 years, the actuarial risk of death from other causes surpasses deaths due to HD (*Ann Oncol* 1997;8:115–118). Most series attribute the majority of excess deaths after treatment for HD to long-term effects of radiation. Currently, there are limited data on both the long-term effects of chemotherapy alone and the dose effect of radiation. These studies will be essential for evaluating new approaches to HD.

   The elimination of MOPP-like drugs from most HD-treatment regimens has dramatically decreased the incidence of treatment-related acute leukemia. Second solid tumors generally have a long latent period and continue to increase more than 30 years after therapy. Examples of the approximate relative risk (RR) of developing second solid cancers after treatment for HD include lung (10.3), breast (4.1), malignant melanoma (11.6), soft tissue sarcoma (24.3), salivary gland (37.9), and thyroid (10.6). An increase in nearly every solid tumor has been reported. The RR of breast cancer is highly dependent on the patient's age at the time of treatment, with a 40-fold increased risk in women treated before the age of 20 and only a slightly elevated risk for those older than 30 years at the time of treatment. The RR of lung cancer increases with higher doses of radiation to the lung. Importantly, there also appears to be a multiplicative effect between the carcinogenic effects of smoking and radiation (*J Natl Cancer Instit* 1995;87:1530–1537).

   Cardiac disease has been responsible for approximately 20% of deaths from causes other than HD itself. After mediastinal RT, there is a more than threefold increase in the risk of cardiac death compared with that in a control population. The majority of deaths are due to myocardial infarction, and the remainder are from congestive heart failure, pericarditis, cardiomyopathy, or valvular heart disease. Of note, the RR of cardiac deaths appears to decrease substantially when mediastinal RT doses are 30 Gy or less. Modern treatment techniques including lower doses per fraction, restricted doses to the whole heart, and delivery of RT equally from back and front should substantially decrease the risk of cardiac complications, but further follow-up is needed.

   Thyroid diseases are common after neck irradiation, with an actuarial risk of 67% at 26 years after therapy (*N Engl J Med* 1991;325:599–605). In most of these patients, hypothyroidism develops, but the risk of Graves disease is 7 to 20 times that for normal subjects. Infertility is uncommon with modern chemotherapy and the near-complete elimination of pelvic RT.

3. **Complications of the disease.** Significant or life-threatening complications of HD are infrequent at diagnosis. Problems related to bulky mediastinal disease are most common, including cough, dyspnea, pleural effusion, and rarely SVC syndrome. Symptoms resolve rapidly after initiation of therapy. Paraneoplastic syndromes are rare and include case reports of nephropathy, cerebellar degeneration, limbic encephalopathy, opsoclonus–myoclonus, intrahepatic cholestasis, hypercalcemia, and immune thrombocytopenia. Paraneoplastic manifestations have been reported months or years before the diagnosis of HD and in many cases do not resolve, despite successful treatment of the underlying disease. HD also is associated with a poorly understood decrease in cell-mediated immunity. Patients with advanced disease exhibit lymphopenia and a depressed $CD4^+/CD8^+$ ratio. Uncommonly, patients with HD experience opportunistic infections including *Listeria* sp., mycobacteria, herpes zoster, and cytomegalovirus. The decreased $CD4^+/CD8^+$ ratio is exacerbated by therapy and is slow to recover.

E. **Follow-up**

The goals of follow-up are to provide reassurance to the patient, detect recurrent HD, and monitor for long-term complications of therapy. Anxiety and depression, often related to fear of recurrence, are common in the early follow-up period. Individual counseling, support groups, and occasionally short-term use of antidepressants may be needed.

Seventy percent of all relapses occur within the first 2 years after therapy, and fewer than 10% occur after 5 years. History and physical examination alone detect 70% to 80% of all recurrences, with at least half of these identified at appointments arranged by the patient for evaluation of symptoms, not at routine follow-up (*BMJ* 1997;314:343–346). Common practice is to perform a history and physical every 3 to 4 months for the first 2 years, and then every 4 to 6 months for the following 3 years. A routine annual CXR for the first 3 years detects most of the remainder of the asymptomatic recurrences (*J Clin Oncol* 1997;15:1123–1130). Additional routine laboratory tests and radiographs rarely detect asymptomatic recurrences. An annual thyroid-stimulating hormone (TSH) test should be done in all patients who received mediastinal or neck irradiation. The cost-effectiveness of routine CT scans has never been evaluated. Scans should probably not be performed any more often than annually for the first 2 years after therapy, if at all, and only for evaluation of symptoms thereafter. After 5 years, a history and physical examination should be obtained annually to screen for late complications; follow-up with either an oncologist or a primary care physician is appropriate at this time.

Greater emphasis should be placed on patient education, rather than on routine follow-up testing. Patients should be familiar with symptoms and patterns of relapse, as well as the signs and symptoms of late complications, including thyroid disease, second cancers, and cardiac disease. Education about the need to minimize sun exposure, avoid smoking, and reduce cardiovascular risk factors is essential. Women who received mediastinal or axillary irradiation should be encouraged to do breast self-examinations, and annual mammograms should be initiated 5 to 8 years after completion of treatment.

F. **Background**

1. **Epidemiology and risk factors.** Approximately 7,500 cases of HD are diagnosed annually in the United States. HD has a bimodal age distribution in

developed countries, with the first peak occurring in the third decade of life and the second peak occurring after age 50 years. Men have a slightly higher incidence than women. There is an association between HD and factors that decrease exposure to infectious agents at an early age, including advanced maternal education, early birth order, decreased number of siblings, and living in a single-family residence. A history of infectious mononucleosis increases the risk of HD two- to threefold and suggests the Epstein–Barr virus (EBV) as an etiologic agent. Although nearly 50% of patients with HD have detectable EBV DNA in the HRS cells, there is no direct evidence of a causative role. There is a slightly increased risk of HD in patients infected with HIV, but not in other conditions associated with chronic immunosuppression. An increased incidence among first-degree relatives, a significant concordance rate among identical, but not fraternal twins, and linkage with certain HLA types suggest a genetic predisposition for HD.

2. **Molecular biology.** The amplification and analysis of genes of single HRS cells has provided overwhelming evidence that at least 95% of HD cases represent monoclonal B-cell disorders. Clonal immunoglobulin gene rearrangements are present in the HRS cells of both classic HD and LPHD.
3. **Genetics.** Cytogenetic analysis in lymph nodes involved by HD is limited because of the low number of obtainable mitoses from lymph node suspensions and the inability to attribute abnormalities to the malignant cells. A specific chromosomal marker of HD has not been identified, but a variety of numeric and structural abnormalities have been found in approximately half of HD cases analyzed.

G. **Current focus**

1. **Ongoing research efforts include:**
   - Tailoring treatments based on prognostic factors, with identification of the minimal effective treatment for the most favorable patients and the role of dose intensity in high-risk patients.
   - Development of better prognostic models that incorporate potential biologic markers of HD such as soluble CD30 levels, soluble IL-2 receptors, IL-10 levels, adhesion molecules, CD44, and EBV.
   - Continued molecular studies to identify the pathogenesis of HD.
   - Effective ways to incorporate new active agents such as vinorelbine and gemcitabine into the treatment of HD.

II. Non-Hodgkin Lymphoma

A. **Presentation**

1. **Subjective.** Presenting symptoms of non-Hodgkin lymphomas (NHLs) vary substantially depending on the pathologic subtype of NHL and the site(s) of disease. Indolent lymphomas such as follicle center cell (FCC) or small lymphocytic lymphomas usually have painless peripheral adenopathy or occasionally present with abdominal pain, bloating, or back pain related to bulky mesenteric or retroperitoneal adenopathy. Because spontaneous regressions occur in up to 20% of patients with FCC, the patient may describe a history of waxing and waning adenopathy. Most patients with indolent lymphoma feel well at presentation, and B symptoms, including fevers, drenching night sweats, and weight loss, are unusual. MALT (mucosa-associated lymphoid tissue) lymphomas, indolent lymphomas occurring in extranodal sites, most commonly stomach and lung, usually have mild symptoms referable to the site of involvement. Indolent lymphomas are uncommon before age 50 years.

   Many aggressive lymphomas, the most common being diffuse large cell (DLC) lymphomas, also often occur as painless, peripheral adenopathy without other associated symptoms. Fevers, night sweats, or weight loss occur in about 20% of patients with advanced-stage disease. Bulky retroperitoneal nodes are common and may be asymptomatic or associated with mild abdominal pain, bloating, or back pain. Mediastinal adenopathy occurs in only a minority of patients, usually young women with DLC lymphoma with sclerosis, and can occur with cough, dyspnea, chest pain, or rarely, SVC syndrome.

   Primary extranodal large cell lymphomas are common, accounting for 15% to 20% of all large cell lymphomas. These varied extranodal presentations expand the presenting symptoms of lymphoma so dramatically that NHL should remain in the differential diagnosis of a mass in any organ until pathology is confirmed. Approximately half of the extranodal lymphomas occur in the gastrointestinal tract, including stomach, bowel, tonsils, nasopharynx, and oropharynx. Other sites include bone, testis, thyroid, skin, orbit, salivary glands, sinuses, liver, kidney, lung, and central nervous system (CNS).

   The very aggressive lymphomas, lymphoblastic and small noncleaved (SNC; Burkitt and non-Burkitt), are rare in the adult population, but can occur with acute symptoms and can be life threatening without rapid intervention. In adults, lymphoblastic lymphomas occur most commonly in young men, and frequently occur with acute respiratory compromise due to bulky mediastinal adenopathy, and pleural or pericardial effusions. Burkitt lymphomas often occur with abdominal pain and occasionally bowel obstruction related to bulky abdominal adenopathy and intestinal involvement.

   Patients with HIV-associated lymphomas (usually DLC or Burkitt subtypes) often have advanced disease, B symptoms, and involvement of liver, bone marrow, or CNS. A unique presentation of HIV-associated lymphomas is primary effusion, or body cavity–based lymphomas, which are characterized by the presence of NHL along serous membranes in the absence of identifiable tumor masses and with ascites or pleural effusions.

   Less common subtypes of NHL often have a unique clinical presentation. Examples include, but are not limited to, mycosis fungoides, a primary cutaneous T-cell NHL characterized by pruritic patches and plaques; mantle cell lymphomas, seen most often in older men with marked hepatosplenomegaly; and primary splenic lymphoma with villous lymphocytes seen as isolated splenomegaly.

2. **Objective.** Despite the availability of CT scans, physical examination with accurate documentation of the size and location of all enlarged lymph nodes, tonsillar enlargement, hepatosplenomegaly, and skin involvement is important at the time of initial diagnosis in patients with NHL. Comparable physical examinations during and after therapy will allow evaluation of ongoing response without the need for frequent scans. Patients with active, indolent lymphomas are often observed without therapy at diagnosis. Regular repeated physical examinations are essential to allow intervention before significant symptoms develop. A thorough neurologic examination should be performed in all patients with lymphoblastic or SNC lymphoma, looking for subtle signs of CNS involvement. Most patients with lymphoblastic or SNC NHL receive prophylactic intrathecal therapy, but active involvement of the cerebrospinal fluid, meninges, or brain parenchyma would require a more intensive approach to the CNS.

B. **Work-up and staging**

An adequate tissue biopsy is critical to the evaluation and treatment of all patients with NHL. The most recent WHO classification includes 30 subtypes of NHL, 15 B-cell neoplasms (representing 80% to 90% of cases) and 15 T-cell neoplasms, many of which have a unique natural history (Table 15.3). Optimal therapy requires accurate subclassification. Historically, diagnosis and subclassification required an excisional lymph node biopsy or alternatively a surgical biopsy of an extranodal site. Although this is still the preferred approach, accurate diagnosis by needle biopsy is now a realistic possibility in some cases of NHL, for example, small lymphocytic lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, and occasionally DLC lymphomas. Lymphomas with a unique immunophenotype are those most likely to be diagnosed accurately with limited material. In patients without easily accessible tissue, it is reasonable to start with a radiographically guided needle biopsy.

TABLE 15.3. PROPOSED WORLD HEALTH ORGANIZATION CLASSIFICATION FOR NHL

Immunohistochemistry (IHC), now routinely performed in most new cases of NHL, is often necessary for accurate subclassification. Common examples include the differentiation of small lymphocytic lymphoma ($CD5^+$, $CD23^+$) and mantle cell NHL ($CD5^+$, $CD23^-$), identification of peripheral T-cell lymphomas with aberrant expression of one or more of the T-cell markers CD3, CD4, CD5, CD7, and CD8, and verification of lymphoblastic lymphoma with TdT stains. Even with the aid of IHC, peripheral T-cell lymphomas can be difficult to diagnose because many have a histologic appearance similar to that of a benign, reactive lymph node and do not have a unique immunophenotype. Biopsies on patients in which the clinical history is suggestive of lymphoma, but initial

histologic review, as well as IHC by flow cytometry or on paraffin-embedded tissue sections is nondiagnostic, should be tested for T-cell receptor and immunoglobulin heavy-chain gene rearrangements. Cases in which the pathologic diagnosis seems inconsistent with the clinical history should be reviewed by an expert hematopathologist.

Additional workup after a diagnostic biopsy includes a history and physical examination with documentation of adenopathy, hepatosplenomegaly, performance status, the presence of B symptoms, laboratory evaluations, radiographic studies, and in most cases, a bone marrow biopsy. Necessary laboratory tests include a CBC, liver-function tests, calcium, creatinine, and LDH. Cytopenias usually signify bone marrow involvement or less commonly hypersplenism. LDH is an important prognostic factor in the International Prognostics Factor Index (*N Engl J Med* 1993;329:987–994), and patients with an elevated LDH may be eligible for more aggressive or experimental therapies.

The Ann Arbor staging system, initially developed for HD, also is used to stage NHL (Table 15.1). Alternative staging systems have been proposed but never adopted. Proper staging requires CT scans of the chest, abdomen, and pelvis, as well as bilateral bone marrow biopsies. Marrow evaluation is not always necessary in asymptomatic, older patients with indolent lymphomas, if a CBC is normal, as the findings are unlikely to alter management of the disease. Patients with lymphoblastic or SNC NHL should have a lumbar puncture. If Waldeyer ring is involved, an upper gastrointestinal (GI) or upper endoscopy should be considered, given the increased incidence of gastric involvement in these patients.

Some investigators recommend a baseline gallium scan in patients with large cell lymphoma to interpret more accurately interim and posttreatment gallium scans. Despite strong evidence that interim and posttreatment gallium scans conferred important prognostic information, this approach was never adopted outside a few specialized centers. PET scans, both as initial staging and to evaluate residual radiographic abnormalities, have supplanted the use of gallium scans in institutions where available. Although they are more sensitive than gallium scans, results should be interpreted with caution because of lack of specificity. As initial staging, they are most useful in patients with equivocal CT findings and in patients who appear to have localized disease at presentation, where finding additional sites of involvement could potentially alter management.

C. **Therapy and prognosis**

1. **Indolent lymphomas.** With the possible exception of a small subset of patients with localized disease, indolent lymphomas are not curable with standard therapies. The disease responds well to both chemotherapy and RT, with 50% to 90% of patients achieving a good partial or complete remission with their first course of treatment. However, recurrence is the rule, and most patients eventually die of their disease. Median survival is 8 to 10 years. Newer biologic therapies, many of which have little or no toxicity, have expanded the number of effective treatments available for this disease, but again do not appear to be curative.

   a. **Stages I or II.** Given the improved sensitivity of staging studies including CT scans, PET scans, and perhaps the use of flow cytometry to evaluate bone marrow specimens, the diagnosis of limited-stage indolent lymphoma is rare. IFRT remains the principal approach for patients with limited-stage disease. Reported relapse-free survival (RFS) rates after RT of 47% at 10 years and 37% at 20 years imply that this therapy may be curative in a subset of patients with localized disease (*J Clin Oncol* 1996;14:1282–1290). Of note, many of the 177 patients in this series received total lymphoid or extended-field RT; however, current practice usually limits RT to an involved field. Another retrospective study reported a 10-year RFS rate of 73% in 91 patients with stage I to II indolent lymphoma treated with combination chemotherapy followed by IFRT (*Ann Oncol* 1996;7:157–163). Observation also may be appropriate for patients older than 70 years with localized indolent lymphoma.

      Gastric MALT lymphoma, an unusual indolent lymphoma, nearly always is seen with early-stage disease. MALT lymphomas appear to occur as a direct result of antigenic stimulation from *Helicobacter pylori* infection. Interestingly, the majority of patients with gastric MALT lymphoma will have complete regression of disease with appropriate therapy for *H. pylori,* including antibiotics and proton-pump inhibitors (*J Natl Cancer Inst* 1997;89:1350–1355). Longer-term follow-up is needed to determine the durability of these remissions. For the subset of patients who do not respond to or relapse after *H. pylori* therapy, or are *H. pylori* negative, results with IFRT are excellent, with one series of 17 patients reporting a 100% event-free survival (EFS) at a median follow-up of 2 years (*J Clin Oncol* 1998;15:1110–1117). Transformation to an aggressive, large cell lymphoma occurs in a minority of patients, but can be resistant to therapy.

   b. **Stage III or IV disease.** No initial therapy, often referred to as a “watch and wait” approach, remains appropriate for many asymptomatic patients because of the indolent nature of most low-grade lymphomas and our inability to cure advanced-stage disease with standard therapies. Despite many effective but noncurative therapies, there has never been any evidence that early intervention improves overall survival in asymptomatic patients. When treatment is indicated, several active agents exist as potential first-line therapies.

      Alkylating agents such as cyclophosphamide or chlorambucil are highly active and can be used as single agents or in combination with vincristine and prednisone (CVP) or doxorubicin, vincristine, and prednisone (CHOP). Although responses are more rapid with combination chemotherapy, large randomized trials have never shown a difference in overall response or survival rates with combination therapy, or a benefit to the addition of anthracyclines as first-line therapy.

      The purine analogues, fludarabine and 2-chlorodeoxyadenosine (2-CDA, cladribine), have excellent single-agent activity in indolent lymphomas with reported response rates of 65% to 88% in previously untreated patients; however, median remission durations are short at 10 to 13 months. Combinations of fludarabine with mitoxantrone ± dexamethasone (*J Clin Oncol* 1996;14:1262–1268) and fludarabine with cyclophosphamide (*J Clin Oncol* 1999;18:987–994) have high reported response rates and longer remission durations. However, significant hematologic and infectious complications have been reported with the fludarabine and cyclophosphamide combinations and should be used with caution. Purine analogues result in a marked reduction in the CD4 count, often lasting 12 or more months and increasing the risk of opportunistic infection, particularly *Pneumocystis carinii* pneumonia and herpes zoster. Trimethoprim–sulfamethoxazole prophylaxis should be considered during purine analogue therapy and for 6 to 12 months after discontinuation of treatment.

      Rituximab, a chimeric anti-CD20 antibody specific for B lymphocytes, became the first monoclonal antibody (mAb) approved by the Food and Drug Administration (FDA) for cancer therapy. Patients with relapsed follicular lymphomas have response rates of 50% with rituximab, with a median remission duration of 10 to 12 months. In contrast, response rates of relapsed small lymphocytic lymphoma (SLL) are less than 20% at standard doses. Preliminary data in patients with SLL show modestly improved response rates (a) with eight weekly doses instead of four, (b) with higher doses, and (c) in previously untreated SLL. Toxicities of rituximab are mild and are limited primarily to infusion-related reactions such as fevers, chills, myalgias, transient hypotension, and rarely bronchospasm.

      In vitro studies demonstrated that the anti-CD20 antibody potentiates the sensitivity of lymphoma cells lines to several chemotherapeutic agents. Based on these data and encouraging preliminary results of phase II studies of CHOP plus rituximab and fludarabine plus rituximab, phase III randomized clinical trials are under way to determine whether rituximab plus chemotherapy is superior to chemotherapy alone as first-line treatment for follicular lymphomas. Studies of mAbs conjugated with radioisotopes also yielded promising results. Response rates of approximately 80% have been reported with both the [^{131}I]-anti-CD20 mAb, Bexxar, and the [yttrium-90]-anti-CD20 mAb, Zevalin. Side effects are modest and self-limited. Although they are not curative, both rituximab and the radiolabeled mAbs represent important advances in the treatment of low-grade NHL with impressive response rates, even in chemotherapy-refractory patients, and have a very favorable toxicity profile.

      Interferon (IFN) has been studied extensively in the treatment of NHL. There is modest single-agent activity, but most trials have tested the benefit of IFN either concurrent with chemotherapy or as consolidation after chemotherapy. IFN may prolong remission duration, but most studies show no survival advantage with the addition of IFN. Interestingly, both of the only two randomized studies to show a survival advantage with IFN included concurrent administration of IFN and an anthracycline-containing chemotherapy regimen. For example, the Groupe d'Etude des Lymphomes Folliculaires reported a 5-year OS rate of 56% for the CHVP (cyclophosphamide, doxorubicin, VM-26, and prednisone) arm compared with 71% for the CHVP + IFN arm (*J Clin Oncol* 1998;16:2232–2338). Despite current FDA approval for IFN-a2b in previously untreated patients with clinically aggressive follicular NHL in conjunction with an anthracycline-containing chemotherapy regimen, it has not become the standard of care for treating symptomatic indolent lymphoma. This may result from the myriad negative IFN trials previously published, as well as the significant toxicities associated with IFN. Encouraging results with longer follow-up may lead to reexamination of treatment approaches and perhaps incorporation of IFN into the standard therapy of high-risk patients with indolent NHL.

   c. **Relapsed disease.** Multiple effective options are available for recurrent indolent lymphoma. If the first remission lasted longer than 1 to 2 years, patients often respond to the same regimen given as first-line therapy. However, remission durations are usually shorter with each subsequent

treatment. All of the agents described earlier have activity in relapsed disease. In patients younger than 70 years who relapse less than 1 year after initial treatment, or have evidence of transformation to an aggressive lymphoma, high-dose therapy with peripheral blood stem cell rescue should be considered. Most studies of autologous stem cell transplantation for relapsed indolent lymphoma show improved remission duration compared with historical controls, but no survival advantage. Small series evaluating allogeneic transplant for patients with refractory disease show encouraging results, but treatment-related mortality rates as high as 30% in the first year limit the use of this approach.

2. **Aggressive non–Hodgkin lymphoma**

Large cell, SNC, and lymphoblastic lymphomas compose the majority of aggressive lymphomas. Standard approaches and prognosis vary for these three subtypes of lymphoma and are addressed separately.

a. **Stage I to II large cell lymphoma.** Two large, prospective, randomized trials confirmed both a DFS and OS advantage when IFRT is added to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy in patients with limited-stage large cell lymphoma. The 5-year PFS and OS rates for patients treated with three cycles of CHOP plus IFRT were 77% and 82%, respectively, compared with 64% and 72%, respectively, for eight cycles of CHOP alone (*N Engl J Med* 1993;328:1002–1006). Similar results were seen when eight cycles of CHOP was compared with eight cycles of CHOP plus IFRT. Based on these results, three cycles of CHOP chemotherapy plus IFRT is the standard of care for patients with stage I or II large cell NHL.

   Several small retrospective studies have shown a potential advantage to the 12-week chemotherapy regimen, VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisone) followed by IFRT, compared with CHOP plus IFRT in the small subset of patients with stage I or II primary mediastinal large B-cell lymphoma with sclerosis. Because of the rarity of this disease, these treatments will not be compared in a randomized, prospective trial. VACOP-B plus IFRT and CHOP plus IFRT are both reasonable choices for these primary mediastinal large cell lymphomas.

b. **Stage III or IV large cell lymphoma.** Six to eight cycles of CHOP chemotherapy has been the standard of care for treating advanced-stage large cell lymphoma for nearly 30 years. Many alternative regimens adding non–cross-resistant agents and increasing dose intensity have been tested and demonstrate no advantage over standard-dose CHOP (*N Engl J Med* 1993;328:1002–1006, *Cancer* 2001;92:207–217). Conflicting results have been reported for high-dose therapy with autologous stem cell rescue as first-line therapy for patients with high-risk large cell lymphoma. A large randomized trial comparing CHOP chemotherapy with CHOP chemotherapy followed by consolidative autologous stem cell transplant is ongoing.

   Preliminary results of a large randomized trial comparing CHOP with CHOP plus the anti-CD20 mAb rituximab in patients older than 60 years showed a significant improvement in 2-year event-free (38% vs. 57%) and OS (57% and 70%) rates with the addition of rituximab (*N Engl J Med* 2002;346:235). Results of a second randomized trial comparing CHOP with CHOP plus rituximab are not yet available. Pending these results, CHOP plus rituximab is considered the standard of care for stage III to IV large cell lymphoma by most oncologists.

   In addition to systemic chemotherapy, the use of prophylactic intrathecal therapy should be considered for patients with testicular, orbital, epidural, paranasal sinus, or extensive bone marrow involvement. These presentations are known to carry an increased risk of CNS relapse, usually meningeal. Despite this increased risk of CNS disease, the benefits of intrathecal therapy are not proven. Specialized protocols using high-dose methotrexate and cytosine arabinoside (ara-C) should be used for patients with primary CNS lymphoma (*J Clin Oncol* 2000;18:3144–3150).

   The International Prognostic Index (IPI) and age-adjusted IPI help predict prognosis for individual patients with advanced-stage large cell lymphoma (*N Engl J Med* 1993;329:987–994). The presence or absence of five independent poor prognostic features (age older than 60 years, stage III or IV disease, more than one extranodal site, performance status 2 or more, and elevated serum LDH) effectively predicts an individual's risk of relapse and death from lymphoma after standard chemotherapy. Based on the IPI, patients with none to one risk factors have a 73% OS compared with 26% for those with four to five factors. The IPI index is useful in stratifying patients for prospective studies, adapting treatment choices, and defining uniform eligibility criteria across studies.

c. **Small noncleaved lymphoma.** SNC lymphomas, including those classified as Burkitt and non-Burkitt, have a poor prognosis with standard CHOP chemotherapy, and several specialized centers have developed more aggressive chemotherapy regimens. All stages of disease are approached similarly, although patients with stage I or II disease, who also have a normal LDH and a good performance status, have an excellent prognosis, and standard-dose therapies, such as those used for large cell lymphoma, may be appropriate for this small subset of patients. For all other patients, short-duration intensive therapies are indicated. Most current protocols prescribe four to six cycles of chemotherapy including intensive doses of alkylating agents such as cyclophosphamide or ifosfamide, vincristine, anthracyclines, and high-dose methotrexate alternating with high dose ara-C and etoposide (*J Clin Oncol* 1996;14:925–934). Two-year EFS rates of 50% to 90% are reported with this approach. CNS prophylaxis with intrathecal methotrexate and ara-C is an essential component of therapy. Prophylactic cranial irradiation has been associated with significant intellectual impairment and is not recommended. Patients with an elevated LDH and bulky disease should be treated with allopurinol and vigorous hydration during initiation of therapy to minimize the risk of tumor lysis.
d. **Lymphoblastic lymphoma.** Treatment for this rare, highly aggressive lymphoma must include intensive combination chemotherapy and CNS prophylaxis. Most centers now use therapies modeled after acute lymphoblastic leukemia (ALL) regimens including induction, consolidation, and maintenance with total treatment duration of 3 years. Five-year survival rates with this approach are approximately 50%.
e. **Mantle cell lymphoma.** There is no standard approach to the treatment of mantle cell lymphoma (MCL). Conventional-dose chemotherapy results in response rates of 50% or less, with median survivals of approximately 3 years and no long-term survivors. Rituximab has minimal single-agent activity in MCL and the addition of Rituximab to CHOP chemotherapy does not appear to improve survivals compared with those seen with chemotherapy alone. Encouraging results have been reported by investigators at the MD Anderson Cancer Center with an approach initially developed for ALL, including hyperCVAD (high-dose cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and ara-C, followed by stem cell transplant for patients younger than 65 years (*J Clin Oncol* 1998;16:3803–3809). However, MCL occurs most often in patients older than 60 years, so dose-intense approaches such as these may have limited utility.
f. **Human immunodeficiency virus–associated lymphoma.** Most patients with HIV-lymphoma continue to present with advanced-stage disease and low CD4 counts, putting them at significant risk of infection during therapy. Treatment approaches have changed with the recent advent of highly active antiretroviral therapy (HAART). Previously, most clinicians favored low-dose chemotherapy because studies comparing low-dose and standard-dose therapy showed similar response and survival rates and more toxicity with standard-dose therapy. However, a more recent study in which all patients received HAART, in addition to chemotherapy, showed a lower response rate (30% vs. 48%) and no difference in toxicity for low-dose chemotherapy compared with standard-dose chemotherapy with granulocyte–colony-stimulating factor (*J Clin Oncol* 2001;19:2171–2178). CNS prophylaxis should be considered in all patients. Studies adding rituximab to standard chemotherapy are ongoing.
g. **Relapsed disease.** Patients younger than 70 years without significant concurrent illnesses should be considered for high-dose therapy and autologous or allogeneic stem cell transplantation at relapse. Several effective salvage regimens are available as cytoreduction before transplant, including most commonly ICE (ifosfamide, carboplatin, and etoposide) or ESHAP [etoposide, methylprednisolone (Solu-Medrol), high-dose ara-C, cisplatin]. In patients with chemosensitive relapse, the 5-year DFS rate after transplant is approximately 40%, whereas in patients with refractory relapse; it is less than 10%. Allogeneic stem cell transplant should be considered for patients with a remission duration less than 1 year after initial therapy, refractory disease at relapse, and all patients with relapsed small noncleaved or lymphoblastic lymphoma.

D. **Complications**

1. **Therapy related.** Most first-line therapies for indolent lymphomas are well tolerated, with minimal risk of severe toxicity. Oral alkylating agents rarely cause hair loss, nausea, or significant cytopenias. Purine analogues also are not associated with hair loss or nausea, but can cause significant myelosuppression, a marked reduction in CD4 counts, and an increased risk of opportunistic infections. Rare cases of hemolytic anemia and immune thrombocytopenia have been reported with fludarabine. Most patients experience moderate to severe infusion-related symptoms, including fevers, chills, dyspnea, and hypotension, during administration of the first dose of rituximab. These side effects are uncommon with subsequent doses.

   Potential complications of CHOP chemotherapy include hair loss, a moderate risk of fever and neutropenia, minimal nausea and vomiting if serotonin-antagonist antiemetics are used, peripheral neuropathy secondary to vinca alkaloids, cardiomyopathy related to anthracyclines, and rarely hemorrhagic cystitis related to cyclophosphamide. Prophylactic growth factors are rarely indicated with the CHOP regimen.

   First-line regimens for SNC and lymphoblastic lymphomas, as well as most salvage regimens for relapsed aggressive NHL, have significant toxicities associated with them, most commonly severe pancytopenias and increased risk of life-threatening infection. Prophylactic growth factors should be used

with these regimens. Renal insufficiency and mucositis occur frequently with regimens containing high-dose methotrexate. Cerebellar toxicity, somnolence, and rarely coma are reported with high-dose ara-C, particularly in older patients. These regimens should usually be administered in a hospital setting with close monitoring of electrolytes, creatinine, and fluid balance.

Patients with advanced-stage SNC or lymphoblastic lymphoma are at significant risk of acute tumor lysis during initiation of therapy. Patients with an elevated LDH or creatinine are at greatest risk. Complications of tumor lysis include hyperkalemia, hyperphosphatemia, hyperuricemia, renal failure, hypocalcemia, and death. Vigorous intravenous hydration (250 to 500 mL/hour) should be given for 2 to 3 days. Bicarbonate should be avoided. Whereas urinary alkalinization improves uric acid excretion, systemic alkalinity increases the chance of hypocalcemia, potentially resulting in tetany and cardiac arrhythmias. Allopurinol should be given before initiation of chemotherapy and continued for 10 to 14 days. If a high urine flow cannot be maintained, urgent hemodialysis may be necessary to treat and prevent life-threatening biochemical abnormalities.

Therapy-related myelodysplastic syndromes and secondary AML are rare but devastating late complications of therapy for NHL. These complications can occur in patients with indolent lymphomas as a consequence of years of intermittent alkylator therapy. There also is an increased risk of MDS/AML after stem cell transplantation, with as many as 12% of patients developing this complication, a median of 4 years after transplant. Most have complex karyotypes with deletions in chromosomes 5 and 7. The prognosis is dismal.

2. **Disease related.** Most patients with indolent lymphomas are asymptomatic at presentation and have no significant complications of the disease until the terminal stages. Occasionally, lymphedema related to pelvic adenopathy or hydronephrosis related to retroperitoneal adenopathy can require urgent therapy. Both radiotherapy and chemotherapy are effective modalities in this setting.

   Patients with aggressive histologies occasionally have serious disease-related complications, particularly those with SNC or lymphoblastic histologies. Such complications include airway obstruction secondary to paratracheal adenopathy, cardiac tamponade, paraplegia secondary to spinal cord compression, gastrointestinal bleeding, bowel obstruction or perforation, SVC syndrome, ureteral obstruction, cranial neuropathies, or radiculopathies related to meningeal involvement, and very rarely hypercalcemia or uric acid nephropathy. When these complications occur at initial presentation or first relapse, rapid initiation of chemotherapy is imperative. In patients with late-stage or refractory disease, these complications are often fatal, and supportive care is appropriate.

E. **Follow-up**

The goals of follow-up are to provide reassurance to the patient, to detect recurrent or progressive NHL, and to monitor for long-term complications of therapy. Anxiety and depression, often related to fear of recurrence, are common in the early follow-up period. Individual counseling, support groups, and occasionally short-term use of antidepressants may be needed.

As described earlier, asymptomatic patients with indolent lymphoma are often observed without therapy. Appropriate follow-up for these patients includes a history and physical examination every 3 to 4 months, and a CBC, LDH, and creatinine levels once or twice a year. Patients with significant intraabdominal disease, but no peripheral adenopathy, need an abdominal and pelvic CT scan annually. In addition to close monitoring, educate patients to report potential symptoms of progression including new or enlarging lymph nodes, abdominal or back pain, bloating, lower extremity edema, or B symptoms. Because of the recurring nature of the disease, most patients with indolent lymphoma need life-long follow-up with an oncologist.

For patients with aggressive lymphomas who achieve remission with initial therapy, definitive recommendations regarding the optimal follow-up strategy are not available. A retrospective study of 36 patients with large cell lymphoma who relapsed after achieving a complete remission with combination chemotherapy revealed that 89% of these relapses were detected during unscheduled evaluations prompted by symptoms (*J Clin Oncol* 1991;9:1196–1203). Only three of 36 relapses were detected by routine screening procedures, two by physical examination and one by routine CT scan. All of these patients had physical examinations every 2 to 3 months the first year and every 4 to 6 months thereafter, a routine CBC and LDH at most visits, and radiographs every 3 months the first year and every 6 months the next 1 to 2 years. The majority of aggressive NHL recurrences happen in the first 2 years after treatment, and rarely after 5 years. Sites of recurrence include at least one previously involved site in 75% of cases and only new sites in 25% of cases. A reasonable approach to follow-up of these patients might include a history and physical examination every 3 months for 2 years and every 6 months for the next 3 years, with a CBC and LDH at each visit. Scans should probably not be performed more than annually for the first 2 years, and only to evaluate new symptoms during years 3 to 5. Routine CT scans might not be indicated at all for patients at low risk for recurrence, including those with no high-risk features at diagnosis.

F. **Background**

1. **Epidemiology and risk factors.** In 2002, 53,900 new cases of NHL are presented, with 24,400 deaths. Since the 1970s, the annual incidence rates have increased by 3% to 4% per year, although over the last 5 years appears to have reached a plateau. The cause for the sustained increase is incompletely understood. The HIV epidemic and the increase in NHL after solid-organ transplants account for only a minority of the new lymphomas. The incidence of NHL is slightly higher in men than women, and increases exponentially with age. The most reproducible environmental risk factors include exposure to certain pesticides or herbicides. Inconsistent associations have been reported with hair dyes, certain occupations, smoking, consuming foods high in animal fat, and receiving blood transfusions. Infectious agents, including Epstein–Barr virus, HIV, human T-cell leukemia virus (HTLV)-1, and *H. pylori* have been proposed as etiologic agents in the pathogenesis of some cases of NHL. Other factors associated with a significant increased risk of NHL include autoimmune disorders, most commonly Sjögren syndrome and rheumatoid arthritis, although it is difficult to separate the effects of immunosuppressive drugs used to treat these diseases and the underlying autoimmune disease.
2. **Molecular biology.** Tremendous advances in our understanding of the biology of lymphomas, particularly B-cell lymphomas, have occurred since 1980. Most cases of follicular lymphoma contain a t(14;18) chromosomal translocation resulting in dysregulation of the bcl-2 gene, one of many important genes thought to play a role in apoptosis. Overexpression of bcl-2 appears to inhibit cell death. Extended cell survival may increase the opportunity of cells to acquire additional genetic defects in growth and proliferation genes. Multiple additional translocations and abnormalities of gene expression have been reported in NHL and are beyond the scope of this chapter. Examples of the better-characterized abnormalities include the t(8;14) translocation in most SNC lymphomas, resulting in dysregulation of the c-*myc* oncogene, and a t(11;14) translocation in most MCLs with dysregulation of bcl-1, and overexpression of cyclin D1. The new DNA microarray technology will allow rapid evaluation of gene expression in a variety of lymphomas and perhaps provide clues to the pathogenesis of this disease (*Nature* 2000;403:503–511).
3. **Genetics.** Familial aggregations of lymphoma are uncommon but reported. The molecular basis of a predisposition for lymphoma is not known. Malignant lymphomas are part of the spectrum of Li–Fraumeni syndrome (LFS), but p53 germline mutations have not been found in familial lymphomas outside the setting of LFS.

G. **Current focus of research**

Examples of ongoing research efforts aimed at improving the therapy for NHL are listed.

1. Development of adjuvant vaccine therapies for patients with follicular lymphoma who achieve a remission with chemotherapy. A preliminary clinical trial of patient-specific vaccines showed that patients who mounted an immune response against their lymphoma-specific idiotype had a marked improvement in time to progression compared with those who did not mount a response (*Blood* 1997;89:3129–3135). Randomized trials designed to confirm these results are under way.
2. Development of additional mAbs directed at targets other than CD20. Trials of anti-CD22 and anti-1D10 mAbs are ongoing, and trials testing combinations of mAbs are planned.
3. Randomized trials to determine the efficacy of mAbs and radioimmunoconjugates in combination with standard chemotherapy compared with chemotherapy alone, and trials designed to determine how best to incorporate mAbs and radioimmunoconjugates into high-dose therapy approaches.
4. Development of new prognostic indices that build on the IPI by adding biologic factors such as the molecular classification of tumors on the basis of gene expression. For example, DNA microarray technology allowed identification of two molecularly distinct forms of diffuse large cell B-cell lymphoma, germinal center B-like DLBCL, and activated B-like DLBCL (*Nature* 2000;403:503–511). Patients with germinal center B-like DLBCL had a significantly better survival than did those with activated B-like DLBCL.

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CHAPTER 16. MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS

William Read and Ravi Vij

Multiple myeloma
Subjective
Objective
Workup and staging
Diagnosis
Staging
Treatment
Adjunct treatments
Complications
Follow-up
Natural history
Background
Research frontiers
Monoclonal gammopathy of uncertain significance/Smoldering myeloma
Solitary plasmacytoma
Subjective
Objective
Treatment
Natural history
Amyloidosis
Subjective
Objective
Workup
Therapy
Natural history
Nonamyloid monoclonal immunoglobulin deposition disease
Heavy-chain disease
Subjective
Objective
Workup and staging
Treatment
Epidemiology
Natural history
Waldenström macroglobulinemia
Subjective
Objective
Workup and staging
Therapy
Natural history
Suggested Readings

I. Multiple myeloma

A. Subjective

Multiple myeloma (MM) should be considered in the differential diagnosis of anemia, recurrent bacterial infection, renal insufficiency, or bone pain. Bone pain is a presenting complaint in 63% to 90% of cases of myeloma. Patients may have pathologic fractures of long bones or vertebral compression fractures, which can be erroneously attributed to osteoporosis. In the Mayo Clinic review of 869 cases, 68% were first seen with bone pain, and 12%, with bacterial infection (*Mayo Clinic Proc* 1975;50:29–40). Other presenting symptoms include weight loss, fatigue, or bleeding. In one third of MM patients, hypercalcemia eventually develops, which presents with nausea, constipation, dehydration, and mental-status changes.

The monoclonal protein (M protein) may itself give rise to symptoms. In amyloidosis and monoclonal immunoglobulin deposition disease (discussed later), M protein accumulates in tissues and organs, causing symptoms often more severe than those caused by the underlying plasma cell dyscrasia. Neuropathy due to M protein has been described both in the context of monoclonal gammopathies of undetermined significance (MGUS) and malignancy. Rarely, an M protein has specific affinity for another cellular molecule, causing “autoimmune” phenomena such as diabetes or trace-metal deficiency. Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes constitute the POEMS syndrome. POEMS syndrome is associated with osteosclerotic myeloma/Castleman disease, rare entities of uncertain kinship to MM. High concentrations of paraprotein, especially immunoglobulin M (IgM) in Waldenström macroglobulinemia (WM) can cause symptoms by increasing serum viscosity; this is discussed later. Tumor fever can occur in MM but is a diagnosis of exclusion, and febrile MM patients are infected until proven otherwise.

B. Objective

Physical examination may reveal pallor, bony tenderness, or swelling secondary to plasmacytoma, organomegaly, or focal neurologic signs secondary to spinal cord compression. Hyperviscosity in the retinal blood vessels may give to rise to “box car appearance” on ophthalmoscopic examination.

C. Workup and staging

The following studies should be done as part of the workup of MM.

- Complete blood cell count (CBC) + differential
- Serum calcium, albumin, and creatinine
- Serum protein electrophoresis and immunofixation
- Urine protein electrophoresis and immunofixation + 24-hour urine collection with protein quantitation
- Quantitative immunoglobulins
- Lactate dehydrogenase (LDH)
- b_2-Microglobulin
- Radiographic skeletal survey
- Bone marrow aspirate and biopsy

1. **Laboratory.** Serum and urine electrophoresis should be performed on patients with unexplained anemia or renal insufficiency. Anemia is common and is usually normocytic. Paraproteins often bind to red cells, causing rouleaux formation on peripheral blood smears. Platelets and white cells are usually preserved, although all lines will be decreased in the context of marrow replacement by MM. Workup of weight loss or other constitutional symptoms may reveal a very elevated erythrocyte sedimentation rate (ESR), caused by paraproteinemia. A high ESR is common in MM: in the Mayo series, 72% of patients had an ESR greater than 50, and 38% were greater than 100. LDH higher than 300 is associated with high tumor load and lymphoma-like clinical features, and is an adverse prognostic factor. Up to 18% of patients have some degree of renal insufficiency on presentation. Hyperuricemia and/or hypercalcemia may contribute to renal insufficiency. Patients with hypercalcemia usually have extensive bone involvement. Lack of osteoblastic repair means that the alkaline phosphatase can remain normal, even with extreme bony destruction.

Immunofixation is more sensitive than electrophoresis and is done to confirm the presence of a paraprotein, as well as to determine its type. Immunofixation can be especially helpful in evaluating IgA paraproteins, which are more difficult than IgG to view on electrophoresis. Light chains may be filtered from the blood by the kidney and thus be undetected on serum protein electrophoresis (SPEP), appearing only on urine protein electrophoresis. If light chains are detected in the urine, collect a 24-hour urine specimen to quantify the protein. The quantity can be used to monitor subsequent disease response to treatment.

IgG is the M protein in two thirds of cases of MM, and IgA is secreted in 20% to 30% of cases. The light-chain component is k (kappa) in two thirds of cases and l (lambda) in one third. From 10% to 15% of MMs secrete only light-chain protein. Heavy- and light-chain synthesis may be disproportionate, resulting in excess light chains appearing in the urine. Other plasma cell dyscrasias may be associated with secretion of only heavy-chain fragments. IgM paraproteins are almost always associated with WM; IgM, IgD, and IgE myelomas are very rare. Fewer than 5% of MMs secrete no detectable paraprotein.

Note that malignancies other than MM may secrete paraproteins. Most patients with high levels of IgM paraprotein will have WM. a-Heavy-chain paraprotein is associated with immunoproliferative small intestinal disease (IPSID), a distinct entity discussed later. Other non-Hodgkin lymphomas [e.g., chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL)] also can secrete paraproteins, although usually not the large amounts secreted in MM or WM.

2. **Radiologic.** Radiographs done to evaluate bone pain or fracture may show the punched-out round lytic lesions typical of MM. Magnetic resonance imaging (MRI) of the spine may demonstrate heterogeneous marrow involvement in patients with asymptomatic myeloma. All patients should have a skeletal survey including the skull, pelvis, femurs, and humeri. Radionuclide bone scans detect osteoblastic response and thus are less sensitive than plain radiographs in detecting skeletal involvement. Bone disease may appear as punched-out lytic lesions, pathologic fractures, or generalized osteopenia. MRI scans have been used to evaluate patients with asymptomatic myeloma; patients with evidence of vertebral marrow involvement progress to frank myeloma more quickly than those who do not.
3. **Bone marrow evaluation.** Patients should undergo bone marrow biopsy and aspiration. Pathologists reading the biopsy specimen should quantitate the percentage of bone marrow involved with plasma cells.

D. **Diagnosis**

To meet diagnostic criteria for myeloma, patients must have a combination of major and minor criteria as follows: I + b, c, or d; II + b, c, or d; III + a, c, or d; a + b + c; a + b + d (Table 16.1).

Major Criteria	Minor Criteria
I. Plasmacytosis on tissue biopsy	a. Marrow plasmacytosis 10%–30%
II. Marrow plasmacytosis of >30%	b. Monoclonal protein present but less than in major criterion III
III. Monoclonal protein >3.5 g/dL for IgG or 2 g/dL for IgA or unequivocal light-chain (Bence Jones) proteinuria	c. Lytic bone lesions
	d. Hypogammaglobulinemia: IgM, <50; IgA, <100, or IgG, <600/dL

Ig, immunoglobulin.

TABLE 16.1. DIAGNOSTIC CRITERIA FOR MYELOMA

E. **Staging**

The Durie–Salmon staging system is most frequently used (Table 16.2).

Stage I	All of the following Hgb, >10 Normal serum calcium 0 or 1 bone lesions on skeletal survey Low quantity of monoclonal paraprotein (IgG, <5 g/dL; IgA, <3 g/dL; or urine light chains <4 g/24 h)
Stage II	Does not meet criteria for stage I or stage III
Stage III	Any one of the following Hgb, <8.5 Serum calcium >12 Advanced (>3) lytic bone lesions High quantity of monoclonal paraprotein (IgG, >7 g/dL; IgA, >5 g/dL; or urine light chains, >12 g/24 h)

Hgb, hemoglobin; Ig, immunoglobulin.

TABLE 16.2. DURIE–SALMON STAGING SYSTEM

F. **Treatment**

1. **Conventional chemotherapy**
   a. **Melphalan and prednisone.** Melphalan and prednisone (MP) and vincristine, doxorubicin (Adriamycin), and dexamethasone; VAD) are the two main regimens used for conventional chemotherapy for MM (Table 16.3). Many different chemotherapy regimens are active against MM, but although responses may be faster and response rates higher with combination chemotherapy, no regimen has produced better overall survival than MP, which remains the standard regimen. MP is well tolerated, and the pill form is convenient. Patients with renal insufficiency should start at a 25% dose reduction. From 40% to 50% of patients treated with MP respond with a greater than 75% decrease in tumor load, although it may take 6 months to achieve this response. Patients with less response may still have amelioration of symptoms. Treatment should be continued for 1 year or until patients reach a plateau phase. The median survival of patients treated with MP is approximately 38 months.

MP (melphalan + prednisone) Melphalan, 0.15 mg/kg/day p.o. × 7 days Prednisone, 60 mg p.o. qd × 7 days Repeat cycle every 6 weeks Increase or decrease melphalan dose to achieve ANC 1,500 at nadir 3 weeks after treatment
VAD Vincristine, 0.4 mg/m^2/day i.v. infusion over 4 days Doxorubicin (Adriamycin), 9 mg/m^2/day i.v. infusion over 4 days Dexamethasone, 20 mg/m^2 p.o. on days 1–4, 9–12, and 17–20 Repeat cycle every 28 days
Thalidomide Begin at 200 mg p.o. qd Increase by 200 mg every 2 weeks for a goal of 800 mg p.o. qd

ANC, absolute neutrophil count.

TABLE 16.3. REGIMENS USED FOR CHEMOTHERAPY FOR MULTIPLE MYELOMA

b. **Vincristine, doxorubicin (Adriamycin), and dexamethasone.** Compared with MP, VAD obtains responses quickly (median, 0.9 months), which may be helpful in controlling disease-related symptoms. VAD is less toxic to marrow than is alkylator-based chemotherapy and thus is used for induction before autologous transplant, with the goal of preserving stem cells for later harvest. VAD can obtain responses in patients relapsed after responding to MP: 70% of these patients obtain a greater than 75% reduction in tumor mass. The 4-day infusional regimen of VAD is cumbersome, requiring a central line and either hospitalization or a portable pump. Early investigations of rapid-infusion VAD or substitution of liposomal doxorubicin seemed to obtain comparable responses.

   Other intravenous (i.v.) alkylator-based regimens such as M2 (vincristine, carmustine, cyclophosphamide, and melphalan) are reserved for patients who relapse after autologous transplant or other special cases.

2. **High-dose therapy/autologous transplant.** High-dose chemotherapy with autologous stem cell transplant should be considered first-line therapy for patients with MM. Ideally, stem cell harvest should occur before the patient is exposed to alkylators. Patients suitable for transplant may undergo induction chemotherapy with several cycles of VAD, and then undergo stem cell collection and consolidative high-dose therapy and transplant. Alternatively, patients may have harvest and stem cell storage first, and then proceed to alkylator-based treatment, postponing transplant until first relapse. Outcomes are similar for these two approaches, although transplant in first relapse entails more total chemotherapy. Single-agent melphalan with or without total-body irradiation (TBI) is the most common high-dose regimen. Repeated high-dose chemotherapy and transplant within 6 months ("tandem transplant") has been advocated by some investigators; the role for this approach is controversial. Overall transplant-related mortality is 1% to 2%.
3. **Allogeneic transplant.** Allogeneic transplant is a consideration for young, fit patients for whom autologous transplant has failed and who have a matched sibling donor. The use of allogeneic transplant in MM has been complicated by the age and comorbidities of MM patients and a high treatment-related mortality, especially from graft-versus-host disease (GVHD). Nonmyeloablative allogeneic transplant may be less toxic initially but retain a therapeutic graft-versus-myeloma effect; GVHD remains a toxicity of this approach.

   Dexamethasone has been described as the single most active agent in MM. In patients with primary refractory MM, dexamethasone (dex) is equivalent to VAD: in these patients, VAD and dexamethasone alone both obtained a 27% response rate (RR). Another study of patients with untreated myeloma found a 43% RR to dexamethasone compared with a historical 55% RR to VAD. Dexamethasone is dosed as described earlier for VAD, with a 28-day or 42-day cycle. Dexamethasone is not myelosuppressive, and so may be especially suited to patients with severe marrow compromise. It also may be used in combination with XRT. To minimize toxicity, some clinicians begin at 10 mg/m^2 in frail or elderly patients.

   Thalidomide has recently been discovered to have considerable activity, even in advanced/refractory myeloma. It is started at 200 mg p.o. daily and increased every 2 weeks to a goal dose of 800 mg p.o. daily, although only 50% of patients will tolerate escalation to this dose. The RR to single-agent thalidomide is 32% in refractory relapsed MM. The mechanism of action of thalidomide is not fully understood, but appears to be different from the actions of melphalan and dexamethasone.

G. **Adjunct treatments**
   1. **Pamidronate.** Pamidronate inhibits osteoclastic resorption of bone, and in patients with MM, this drug is effective in decreasing skeletal events, including fractures and hypercalcemia. It is well tolerated, and all patients with MM should be considered for treatment. Pamidronate, 90 mg, is administered i.v. over a 1- to 2-hour period once a month. Zoledronate is a new bisphosphonate that appears equally effective.
   2. **Erythropoietin.** Anemia is a common complication of MM, and some patients become transfusion dependent. Erythropoietin at 150 U/kg s.q., 3×/week (or 450 U/kg once a week) decreases transfusion requirements in MM patients, including patients with refractory disease.
   3. **Radiation.** MM is a radiosensitive tumor, and external-beam XRT delivering 20 to 30 Gy can effectively palliate discrete areas of bone pain or areas of mass effect (such as spinal cord compression). Although MM patients often have many bones involved, radiation fields should include only symptomatic areas to minimize marrow damage. Radiation treatment does not benefit systemic disease and should be reserved for patients whose pain does not respond to opiates and chemotherapy.
   4. **Surgery.** Radiographs of long bones done for staging or to evaluate pain may reveal lytic lesions large enough to threaten impending fracture. Orthopedic surgery consultation and prophylactic surgical pinning may avoid some of the morbidity of a fracture. Patients who undergo pinning should generally receive XRT to the area 1 to 2 weeks postoperatively.
   5. **Hemodialysis.** Renal failure is common among patients with MM and may occur early in the course of disease. Renal impairment may be reversible if the MM responds to treatment, and support with hemodialysis is appropriate.
   6. **Infection prophylaxis.** MM patients have a deficit in humoral immunity because of their decreased levels of normal immunoglobulins. This predisposes them to infections by encapsulated organisms. All MM patients should be vaccinated against *Staphylococcus pneumoniae*.
   7. **Interferon.** Studies of maintenance treatment with a_2-interferon have shown that this agent can prolong time to progression at the cost of moderate to severe toxicity. Many centers routinely offer patients maintenance IFN at 3 million units s.q., 3 ×/week after high-dose chemotherapy. Despite its activity, IFN does not prolong overall survival.

H. **Complications**

   The chief complication of MM treatment is infection: these patients are already prone to infection because of their disease, and the risk is increased both by direct marrow suppression from chemotherapy as well as immunosuppression associated with long-term, high-dose corticosteroids. Central-line infections are a risk of VAD treatments as well as high-dose chemotherapy, both of which require a central venous catheter. Possible cardiotoxicity associated with doxorubicin makes VAD less suitable for patients with heart disease. The vincristine component of VAD may cause neuropathy, including autonomic neuropathy. Long-term treatment with melphalan or other alkylators may make stem cell harvest and autologous transplant difficult. Alkylators also increase the risk for developing myelodysplastic syndrome/acute myelocytic leukemia (MDS/AML). Corticosteroids, especially high-dose dexamethasone, may cause gastric ulcers, hyperglycemia, or psychiatric side effects such as agitation or depression. Constipation, neuropathy, and somnolence are common adverse effects of thalidomide, but marrow toxicity is not seen. Pneumonia/pneumonitis and central-line infections during the neutropenic period are the main toxicities of high-dose therapy. Extramedullary toxicity is mainly stomatitis and gut toxicity associated with melphalan. Extramedullary toxicity may be worse with melphalan + XRT than with melphalan alone.

I. **Follow-up**

   MM remains incurable with current therapies. Palliation of symptoms and slowed progression are the goals of treatment. M protein levels in the serum or urine fluctuate with tumor load and can be used as an index to monitor MM response to treatment. Other markers such as the CBC or creatinine also may correlate with disease progression/response. Repeated skeletal surveys are not a good way to monitor disease response, as even with good responses, lytic lesions may not show healing on radiographs.

J. **Natural history**

   In MM, conventional chemotherapy ameliorates symptoms and prolongs life from a median of 6 months to 2 to 3 years. The randomized study by Attal et al. comparing autologous transplant with standard chemotherapy found a higher overall RR for transplant (81% vs. 57%) as well as better 5-year overall survival (52% vs. 12%; *N Engl J Med* 1996;335:91–97). Selection bias may in part be responsible for good outcomes with autologous transplant—clearly patients fit enough to withstand high-dose treatment have a better overall prognosis. All patients eventually relapse with chemoresistant disease. Serum b_2-microglobulin levels are highly correlated with prognosis. A prognostic system based on this laboratory value is as follows in Table 16.4.

β_2M <6 μg/mL and serum albumin >3 g/dL	Median survival, 55 mo
β_2M >6 μg/mL and serum albumin >3 g/dL	Median survival, 19 mo
β_2M >6 μg/mL and serum albumin <3 g/dL	Median survival, 4 mo

β_2-M, β_2-microglobulin.

TABLE 16.4. PROGNOSTIC SYSTEM BASED ON b_2-MICROGLOBULIN

Other poor prognostic factors include high LDH, high plasma-cell–labeling index, and chromosome 13 abnormalities. Chromosome 13 abnormalities (D13) occur in at least 16% of MM. A retrospective study by Desikian et al. of 1,000 MM patients who received high-dose therapy showed that among patients without D13, 35% were in continuous complete remission, and 44% were alive at 5 years. Only 16% of patients with D13 were alive at 5 years, and none were in continuous remission. End-stage, accelerated myeloma may dedifferentiate to become more like a non-Hodgkin lymphoma (NHL). MM cells may lose their requirement for stromal contact and proliferate outside the marrow. Decreased paraprotein synthesis and bulky soft tissue disease may be seen in this late phase, as well as circulating plasma cells. Plasma cell leukemia also can occur *de novo;* median survival of the *de novo* form is 6 months, but median survival in the late terminal form is only 1 to 2 months. Patients with high-grade plasmacytic malignancies may be candidates for aggressive, leukemia-type induction regimens. Patients with MM have a 10 to 17 times higher risk for developing AML, and AML may be a terminal event. This is thought to occur both from long-term alkylator therapy and some predisposition inherent in MM. Like those with other hematologic malignancies, patients with advanced MM usually die of infection.

K. **Background**

1. **Epidemiology.** The incidence of MM is four per 100,000 per year. MM represents 1.1% of all new cancer diagnoses and 2% of all cancer deaths. It is the most common hematologic malignancy in Western countries. Incidence in black Americans is double that in whites. The median age of patients is 65 years. The only identified risk factor for MM is the presence of an MGUS. There are no other known risk factors, although the role of benzene exposure is still debated. The etiology of MM is unknown.
2. **Molecular biology.** MM cells rely on contact with bone marrow stromal cells. The marrow cytokine microenvironment is complicated, but the essential role of interleukin 6 (IL-6) in MM is well established. Adhesive interactions between MM cells and normal stromal cells induce the stromal cells to secrete IL-6, which then acts as a paracrine growth factor to inhibit apoptosis and promote survival of the MM. IL-1b, transforming growth factor b (TGF-b), and other cytokines secreted by MM cells are responsible for osteoclast stimulation/osteoblast suppression, resulting in the purely lytic bone disease pathognomonic of MM.

   Conventional cytogenetics on MM has historically been difficult because of the low growth fraction and paucity of mitotic cells. Fluorescent *in situ* hybridization (FISH) techniques done on interphase cells have revealed that complex cytogenetic abnormalities are common in MM, occurring in 20% to 60% of cases. No single mutation is *sine qua non* for myeloma, although abnormalities in chromosome 14 (containing the heavy-chain gene), chromosome 1, and chromosome 13 are common. Ongoing studies attempt to correlate specific cytogenetic abnormalities with clinical and biologic features. Many cases of MGUS also have cytogenetic abnormalities detectable in clonal plasma cells, and cytogenetics may someday make it possible to predict which cases of MGUS will transform.

   Terminally differentiated malignant plasma cells are the only grossly evident malignant cells in MM. Patients with MM also have a clonal population of B cells that reside in the circulation. These plasmablasts have undergone Ig rearrangement and express B-cell markers CD19 and CD20, markers not generally expressed by plasma cells. The circulating cells are presumably analogous to B lymphocytes that have undergone selection in lymph nodes and are migrating to the marrow, where they will complete differentiation into plasma cells. The exact relation between circulating plasmablasts and malignant plasma cells remains unclear.

L. **Research frontiers**

The novel mechanisms of thalidomide and related compounds have opened new avenues of investigation into MM biology. Attempts are under way to design new drugs that have the immune-modulatory effects of thalidomide with fewer side effects. Thalidomide and dexamethasone are synergistic *in vitro,* and the combination of these two drugs can achieve responses in patients whose MM is resistant to either drug alone. Preliminary results using the combination are very encouraging, and larger trials are under way.

Current research is exploring many other treatment options for MM. The important role of IL-6 makes it an obvious therapeutic target, and different strategies target IL-6/IL-6 receptors or other molecules downstream. Immunologic manipulations are another area of research: each myeloma clone expresses a specific paraprotein idiotype, which might be targeted by an antiparaprotein antibody. Such treatments would have to be individually tailored. Other possible target molecules expressed by MM include MUC-1 and CD-138. Other therapeutic agents being investigated include proteosome inhibitors, Bcl-2 oligonucleoside antisense drugs, and [^{166}Ho]-DOTMP, a bone-seeking radiopharmaceutical used with autologous transplant rescue.

M. **Monoclonal gammopathy of uncertain significance/Smoldering myeloma**

1. **MGUS.** The term MGUS implies the presence of paraprotein without malignancy. A paraprotein is present in 2% to 14% of well elderly people, with the incidence increasing with age. Sometimes a monoclonal protein is detected as a component of a polyclonal hypergammaglobulinemia, as is seen in chronic inflammatory diseases. It is often discovered when an SPEP done as part of the workup for renal insufficiency or other illness reveals the presence of a small amount of paraprotein. MGUS usually quantitates at less than 2 g/dL and often less than 1.5 g/dL. If truly of “uncertain significance,” the paraprotein should be accompanied by normal levels of immunoglobulin and a lack of criteria for myeloma, amyloid, or other malignancy. There is no urinary correlate of MGUS: the presence of Bence Jones proteinuria usually indicates malignancy. In one third of patients with MGUS, myeloma or other hematologic malignancies eventually develop. Progression may take 5 years or more. MGUS patients should be monitored with SPEP every 6 months to assess the level of the paraprotein; an increasing level suggests imminent progression.

   MGUS paraproteins may sometimes cause symptoms such as neuropathy, as noted earlier, in which case “uncertain significance” seems a misnomer. An MGUS present in very small amounts may be associated with gradual M-protein accumulation in tissues, causing the syndrome of amyloidosis or monoclonal immunoglobulin deposition disease (discussed later).

2. **Smoldering myeloma** (also called **indolent myeloma**) is a category for patients who meet criteria for MM but are not symptomatic and do not need treatment. This condition is distinguished from MGUS by more than 15% marrow plasma cells, an M protein more than 2 g/dL and hypoglobulinemia in one or more immunoglobulin fractions. Factors suggesting more severe disease include Bence Jones proteinuria, M protein more than 3 g/dL, or lytic lesions; patients with these findings will not remain asymptomatic for long. Early chemotherapy does not improve outcomes or forestall progression, thus patients with MGUS and asymptomatic patients with smoldering myeloma or stage I myeloma should be followed up but not treated.

II. **Solitary plasmacytoma**

A. **Subjective**

Solitary plasmacytomas are divided into solitary plasmacytoma of bone (SPB) and extramedullary plasmacytoma (EMP). As in MM, pain in the most common presenting symptom of SPB. The majority of SPB occurs in the vertebrae, and expansion of the SPB into nerve roots or the spinal canal may cause neurologic symptoms. EMP most commonly presents as a head and neck mass, with symptoms arising from mass effect.

B. **Objective**

Monoclonal paraprotein is detectable in 24% to 72% of patients with SPB. Discovery of any plasmacytoma should prompt a workup for MM, as described earlier. Patients who truly have a solitary plasmacytoma should not meet criteria for MM and have normal marrow and no evidence of systemic disease.

C. **Treatment**

XRT is the treatment of choice for plasmacytoma. The treatment is 5,000 to 6,000 cGy over a 5- to 7-week period.

D. **Natural history**

Patients with solitary plasmacytoma are generally younger than patients with MM. It has been theorized that all MM initially begins as solitary plasmacytoma,

which then spreads systemically, but the relation between these diseases remains unclear. Solitary plasmacytomas may recur as MM after XRT treatment. Local recurrence is rare, and 36% of SPBs eventually transform into MM; the median time to relapse as MM is 39 months, although it can occur much later. Of extramedullary plasmacytomas, 23% recur as MM in a median of 23 months. Patients who have been treated for MM should be monitored with protein electrophoresis. Reappearance of paraprotein heralds relapse, and workup as for *de novo* myeloma is appropriate.

III. Amyloidosis

A. Subjective

Most patients with amyloidosis have nonspecific complaints: fatigue, weight loss, and lightheadedness are common. Orthostasis may result from nephrotic syndrome and intravascular depletion, from restrictive cardiomyopathy, or from autonomic instability. Nephrotic syndrome also may cause hypoalbuminemia, edema, and renal failure. Cardiac amyloid can cause congestive heart failure symptoms, especially right-sided symptoms (e.g., jugular venous distention, peripheral edema). Infiltration of soft tissues can cause capillary fragility and purpuric bruising; periorbital ecchymosis is a classic symptom of amyloidosis. Less common symptoms include tongue enlargement, endocrine symptoms, neuropathy, and carpal tunnel syndrome.

B. Objective

Physical findings in amyloidosis vary widely depending on which organ systems are affected by amyloid deposits. Symptoms are often misattributed to more common diseases. The organs most often involved are the kidneys and the heart. In renal amyloid, patients may have severe nephrotic syndrome, hypoalbuminemia, and edema, but normal serum creatinine. Amyloid infiltration of the heart may appear on echocardiography as hypertrophic cardiomyopathy with a restrictive filling pattern. The intraventricular septum also is thickened in cardiac amyloid; this is not the case in other cardiomyopathies. The heart wall may show increased “sparkling” echogenicity when infiltrated by amyloid. The electrocardiogram (ECG) may show low voltage. Hard hepatomegaly may be palpable if the liver is involved.

C. Workup

“Amyloidosis” is actually a group of syndromes in which symptoms arise from infiltration of tissue with proteinaceous material. In primary amyloid (AL), the amyloid is composed of paraprotein light chains secreted by a plasma cell dyscrasia. Other syndromes include secondary amyloidosis (AA), which is associated with chronic inflammation, dialysis-associated amyloidosis, and familial amyloidosis. In each of these diseases, the amyloid is composed of a different protein, but the microscopic appearance of the depositions is the same. Amyloid is a tissue diagnosis: the protein deposits stain with Congo red and show apple-green birefringence under polarized light. Immunoperoxidase stains on tissue specimens can differentiate between different types of amyloid.

The first step in the workup of amyloidosis is to suspect the diagnosis. A clue to the possibility of AL is the discovery of a paraprotein in the serum or urine of the patient. Urine electrophoresis is essential in such patients, as the light-chain paraprotein responsible may appear only in the urine. The paraprotein may be a complete immunoglobulin (e.g., IgGl), although only the light-chain component contributes to amyloid formation. Only a small quantity (less than 1 g/dL) of paraprotein may be present; such small quantities of paraprotein would otherwise be considered an MGUS.

Amyloid may heavily involve one organ system and completely spare another. Biopsy of abdominal fat is often done in the attempt to make a tissue diagnosis while avoiding biopsy of vital organs. The presence of amyloid is 100% specific, but sensitivity varies and can be less than 75%. If fat-pad biopsy is negative and clinical suspicion for amyloidosis is high, it may be necessary to perform a biopsy of the kidney, myocardium, or other affected organ.

D. Therapy

1. **Chemotherapy.** The underlying process in all amyloidoses is an imbalance between secretion and destruction of amyloid precursor proteins, which in AL is immunoglobulin light chains. Because we lack any means to accelerate amyloid destruction, treatment has centered on chemotherapy directed at the underlying plasma cell dyscrasia with regimens active against myeloma. The response rate to melphalan and prednisone (MP) is 28%, but this can take 6 months or more. This may be too slow to benefit patients with symptomatic cardiac amyloid.
2. **Supportive care.** Medical treatments aim to control symptoms caused by organ dysfunction. Cardiac amyloid is the most difficult and life-threatening manifestation. Patients are usually treated with angiotensin-converting enzyme (ACE) inhibitors and diuretics; digoxin is controversial, and calcium channel blockers should not be used. Implantable defibrillators may be required to prevent arrhythmia. Patients with nephrotic syndrome may require diuretics to manage edema. Hemodialysis may improve edema and functional status by rendering patients anuric and preventing ongoing urinary albumin losses. The evaluation of orthostasis should include evaluation of the adrenal glands. Orthostatic patients may benefit from a trial of midodrine or steroids. Many other symptoms have been reported in patients with AL including malabsorption, peripheral neuropathy, bleeding due to acquired coagulation-factor deficiencies, endocrine dysfunction, and others.
3. **Research/future treatments**
   a. **High-dose therapy/autologous transplant.** A study of 25 patients treated with high-dose melphalan chemotherapy and autologous transplant found that 68% of patients were still alive at a median of 2 years after transplant, of which 11 of 17 experienced improvement in amyloid-related symptoms, and four of 17 had stable disease (*Blood* 1998;91: 3662–3670).

      Survivors included three of eight patients with cardiac amyloidosis. Other small trials found similar results. Given the poor prognosis of AL and the success of high-dose treatment in MM, it is reasonable to consider autologous transplant as first-line therapy for patients with AL. Many of these patients are first seen with end-organ dysfunction because of their disease, making it difficult to administer high-dose chemotherapy.

      A new chemotherapeutic, 4¢-iodo-4¢-deoxydoxorubicin (I-DOX) may be able to interact with existing amyloid deposits and facilitate their breakdown. A recent phase II trial of I-DOX in 35 patients with AL reported low toxicity and a response rate of 12.5%. Research is ongoing into the therapeutic use of I-DOX, as well as its mechanism of action.

E. Natural history

Primary amyloidosis is rare and probably underdiagnosed. The estimated incidence is 5.1 to 12.8 new cases per million per year. Systemic AL is invariably fatal, although median survival depends on the organs affected. Median survival is 2 to 3 years but only 6 months in cardiac amyloid. The biology of AL is that of an MGUS in which the protein product is especially troublesome. Clonal plasma cells represent less than 10% of the marrow in most cases of AL, and circulating or urinary M protein is usually present in very small quantities. MM and AL sometimes coexist: 20% of patients with amyloidosis are found on workup to have myeloma, and in 10% to 15% of patients with MM, amyloidosis will eventually develop. In patients who have both diseases, amyloidosis symptoms typically dominate. Although light-chain amyloid can accumulate almost anywhere in the body, it does not enter the central nervous system.

Sequence characteristics of the light-chain M protein determine whether it will be normally cleared or accumulate as amyloid. The l light chains are more commonly associated with AL, presumably because these types more often possess amyloidogenic characteristics. As noted earlier, in MM and MGUS, k light chains are more frequent, but in AL, the ratio of l to k is 3:1. Amyloid is eventually cleared from tissues, and this accounts for gradual clinical improvement if effective chemotherapy can suppress new M protein deposition. Current investigations use molecular genetics to understand better what allows certain light chains to escape normal breakdown.

IV. Nonamyloid monoclonal immunoglobulin deposition disease

Some patients with the clinical features of amyloidosis but without detectable tissue amyloid may have nonamyloid monoclonal immunoglobulin deposition disease (MIDD). The development of immunoglobulin-specific antibodies led to the discovery of this syndrome. Deposits may consist of light chains, abnormal truncated heavy chains, or both. Unlike amyloidosis, k light chains predominate over l, but in other respects, MIDD is clinically similar to amyloidosis except for the fact that the deposits do not take on the amyloid structure nor stain with Congo red. Most patients have detectable circulating or urinary M protein and may have associated MM or other malignancy. Clinical manifestations and treatment are as described earlier for amyloidosis. The key to diagnosis is the use of immunohistochemistry in the appropriate clinical situation.

V. Heavy-chain disease

Rarely an M protein is found to be a truncated heavy chain with no associated light chain. There are three types of these monoclonal heavy chains: g, µ, and a. The g and µ heavy-chain paraproteins are rare and are usually associated with NHLs. a-Heavy chain disease [also called *immunoproliferative small intestinal*

disease (IPSID) and Mediterranean lymphoma] is a distinct and unusual entity and is discussed separately.

A. **Subjective**

Patients with IPSID are generally impoverished and have malnutrition and chronic intestinal parasitic/bacterial diseases, the symptoms of which may coexist with those of IPSID. Most patients are first seen with chronic diarrhea and weight loss. Advanced disease may cause abdominal pain.

B. **Objective**

Malabsorption is common and may be severe. Clubbing of fingers and toes may develop. Peripheral adenopathy is rare, but retroperitoneal adenopathy may be palpable as an abdominal mass. Diffuse infiltration of the intestine by lymphocytes or plasma cells results in a thickened, hard, pipe-like intestine on endoscopy or imaging. The infiltrating cells may not appear histologically malignant.

The truncated a-heavy chain M protein associated with IPSID is an abnormal IgA molecule and might be detectable by immunofixation on serum, urine, or jejunal secretions sampled by endoscopy. It also may be detected by immunohistochemistry done on tissue samples. Electrophoresis is less effective at detecting heavy chains, as they migrate as a smear rather than a discrete band.

C. **Workup and staging**

Biopsy of the intestine and/or mesenteric nodes is necessary for tissue diagnosis, as IPSID rarely involves peripheral lymph nodes or bone marrow. IPSID cells may involve only deep layers of the small intestine and spare the mucosa, making laparoscopy or laparotomy necessary to obtain tissue. IPSID is now considered to be a mucosa-associated lymphoid tissue (MALT)oma, a variety of marginal zone lymphoma, and is staged as such (see Chapter 15, Lymphomas). Spread beyond the intestine and mesenteric nodes is rare. In addition to tissue diagnosis, patients should be evaluated for intestinal pathogens such as *Giardia* sp.

D. **Treatment**

Like *Haemophilus pylori*–associated gastric MALTomas, early stage IPSID may respond to broad-spectrum antibiotics (e.g., tetracycline, metronidazole, and ampicillin). Therapy should be directed against any intestinal pathogens or parasites found to be present. More advanced disease requires chemotherapy appropriate for low-grade NHL, to which antibiotics may be added.

E. **Epidemiology**

IPSID patients are generally young (aged 15 to 35 years) and impoverished, with histories of poor hygiene and chronic diarrhea. It occurs in Europe, Africa, and Asia and is extremely rare in the Western hemisphere. Possibly some undiscovered intestinal bacterium endemic in the Old World plays a role analogous to that of *H. pylori* in gastric MALToma, colonizing the intestine and creating an antigenic stimulus for IgA-secreting B cells, which occasionally mutate into lymphoma.

F. **Natural history**

IPSID has an indolent course comparable to those of other low-grade lymphomas. The reported 5-year survival rate is 67%.

VI. Waldenström macroglobulinemia

A. **Subjective**

The classic clinical triad seen in Waldenström macroglobulinemia (WM) is that of hyperviscosity syndrome (HVS): easy bleeding, ocular/visual changes, and neuropsychiatric symptoms. Easy bleeding comes from paraprotein coating of platelets and interference with coagulation factors. Gingival bleeding, epistaxis, or other bleeding diatheses are present in 60% of patients with WM. Patients (or their families) may note very red conjunctiva and bloodshot eyes, which occurs from stagnant, viscous blood flow. Symptoms of visual impairment are relatively nonspecific. Retinal bleeding or blindness may occur. Neuropsychiatric symptoms may be mistaken for transient ischemic attacks (TIAs) or dementia; paralysis, seizures, and coma have developed. Frank HVS occurs in 10% to 30% of patients with WM. Other symptoms due to IgM include neuropathic symptoms as described earlier in other paraproteinemias. IgM deposits in the skin may cause purpuric lesions. In fewer than 5% of patients, the IgM paraprotein is a cryoglobulin and causes Raynaud syndrome and acral cyanosis.

Underlying WM is a low-grade NHL, and although WM is best known for the strange symptoms caused by high IgM levels; most patients have symptoms common to NHL. In a series of 167 patients, 64% had general symptoms such as fatigue and weight loss. Other B symptoms include fever and night sweats. Unlike MM, bone pain is rare in WM.

B. **Objective**

Many patients with WM have no obvious physical findings. In patients with HVS, a pathognomic retinopathy, the “fundus paraproteinaemicus” may be seen on ophthalmoscopic examination: this consists of sausage-like constrictions and distentions of retinal veins, exudates, and hemorrhages. Patients may even have papilledema. About half of WM patients have detectable lymphadenopathy and hepatosplenomegaly.

The most common laboratory abnormality in WM is anemia, which occurs in 57% of patients and can be severe. Anemia and refractory hypertension arise from massive plasma expansion due to increased oncotic pull from the paraprotein. A leukemic phase much like that of CLL is present in up to 18% of patients.

As in MM, paraprotein binding to red blood cells (RBCs) may cause rouleaux formation on peripheral blood smears. Laboratory abnormalities may first be noted by laboratory personnel when viscous serum causes difficulty in making blood smears or running samples through machines. High paraprotein levels can cause a very high (greater than 100) or spuriously low erythrocyte sedimentation rate (ESR) or pseudohyponatremia. Symptomatic hyperviscosity usually does not occur until IgM is greater than 3 g/dL and the serum viscosity more than 5 centipoise (normal serum viscosity is 1.4 to 1.8 cp), although symptoms can occur at lower levels of paraprotein and lower serum viscosities.

C. **Workup and staging**

In the World Health Organization (WHO) update of the REAL classification of NHLs, WM is a subset of lymphoplasmacytic lymphoma (LPL), a mature B-cell neoplasm closely related to CLL/small lymphocytic lymphoma (SLL). The WM subset is characterized by bone marrow involvement and IgM paraproteinemia. The diagnosis of LPL may be made on bone marrow biopsy or lymph node biopsy. LPL cells express cytoplasmic Ig, distinguishing them from CLL/SLL cells, which do not. Other immunophenotypic markers are similar to those of CLL, including expression of CD19 and CD20. Once diagnosed, patients with LPL/WM should have serum protein electrophoresis and immunofixation. In HVS, the challenge is to realize that symptoms are arising from hyperviscosity; after this, the workup should include measurement of serum viscosity, SPEP, and tissue diagnosis (usually bone marrow aspirate and biopsy). Communication with the clinical laboratory is important when working up hyperviscosity, especially if done on an emergency basis. Laboratory personnel may have procedures for dealing with viscous specimens that will allow tests to be done correctly the first time.

D. **Therapy**

Treatment of WM is divided into treatments aimed at reducing serum IgM/serum viscosity and treatment of underlying lymphoma. The treatment of HVS is plasmapheresis. All symptomatic patients with hyperviscosity should receive a trial of plasmapheresis. Plasmapheresis requires a dialysis-caliber central venous catheter and nurses trained in the procedure. Of total IgM, 80% is in the serum, and removal/replacement of 6 to 7 L of plasma in an emergency situation may rapidly and completely stop symptoms of HVS. Removal of 3 to 4 L of plasma per session may be sufficient in nonemergency situations.

Increasing IgM levels/serum viscosity will determine the frequency of repeated sessions; once or twice a week may control symptoms until chemotherapy can control the underlying tumor. Plasmapheresis alone is sometimes used to palliate refractory or frail patients. Note that HVS can be an oncologic emergency. Severe neurologic symptoms or intractable bleeding require urgent plasmapheresis.

With the addition of plasmapheresis when necessary, LPL is treated the same as CLL/SLL. Treatment should be reserved for patients who are symptomatic either from the NHL or from high levels of IgM. Fludarabine is an active agent often used as first-line treatment. Oral alkylators (e.g., chlorambucil) also have established efficacy.

E. **Natural history**

WM is uncommon, occurring in 3.4 per million men and 1.7 per million women. It is a disease of the elderly, with a median patient age of 65 years. Unlike myeloma, WM occurs much more often in white than in black people. WM is indolent, with a median survival of 5 years and a significant fraction of patients surviving 10 years or longer. Like CLL/SLL, eventually patients with WM develop refractory disease or undergo transformation into a higher-grade neoplasm.

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CHAPTER 17. MYELODYSPLASTIC SYNDROME AND MYELOPROLIFERATIVE SYNDROME

Charles Eby and Doug Adkins

Presentation/workup and staging
Therapy and prognosis
Supportive care
Background
Current focus
Other Myeloproliferative Disorders
Polycythemia vera
Prognosis and therapy
Background
Current focus
Primary (essential) thrombocytosis
Workup and staging
Therapy and prognosis
Background
Current focus
Idiopathic myelofibrosis
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Background
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Chronic myelogenous leukemia
Suggested Readings

The myelodysplastic syndrome (MDS) is a group of acquired, clonal, preleukemic disorders characterized by ineffective and dysplastic hematopoiesis. Most cases arise *de novo* in elderly people; however, MDS can occur after bone marrow damage from chemotherapy and radiation. The disorder may remain relatively indolent, progress to life-threatening cytopenias, or evolve into acute myelogenous leukemia (AML). Diagnosis requires elimination of other causes of peripheral blood cytopenias and bone marrow examination. Prognosis can be reasonably predicted based on bone marrow myeloblast percentage, cytogenetics, and peripheral blood cytopenias. Treatment is supportive for most MDS patients. However, younger patients with a poor prognosis may be candidates for stem cell transplantation (SCT) or chemotherapy. Whenever possible, MDS patients should be enrolled in clinical trials to advance our understanding and treatment of this common malignant disease.

I. Presentation/workup and staging

Typically, MDS is suspected in a patient with an isolated anemia and who has no evidence of chronic bleeding or hemolysis, deficiency of B_{12} or folic acid, human immunodeficiency virus (HIV) infection, renal insufficiency, or a chronic infectious, inflammatory, or malignant process that could produce an anemia of chronic disease. Patients are frequently asymptomatic and are incidentally diagnosed with MDS; however, some patients have symptoms attributable to anemia, or more rarely, with bleeding or an infection due to quantitative or qualitative platelet or granulocyte disorders, respectively. Usually the anemia is hypoproliferative and normocytic or slightly macrocytic, except for patients with refractory anemia with ringed sideroblasts who may have a dimorphic red cell population containing microcytic, hypochromic red cells in addition to macrocytes. Platelet count is typically normal or slightly decreased, although patients with 5q- karyotype may have thrombocytosis. In addition to neutropenia, evidence of abnormal myeloid maturation may occur as hypogranulated or hyposegmented (pseudo Pelger–Huet anomaly) neutrophils. A peripheral monocytosis will be present in patients with the chronic myelomonocytic leukemia (CMML) subtype of MDS. No typical physical findings are associated with MDS other than pallor proportionate to the degree of anemia. Adenopathy is rare, and splenomegaly is uncommon, except with the CMML subtype.

When MDS is suspected, a complete evaluation requires a review of peripheral blood and bone marrow aspirate smears, bone marrow biopsy sections, bone marrow iron stains, and cytogenetics. The morphologic information is used to diagnose and classify MDS, and, combined with cytogenetic and clinical data, to determine the patient's prognosis.

The 1982 French–American–British (FAB) classification of MDS was the first system to gain wide acceptance, and it continues to be used by most hematopathologists today. Key elements for diagnosing and classifying MDS are (a) percentage of myeloblasts in the peripheral blood and bone marrow aspirate; (b) evidence of dysplastic maturation in two or more bone marrow lineages (erythroid, myeloid, or megakaryocytic); (c) abnormal iron staining of erythrocyte precursors (ringed sideroblasts); and (d) percentage of peripheral blood monocytes. Table 17.1 contains revised FAB criteria recently adopted by a MDS risk-analysis workshop and used to develop an **International Prognostic Scoring System** (**IPSS**) based on a retrospective review of 816 cases of primary, untreated MDS.

Category[a]	Peripheral Blood		Bone Marrow
Refractory anemia (RA)	<1% blasts	and	<5% blasts
Refractory anemia with ringed sideroblasts (RARS)	<1% blasts	and	<5% blasts ≥15% erythroid ringed sideroblasts
Refractory anemia with excess blasts (RAEB)	<5% blasts	and	5%–20% blasts
Refractory anemia with excess blasts in transformation (RAEB-t)	>5% blasts	or	21%–30% blasts
Chronic myelomonocytic leukemia (CMML)[b]	<5% blasts >1000/ monocytes	and	≤20% blasts

MDS, myelodysplasia syndrome
[a]Dysplastic features in at least two bone marrow lineages are required for all categories.
[b]Excludes hyperproliferative CMML with WBC > 12 × 10^9/L.

TABLE 17.1. FRENCH–AMERICAN–BRITISH (FAB) CLASSIFICATION OF MDS

Despite good concordance between morphologists using the FAB system to diagnose and classify MDS, prediction of clinical outcomes based solely on FAB subtype has been imprecise. The IPSS stratifies MDS patients into four prognostic risk groups for evolution into acute myelogenous leukemia (AML) and survival based on three criteria: (a) cytogenetics, (b) bone marrow myeloblast percentage, and (c) number of peripheral blood cytopenias (Table 17.2 and Table 17.3). In addition, patients younger than 60 years with low or intermediate-1 risk MDS survived longer than their counterparts older than 60 years, even though rate of evolution to AML was not different. This is most likely due to a higher mortality rate from cytopenias and other comorbidities in elderly patients with indolent MDS. Investigators are now incorporating the **IPSS** for MDS into treatment recommendations and clinical trial designs, and clinicians should become familiar with using it to guide therapeutic decisions for their patients.

Risk Level (Total Points)	Median Time to 25% Evolution to AML (yr)	Median Survival (yr)
Low (0)	9.4	5.7
Intermediate-1 (0.5–1.0)	3.3	3.5
Intermediate-2 (1.5–2.0)	1.1	1.2
High (≥2.5)	0.2	0.4

MDS, myelodysplasia syndrome; AML, acute myelocytic leukemia.
Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89:2079–2088, with permission.

TABLE 17.2. INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MDS

Points	Bone Marrow Blasts (%)	Karyotype[a]	Cytopenias[b]
0	<5	Good	0 or 1
0.5	5–10	Intermediate	2 or 3
1.0		Poor	
1.5	11–20		
2.0	21–30		

IPSS, International Prognostic Scoring System.
[a]Good prognosis: normal, -Y only, del(5 q) only, del(20 q) only; intermediate, trisomy 8, miscellaneous single or double abnormalities; poor, ≥3 abnormalities or any chromosome 7 abnormality.
[b]Hemoglobin <10 g/dL; absolute neutrophil count, <1.5 × 10^9/L; platelet count, <100 × 10^9/L.

TABLE 17.3. IPSS RISK FACTOR CATEGORIES

II. Therapy and prognosis

After the initial diagnosis of MDS, patients with low-risk MDS (IPSS good/intermediate-1) should be monitored for several months to determine whether their disease will remain stable or rapidly progress. If a cytopenia worsens or a new one develops, repeating bone marrow and cytogenetics studies is encouraged to determine whether the disease is progressing to a more unstable clonal disorder (an increasing percentage of blasts and/or the development of new cytogenetic abnormalities), which may change management.

Chemotherapy treatment of both indolent and advanced MDS has generally been disappointing, and supportive care with transfusion of red cells and platelets, and antibiotic treatment for infections are the mainstay of treatment. However, recent retrospective analysis of patients with refractory anemia with excess blasts (RAEB-t) thought initially to have AML, and who therefore received standard induction chemotherapy for AML, actually experienced similar response rates with chemotherapy, as did patients with AML. Selection of patients for more aggressive, myeloablative treatment followed by transplantation of human leukocyte antigen (HLA)-compatible donor stem cells based on young age, good performance status, and poor prognosis also has produced encouraging results. Between 25% and 50% of such patients are cured with this treatment. In addition, erythropoietin (EPO) and granulocyte–colony-stimulating factor (G-CSF) offer the potential for improving the anemia and neutropenia of selected MDS patients without accelerating transformation to AML.

The treatment algorithm outlined in Fig. 17.1 provides a reasonable starting point for patient-management decisions. Hematologist and oncologists individualize treatment recommendations based on each patient's prognosis, comorbidities, and expectations. A minority of all MDS patients will be young and healthy enough to be candidates for allogeneic stem cell transplantation (SCT). Nevertheless, this is the only therapy that produces durable clinical remissions. Overall, about 40% of SCTs for MDS are successful. Younger patients (younger than 55 years) with indolent MDS (RA/RARS or IPSS score low/intermediate-1) have higher complete remission rates (CRs), fewer relapses, and lower transplant-related mortality.

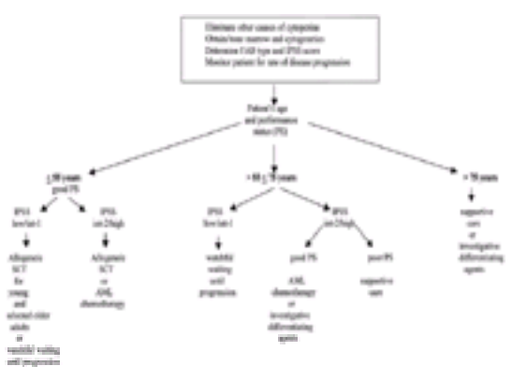

FIG. 17.1. Diagnosis and treatment of myelodysplastic syndrome. AML, acute myelogenous leukemia; PS, performance status; SCT, stem cell transplant.

AML induction chemotherapy regimens are an alternative for SCT-eligible patients and for older patients with good performance status and poor prognostic disease (IPSS intermediate-2/high). The latter will typically have RAEB with complex cytogenetics or RAEB-t. Complete remission rates with cytosine arabinoside (ara-C) + doxorubicin (Adriamycin)/idarubicin regimens in MDS patients range from 30% to 60% and are comparable to CR rates obtained in AML patients. However, with MDS, event-free survival rates are much lower, and treatment-related morbidity and mortality are higher compared with those with AML. Preliminary trials with topotecan alone or in combination with ara-C have produced higher CR rates but similarly poor remission durations in RAEB and RAEB-t patients with unfavorable cytogenetic profiles. Investigative efforts to improve the durability of postinduction CR in MDS patients include intensive consolidation chemotherapy with or without autologous stem cell rescue.

The majority of patients who have or evolve into a poor prognostic form of MDS will not be candidates for high-dose chemotherapy regimens because of advanced age (about one third are older than 80 years at diagnosis), comorbidities that would lead to unacceptable chemotherapy-associated mortality, and the lack of an HLA-compatible donor. An attractive alternative would be treatment with low-dose chemotherapy, or biologic-response modifiers, based on the premise that some drugs can induce differentiation of malignant myeloid progenitor cells leading to improvement in cytopenias without the complications of severe myelosuppression. Preliminary reports with low-dose ara-C were encouraging. However, results from a randomized trial of low-dose ara-C versus supportive care indicated that there was no survival benefit and significant mortality associated with infectious complications due to myelosuppression with low-dose ara-C. In addition, there was a positive association between degree of myelosuppression and survival for patients with RAEB and RAEB-t, confirming that any positive impact of low-dose ara-C on the course of MDS was due to myelosuppression and not differentiation. There does not appear to be a role for routine use of low-dose ara-C, given the lack of a proven survival benefit compared with supportive care alone. Preliminary results from trials with alternative differentiating agents are encouraging, but are not ready for routine use.

III. Supportive care

Almost all MDS patients will eventually require red cell and platelet transfusions for symptomatic anemia and thrombocytopenia. The hemoglobin threshold for

red cell transfusion must be individualized, based on an assessment of each patient's symptoms and cardiopulmonary status. Platelet transfusions should be used to treat acute bleeding events, or before anticipated invasive procedures, rather than to maintain an arbitrary minimal platelet count. To minimize the risk of HLA alloimmunization and future refractoriness to platelet transfusions, all red cell and platelet products should be leukoreduced. As the cumulative number of red cell transfusions reaches 30 to 40 units, transfusion-associated iron overload becomes a concern. In MDS patients with a low IPSS score, significant red cell transfusion burden, elevated ferritin, and life expectancy of several years, iron chelation with desferroximine (30 to 40 mg/kg s.c. daily, 5 days/week) is an option to consider. However, no prospective studies validate the success of and compliance with chelation therapy for transfusion-associated iron overload in MDS patients.

Treatment with hematopoietic growths factors can reduce or eliminate red cell transfusion requirements of anemic MDS patients by increasing endogenous red cell production. However, most patients will not have a meaningful response to EPO, and those that do, require daily, expensive injections. Response rates exceed 50% for patients with endogenous EPO levels less than 100 U/L and transfusion requirements less than 2 units/month. Patients with EPO levels greater than 500 U/L or requiring transfusion of more than 2 units of red cells/month are very unlikely to respond. Anemic patients with the refractory anemia with ringed sideroblasts (RARS) subtype of MDS are particularly resistant to EPO. However, response rates improve significantly when EPO and G-CSF are administered together. Beginning with EPO and adding G-CSF if there is no response after 2 months is a reasonable approach for the non-RARS anemic MDS patient (Table 17.4). Attempts to find minimally effective doses of EPO or G-CSF in responsive patients, by gradually tapering the doses, is safe because most patients will respond to a subsequent increase if anemia recurs. Trials of EPO and granulocyte–macrophage (GM)-CSF have not been encouraging, and this combination is not recommended. Prophylactic treatment of neutropenia with G-CSF or GM-CSF does not clinically benefit patients and may reduce platelet counts. These growth factors should be reserved for treatment of acutely infected neutropenic patients.

Cytopenia	EPO[a]	G-CSF[a]
Anemia		
EPO >500 U/L	No	No
EPO ≤500 U/L		
FAB: RARS	150–300 U/kg/day + s.c.	0.3–3.0 μg/kg/day, s.c.
FAB: Other	150–300 U/kg/day → s.c.	0.3–3.0 μg/kg/day s.c. if no response to EPO after 2 mo
Neutropenia		
Asymptomatic	—	No
Active infection	—	5.0 μg/kg/day s.c.

MDS, myelodysplasia syndrome; G-CSF, granulocyte-colony-stimulating factor; EPO, erythropoietin; FAB, French–American–British; RARS, refractory anemia with ringed sideroblasts.
[a]If no response after 2 months @ maximal dose, stop.

TABLE 17.4. HEMATOPOIETIC GROWTH FACTOR SUPPORT FOR MDS PATIENTS

IV. **Background**

Most cases of MDS arise *de novo* (i.e., not treatment related) with an average age at diagnosis of about 75 years and with a prevalence equal to or greater than that of AML. MDS occurs rarely in children and young adults or as a familial disease. Chemotherapy-related MDS (t-MDS) can be a delayed complication of exposure to alkylating drugs and topoisomerase II inhibitors such as doxorubicin and VP-16 or etoposide. The latency period varies from 2 to 5 years. Complex cytogenetic abnormalities are common, frequently involving chromosomes 5 and 7, and the poor prognosis for patients with t-MDS is similar to that for the IPSS high-risk primary MDS group.

A popular model for the pathogenesis of MDS combines cumulative DNA damage from environmental exposures (organic solvents, pesticides, heavy metals, ionizing radiation) with currently unknown inherited genetic predispositions. Subsequent genetic instability, evident as cytogenetic abnormalities associated with poor prognosis, is responsible for changes in the behavior of the malignant clone. However, no candidate tumor suppressor or oncogenes associated with common MDS breakpoints have been identified. Clinically, MDS is a heterogeneous group of hematopoietic disorders characterized by different degrees of ineffective hematopoiesis due to increased apoptosis, and proliferation of undifferentiated myeloid stem cells. In the more indolent types (RA, RARS), apoptosis dominates, and cytopenias are the primary clinical manifestation. In the more advanced types (RAEB, RAEB-t), with complex cytogenic abnormalities, proliferation and dedifferentiation dominate. In addition, the bone marrow cytokine environment appears to influence apoptosis. Overexpression of tumor necrosis factor-a and T cell–mediated myelosuppression have been associated with MDS cytopenias and aplastic anemia, suggesting that immunomodulating therapies could play a role in reducing MDS-associated apoptosis and correction of peripheral cytopenias. Recent studies have shown that a minority of patients with MDS do respond to anti–thymocyte globulin–based immunosuppressive regimens used to treat patients with severe aplastic anemia.

V. **Current focus**

Effective and minimally toxic differentiation agents would have the greatest impact on treatment of MDS because most patients are not candidates for intensive therapies. Many such agents are currently being investigated as potential treatments for patients with MDS. Pilot studies with two hypomethylating agents, 5-azacytidine and 5-aza-2¢-deoxycytidine (DAC) were promising. However, there was still considerable morbidity due to myelosuppression with the DAC dosing regimen. Amifostine, a free radical scavenger and cytoprotective agent, also stimulates hematopoiesis and may be an effective differentiating agent in MDS. Other novel treatment approaches undergoing investigation include low-dose melphalan, thalidomide, and combination therapy with growth factors, differentiating agents, and cytotoxic drugs.

Supportive therapy would be enhanced if symptomatic thrombocytopenia could be ameliorated with recombinant thrombopoietin (TPO). Clinical investigations are in progress. As our understanding of the complex genetic, cellular, and immunologic mechanisms involved in MDS increases, so will new treatment approaches for evaluation in clinical trials.

OTHER MYELOPROLIFERATIVE DISORDERS

Patients with Philadelphia-negative myeloproliferative disorders can usually be classified into one of three groups: polycythemia vera, primary (essential) thrombocytosis, or myelofibrosis with myeloid metaplasia. They share a similar pathobiology, evident in their clonal origins from pluripotential stem cells, phenotypic overlap, and risk for eventual transformation into acute leukemia.

I. **Polycythemia vera**

The hallmark of polycythemia vera (P vera) is an elevation in venous blood hematocrit (Hct). Sometimes the presenting symptom is an arterial or venous thromboembolic event. Additional symptoms are headache, dizziness, plethora, weakness, pruritus after hot baths or showers, and erythromelalgia (intermittent digital pain due to microarteriolar occlusions). Bleeding events are less common and are usually mild. Incidental discovery of an elevated Hct on a complete blood count (CBC) drawn for other reasons also is a common presentation.

Findings on physical examination can include a ruddy, cyanotic complexion, injected conjunctiva, and red, painful fingertips or toes in patients with erythromelalgia. A palpable spleen is common, hepatomegaly less so, and adenopathy is rare. Leukocytosis and thrombocytosis are present in about 66% and 50% of patients, respectively. Red cell morphology is either normal or microcytic and hypochromic secondary to iron deficiency due to gastrointestinal bleeding or phlebotomy. Occasionally, patients have an isolated erythrocytosis and no additional myeloproliferative signs, or an elevated white blood cell count (WBC) and platelet count, and a normal Hct due to either recent blood loss or an elevated plasma volume, which can occur with significant splenomegaly. Hyperuricemia is a common finding, and treatment with allopurinol should be initiated to prevent gout symptoms. Spuriously prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) results may be obtained when the Hct is greater than 55%. The final plasma concentration of citrate is a function of citrate volume in the collection tube (constant), and the plasma volume in the whole blood added to the tube (inversely related to the Hct). To perform a PT or aPTT, a fixed amount of $CaCl_2$ is added to the patient's plasma to neutralize the citrate. When the Hct is more than 55%, the plasma citrate concentration is higher, recalcification is incomplete, and *in vitro* clotting times are prolonged. This artifact can be avoided by collecting blood for coagulation

tests into a syringe with a smaller volume of citrate proportional to the elevated Hct.

To diagnose a patient with P vera accurately, one must (a) confirm that an elevated Hct represents an increased red cell mass (RCM), and (b) rule out causes of secondary erythrocytosis. Although there is no consensus on the diagnostic criteria for P vera, the algorithm outlined in Fig. 17.2 is consistent with recent strategies that incorporate bone marrow histology and serum EPO levels, use radioisotope dilution to determine RCM more selectively, and eliminate nonspecific tests such as leukocyte alkaline phosphatase and total B_{12}-binding capacity. When P vera is suspected, and the Hct is less than 55%, erythrocytosis requires confirmation. RCM is performed by injecting autologous red cells labeled with ^{51}Cr, and measuring the decrease in signal due to dilution on a subsequent venous sample. False-negative results can be obtained in obese patients when RCM is reported as milliliters per kilogram because of the decreased amount of blood in adipose tissue. To improve sensitivity, RCM results should be adjusted to reflect a patient's lean body mass (i.e., calculated surface area) and reported as elevated if they exceed the reference mean by more than 25%. Both low and normal serum EPO levels can be consistent with P vera, whereas an elevated EPO level is consistent with secondary erythrocytosis. A bone marrow aspirate and biopsy are performed for karyotype analysis, to assess fibrosis, and to identify abnormal megakaryocyte proliferation and clustering, which is typical in P vera and absent in secondary and unclassifiable erythrocytosis. The most definitive method for confirming P vera is to culture a patient's bone marrow in the presence and absence of EPO. Erythroid progenitor cells from P vera patients will differentiate into erythroid colonies in the absence of EPO, but normal precursors will not. However, *in vitro* bone marrow culture techniques are not standardized or readily available and should not be considered part of a routine evaluation.

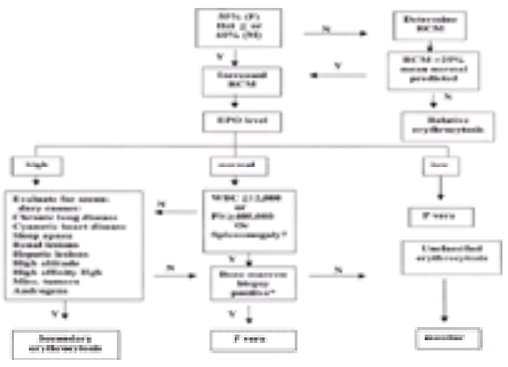

FIG. 17.2. Evaluation of patients with elevated hematocrits (F, greater than 45%; M, greater than 50%). *Abnormal megakaryocyte proliferation and clustering.

A. **Prognosis and therapy**

The natural history of P vera can be divided into several stages, beginning with asymptomatic, isolated erythrocytosis, progressing to more generalized myeloid proliferation, splenomegaly, and thrombosis, followed by myelofibrosis, leukoerythroblastosis, cytopenias, and myelodysplasia, and sometimes, acute leukemia. Survival for treated P vera patients ranges from 10 to 15 years. Strokes, myocardial infarctions, and venous thromboembolic events are the major causes of death, followed by acute leukemia, other cancers, and complications of myelofibrosis.

The goals of therapy for P vera are to prevent thromboembolic complications by controlling erythrocytosis, while not hastening transformation to acute leukemia. Once a diagnosis of P vera is confirmed, all patients should undergo aggressive therapeutic phlebotomy (500 mL every other day or 250 mL 2 times a week, based on patient tolerance) until the hematocrit is less than 45%. Once iron deficiency develops, mean cell volume (MCV) decreases, and phlebotomy frequency drops to 3 to 4 times/year.

For patients younger than 60 years who have no arterial or venous thromboembolic risk factors, periodic phlebotomy is sufficient for long-term management. However, if Hct control with phlebotomy is suboptimal, thrombotic complications occur, pruritus is unresponsive to antihistamines, or splenomegaly becomes intolerable, interferon-a (IFN-a, 1 to 3 × 10^6 units subcutaneously, 3 times/week, modified based on response and toxicity), is the next-line therapy. Hydroxyurea (HU, 10 to 30 mg/kg/day) is the third choice for this population. It is effective and well tolerated; however, concerns remain over its potential for causing secondary leukemia, infertility, and fetal toxicity. Management of asymptomatic thrombocytosis (platelet count greater than 600 × 10^9/L) in young P vera patients whose Hct is controlled by phlebotomy is controversial. Options include prophylactic low-dose aspirin, anagrelide, or no treatment.

Thromboembolic complications are more likely in older P vera patients (older than 60 years), those with a prior event, or those who require frequent phlebotomies to maintain an Hct less than 45%. In addition to phlebotomy, a trial of IFN-a should be considered. However, many older patients will not tolerate its side effects. As a result, HU is typically prescribed. Although radioactive ^{32}P injections and oral alkylating agents like busulfan and chlorambucil control P vera myeloproliferation, they are definitely leukemogenic, and should be used only in patients with a short life expectancy or who cannot tolerate IFN-a and HU, or are not helped by them.

Anagrelide is effective in controlling HU-resistant thrombocytosis. However, the vasodilation and positive inotropic actions of anagrelide may be poorly tolerated in older patients. Side affects include headache, fluid retention, atrial fibrillation, and gastrointestinal distress. The initial dose is 0.5 mg b.i.d. to q.i.d. Dosing limits are 2.5 mg per dose and 10 mg per day.

Patients who have experienced thromboembolic complications should receive aspirin prophylaxis. However, aspirin prophylaxis of asymptomatic P vera patients is controversial. In earlier trials, doses of 500 to 1,000 mg/day were associated with increased bleeding complications. However, a recent pilot study evaluating a daily aspirin dose of 40 mg did not report an increase in bleeding complications. The results from an ongoing, larger, prospective, randomized study of low-dose aspirin in P vera patients may provide clearer guidance. The decision to prescribe aspirin prophylaxis should be based on an assessment of the benefits versus risks for each patient. Those with significant atherosclerotic or cardiac disease would be strong candidates. The optimal dose is unknown, but 100 mg/day or less would appear to be reasonable. Contraindications include a history of abnormal bleeding or acquired von Willebrand disease due to absorption of large multimers onto the surface of platelets. The likelihood of the latter hemostatic defect is increased if the platelet count is greater than 1,000 × 10^9/L.

B. **Background**

The prevalence of P vera is low, reported rates varying from 0.02 to 2.6 /100,000 population/year. The average age at diagnosis is approximately 60 years. However, cases have been reported in all age groups. Although P vera has been associated with both radiation exposure and organic solvent exposure, these appear to represent risk factors for hematopoietic malignancies in general. P vera is an acquired clonal stem cell disorder in which erythroid progenitor cell proliferation is either independent of or increasingly sensitive to growth factors like EPO. However, no definitive cytogenetic or molecular discoveries into the etiology of P vera have occurred. Current attention is focused on alterations in postreceptor intracellular signaling pathways because most evidence indicates that cytokine and EPO receptors on hematopoietic cells from P vera patients are not mutated, except in rare cases of familial erythrocytosis associated with truncated EPO receptors.

The mechanisms involved in P vera–associated thromboembolic complications also are incompletely understood. Increased blood viscosity is clearly an important risk factor, but normalization of RCM does not totally reverse the risk. Qualitative abnormalities of P vera platelets most likely contribute to the thrombotic complications as well, although no currently available platelet-function test is useful in predicting the risk for individual patients.

C. **Current focus**

Additional large, prospective clinical studies are needed the better to define the relative roles of IFN-a, anagrelide, and low-dose aspirin in the management of patients with P vera. Newer therapeutics await progress in understanding the biochemical and molecular mechanisms involved in abnormal hematopoietic proliferation, thrombosis, and clonal evolution into acute leukemia.

II. **Primary (essential) thrombocytosis**

The hallmark of primary thrombocytosis is a persistently elevated platelet count, arbitrarily defined as greater than 600,000/µL, in the absence of an underlying secondary disorder. Many patients are asymptomatic when thrombocytosis is noted on review of CBC results ordered for another indication. When symptoms are present, they are typically due to arterial thrombosis, ranging from distal arterial ischemia, headaches, visual disturbances, and transient ischemic attacks, to strokes and myocardial infarctions. Inflammation and thrombosis of arterioles in the distal extremities produces a clinical condition called erythromelalgia, characterized by patient complaints of painful, red, swollen toes. Symptoms are exacerbated by heat and relieved by cooling or ingestion of aspirin. Venous thromboembolic events are relatively uncommon, but may occur in unusual locations such as hepatic or mesenteric veins. Bleeding is a less frequent presenting complaint and is usually minor except for occasional gastrointestinal hemorrhages. Splenomegaly is detectable in about half of patients, but is rarely massive or symptomatic. Aside from signs of thrombotic or hemorrhagic events, the physical examination is unremarkable, and patients generally feel well.

Thrombocytosis based on an automated CBC report requires review of a peripheral smear for confirmation, although causes of false-positive elevated platelet counts are rare. Abnormally large platelets are typical, as well as a leukocytosis (usually less than 20×10^9/L), with occasional immature myeloid cells. Most patients will have normal hemoglobin, and normal or minor changes in red cell morphology. Prophylactic allopurinol therapy should be considered if urate levels are elevated. Artifactual hyperkalemia due to *ex vivo* release of potassium from platelets may occur when the platelet count is extremely elevated.

A. Workup and staging

A diagnosis of primary thrombocytosis requires ruling out an underlying cause for reactive thrombocytosis and other myeloproliferative disorders, especially chronic myelogenous leukemia (CML). Secondary causes of thrombocytosis include iron-deficiency anemia, acute and chronic infections, trauma, malignancies, and inflammatory disorders. Although the degree of thrombocytosis does not distinguish primary from secondary causes, bleeding and thrombotic complications are rare, and an elevated C-reactive protein is common in reactive thrombocytosis.

A bone marrow biopsy and aspirate should be performed in all patients with thrombocytosis in whom there is a reasonable suspicion for a myeloproliferative disorder. The expected findings in primary thrombocytosis are stainable iron; increased myeloid, erythroid, and megakaryocytic cellularity; and abnormal clusters of large megakaryocytes with increased nuclear ploidy. Increased reticulum staining may be present, but severe distortion of marrow architecture due to collagen fibrosis is rare. If stainable iron is not present, or the patient has a microcytic anemia or low ferritin, the patient should be reassessed for P vera after iron repletion. Clinically, CML can be indistinguishable from primary thrombocytosis. Because the prognosis and management of these disorders are so different, karyotype analysis should be done on all bone marrows, and if Philadelphia chromosome negative, molecular screening for bcr/abl gene rearrangement should be performed. Primary thrombocytosis patients typically have normal karyotypes. Rarely, thrombocytosis accompanies MDS. Marrow dysplasia and an abnormal karyotype help to distinguish MDS from primary thrombocytosis.

B. Therapy and prognosis

The major causes of morbidity and mortality in primary thrombocytosis patients are arterial and venous thromboembolic events and, less commonly, major bleeding complications. Although *in vitro* platelet-function studies have confirmed a wide range of qualitative platelet abnormalities, none is sufficiently predictive of thrombotic or hemorrhagic complications to recommend for routine testing. This includes the bleeding time. Although there is no correlation between platelet count and thrombosis risk, major bleeding complications are more likely when platelet counts exceed $1{,}000 \times 10^9$/L, and are associated with an acquired type 2 deficiency of von Willebrand factor (vWF), presumably due to absorption of large vWF multimers onto the surface of platelets. With reduction of the platelet count, large multimers reappear, and bleeding risk diminishes. Survival rates for patients with primary thrombocytosis are similar to those of age-matched controls, and transformation into a clinically apparent myelofibrotic disorder or acute leukemia is rare.

Patients who are at high risk for major thromboembolic events should receive platelet-reduction therapy. This group includes patients with a history of thromboembolic events, major cardiovascular risk factors (hypertension, hyperlipidemia, smoking), and who are older than 60 years. Smokers should be strongly encouraged to stop smoking. Although not supported by prospective investigations, the recommended goal of platelet-lowering therapy is normalization of the platelet count (400×10^9/L or lower). When this is not feasible because of intolerance of, or poor compliance with therapy, a reduction to at least 600×10^9/L is acceptable. There is no consensus on management of asymptomatic, low-risk patients. Approaches include no intervention, low-dose aspirin (100 mg/day or less), and platelet-lowering therapy. Younger, low-risk patients who develop erythromelalgia rapidly respond to aspirin and may not require normalization of their platelet counts. Another difficult management situation is an asymptomatic pregnant woman with primary thrombocytosis. The risk of an adverse fetal outcome, typically early spontaneous abortion, is high, especially for a woman with a history of fetal loss. Treatment options include observation, low-dose aspirin, or IFN-a to reduce the platelet count.

When primary thrombocytosis patients have life-threatening bleeding or thromboses, plateletpheresis is an effective and rapid platelet-lowering intervention. Maintenance therapy options include the antimetabolite HU, IFN-a, and anagrelide. Because of concerns that HU may be leukemogenic, it is usually reserved for patients older than 60 years or for whom alternative drugs fail or cannot be tolerated. An initial dose of 30 mg/kg/day of HU will dependably produce a decline in platelet count within 7 to 10 days, without severe leukopenia. Subsequently, the dose is adjusted to maintain the platelet count below the target threshold. Side effects are modest and frequently resolve with continued treatment. IFN-a depresses platelet production through both direct and indirect cytokine effects on megakaryopoiesis. It is an effective agent for controlling thrombocytosis in a patient who cannot tolerate HU or for whom it fails, is symptomatic and younger than 60 years, or is pregnant. Starting dose is 3×10^6 units 3 times a week subcutaneously, and then adjusted based on platelet-lowering response and toxicity. However, many patients will not tolerate the side affects of IFN, limiting its overall effectiveness. Anagrelide is an imidazoquinazoline compound that reduces platelet production by unknown mechanisms. The accumulated clinical experience with this relatively new drug has been encouraging. Response rates are excellent and durable, even in refractory patients. The onset of action is usually apparent with in a week or two. Initial dose is 0.5 mg b.i.d. or q.i.d. The dose can be gradually increased by 0.5 mg/week until the platelet target is achieved. The maximal recommended single and total daily doses are 2.5 mg and 10 mg, respectively. Side effects of anagrelide include mild anemia, gastrointestinal discomfort, headaches, tachyarrhythmias (predominantly atrial fibrillation), and fluid retention due to drug-induced vasodilation and increased myocardial contraction. Anagrelide should not be administered to patients with significant cardiovascular diseases and cautiously prescribed to elderly patients in general. It probably crosses the placenta and therefore is contraindicated in pregnancy. However, it is well tolerated in younger primary thrombocytosis patients and is the preferred drug for this population.

Rarely IFN-a, HU, and anagrelide will fail. Long-term plateletpheresis is not feasible. Alternative, effective myelosuppressive agents include busulfan, chlorambucil, and intravenous radioactive phosphorus (^{32}P). However, each is associated with an increased risk of transition into acute leukemia. Bone marrow transplantation for primary thrombocytosis not a treatment option because potentially eligible patients have such a good prognosis that the risk of transplant-associated mortality would not be acceptable.

C. Background

Primary thrombocytosis is an uncommon myeloproliferative disorder typically occurring after age 50 years, with an incidence of about three cases per 100,000/year. However, younger people are being diagnosed more frequently with the disorder because of increased ordering of automated CBCs for various indications. The pathogenesis of primary thrombocytosis is unknown, and no environmental exposures have been linked to this disorder. Rare, familial forms of thrombocytosis have been reported, and preliminary investigations support mutations in either the gene for thrombopoietin or its receptor as likely mechanisms. However, searches for mutations in these genes among cases of sporadic primary thrombocytosis have been unproductive.

D. Current focus

Prospective investigations are necessary to determine the optimal platelet-count threshold that will minimize thromboembolic complications and provide guidelines for platelet-lowering therapy in young, asymptomatic patients. In addition, prophylactic platelet inhibition with low-dose aspirin requires further study as monotherapy in asymptomatic patients, and in combination with platelet-lowering drugs. Although both IFN-a and anagrelide are effective, nonleukemogenic therapies, broader application is limited by their side effects. Newer analogues may maintain an inhibitory affect on thrombogenesis while reducing constitutional and cardiovascular side effects.

III. Idiopathic myelofibrosis

The dominant features of idiopathic myelofibrosis (IM) are progressive bone marrow fibrosis, prominent splenomegaly due to extramedullary hematopoiesis, and

a leukoerythroblastic peripheral blood appearance with teardrop red cells. Alternative names for this disorder include agnogenic myeloid metaplasia and myelofibrosis with myeloid metaplasia.

Most patients are symptomatic when IM is diagnosed. Constitutional symptoms (fatigue, weight loss, night sweats) and complaints related to an enlarged or infarcted spleen are most common. Occasionally, abnormal bleeding, jaundice, or acute urate arthropathy will precipitate medical attention. Unusual sites of extramedullary hematopoiesis can occur as ascites or pleural effusions, symptomatic brain or spinal cord compression, and pulmonary, gastrointestinal, or genitourinary masses.

Splenomegaly, frequently massive, is almost always appreciated on physical examination. Mild to moderate hepatomegaly also is consistently present and is sometimes accompanied by signs of portal hypertension due to intrahepatic venous occlusion or congestion due to increased splenic blood flow. At presentation, most patients are anemic, whereas platelet and WBC counts vary widely. Two defining features of IM are evident on examination of a peripheral smear: nucleated red blood cells and immature myeloid cells (leukoerythroblastic picture); and teardrop-shaped red cells. In addition, abnormally large platelets or megakaryocyte fragments are present. The bone marrow must be evaluated in all cases. An inadequate aspirate is common because of fibrosis (dry tap). Typical findings on the biopsy include diffuse increase in the normal reticular pattern of collagen demonstrated with silver stains; islands of hematopoietic tissue separated by thick, fibrotic bands of collagen; increased numbers of dysplastic megakaryocytes, sometimes in clusters; and expanded sinusoids containing hematopoietic foci. Cytogenetics [and polymerase chain reaction (PCR) for bcr/abl rearrangement if Philadelphia chromosome negative] should be performed on peripheral blood or bone marrow to rule out CML with marked fibrosis.

Secondary myelofibrosis can mimic the clinical findings of IM and should be considered during the initial evaluation. Causes include metastatic cancer (breast, colon, lung, gastric, and prostate), lymphoid malignancies (Hodgkin disease, hairy cell leukemia, plasma cell dyscrasias), tuberculosis, and fungal infections. Occasionally myelofibrosis can be a significant feature in MDS or an underlying autoimmune disorder. Acute megakaryocytic anemia can have some of the clinical and histologic features of IM, although marked splenomegaly is absent, and blasts are increased in both peripheral blood and bone marrow. In addition, both P vera and primary thrombocytosis can evolve into a myelofibrotic, or spent phase, with progressive splenomegaly and extramedullary hematopoiesis.

A. **Therapy and prognosis**

The median survival for IM patients is approximately 5 years, worse than that for P vera or primary thrombocytosis, although individual survival rates vary widely. Advanced age and hemoglobin less than 10 g/dL appear to be the most important predictors of a poor prognosis. Other features associated with shortened survival include leukocytosis (WBC greater than 10 to 30 × 10^9/L), circulating blasts, thrombocytopenia (platelet count less than 100 × 10^9/L), constitutional symptoms, and an abnormal karyotype. However, no risk-stratification criterion has been prospectively evaluated. Transformation to acute leukemia occurs in about 15% to 20% of IM patients. Other major causes of deaths are infection, thromboembolic events, and cardiac or hepatic failure.

In general, the management strategies for IM are palliative, and sometimes controversial. Symptomatic splenomegaly, constitutional symptoms, and thrombocytosis are usually responsive to HU (10 to 30 mg/kg/day), although the duration of response may be brief. Complications secondary to splenomegaly include pain, early satiety, portal hypertension, transfusion-dependent anemia, and thrombocytopenia. Treatment options include splenectomy, splenic irradiation, and IFN-a.

Even in carefully selected patients, the operative mortality for splenectomy in this population ranges from 7% to 15%. Complications include bleeding [secondary to disease-associated disseminated intravascular coagulation (DIC) and qualitative platelet dysfunction], infection, postsplenectomy thrombocytosis, venous and arterial thromboemboli, and progressive hepatomegaly secondary to increased extramedullary hematopoiesis. A retrospective review of 233 splenectomies for IM from the Mayo Clinic produced several notable findings. Postoperative fatality rate was 9%, and 31% developed major complications. Surgery was very effective at relieving mechanical or constitutional symptoms associated with splenomegaly, reduced the transfusion requirements in 23% of patients in whom anemia was a motivation for surgery, and did not improve platelet counts in patients with severe thrombocytopenia. Postsplenectomy median survival was 2 years.

Splenic radiation is an alternative for symptomatic patients who are too ill for, or choose not to undergo splenectomy. However, improvement lasts for only about 6 months, and severe, often fatal, cytopenias, independent of radiation dose, occur in about 25% of patients. Splenectomy should not be performed in IM patients who have previously been irradiated because of increased bleeding complications. Low-dose radiation is effective for controlling symptomatic sites of extramedullary hematopoiesis other than the liver or spleen, and for localized bone pain.

Younger patients with a histocompatible donor should be considered for curative therapy with allogeneic bone marrow transplantation. However, young, minimally symptomatic IM patients also may do well with supportive treatment alone. Based on the results of transplants in 66 patients, 5-year survival rates were 62% for patients younger than 45 years, and 14% for patients 45 years and older. In addition to age, anemia (hemoglobin less than 10 g/dL) and osteosclerosis are associated with poor posttransplantation survival. Bone marrow fibrosis is not a significant impediment to engraftment and will gradually resolve after successful transplantation. Autologous SCT may have some palliative benefits in selective cases and should now be considered an investigative therapy. Whether aggressive treatment of asymptomatic or minimally symptomatic IM patients with different cytotoxic or myelosuppressive regimens alters the natural course of the disease requires further investigation.

Anemia is a major complication for most patients. Potential etiologies include iron deficiency due to variceal bleeding, folate deficiency due to increased utilization, ineffective erythropoiesis, and autoimmune hemolytic anemia. Increased plasma volume secondary to massive splenomegaly can produce a misleadingly low Hct. A radioisotope dilution study to determine RCM is a more accurate guide for red cell transfusions in this situation. Prolonged transfusion support may lead to iron overload, necessitating chelation therapy, for patients with a reasonable life expectancy. EPO is rarely effective and should not be administered routinely. Some patients will respond to androgens such as oxymetholone, 50 to 200 mg/day, or a synthetic androgen, danazol (400 to 600 mg/day). It may take 3 to 6 months to see a response with these drugs, and periodic monitoring for hepatic toxicity is required. In patients with evidence of shortened red cell survival, prednisone (1 mg/kg) may decrease transfusion requirements.

B. **Background**

An incidence of about one per 100,000 population/year and average age at presentation of 60 years for idiopathic myelofibrosis are similar to those for P vera and primary thrombocytosis. Although the pathogenesis of IM remains unknown, radiation and organic solvent exposures have been linked with the disease. Two major processes are involved in the pathobiology of IM. A primary stem cell clonal proliferation produces hematopoietic cells that secrete an abnormal cytokine environment. The result is a polyclonal proliferation of marrow stromal cells leading to increased deposition of collagen, fibrosis, angiogenesis, and osteosclerosis. Likely mediators of these processes are transforming growth factor b (TGF-b) and platelet-derived growth factor (PDGF). Secretion of fibroblast-stimulating growth factors has been demonstrated from both megakaryocytes and monocytes isolated from IM bone marrow. Clonal proliferation and disruption of normal bone marrow architecture facilitate escape of stem cells, leading to extramedullary hematopoiesis. Despite a high rate of karyotype abnormalities, a unique molecular mutation has not been identified.

C. **Current focus**

Insights into the role of cytokine expression in promotion of marrow fibrosis have led to treatment strategies to neutralize growth factors like TGF-b or to selectively inhibit proliferation of megakaryocytes. However, results from preliminary trials with suramin, a TGF-b antagonist, and anagrelide, an inhibitor of megakaryopoiesis, were negative. New genetic and biochemical insights into the myelofibrotic process may lead to the design of novel inhibitory agents. Meanwhile, clinical investigations are needed to determine if IFN-a can delay the rate of progression of myelofibrosis in mildly symptomatic patients.

IV. **Chronic myelogenous leukemia**

A detailed discussion of chronic myelogenous leukemia can be found in Chapter 14 (leukemia).

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CHAPTER 18. SARCOMA

Arnel M. Pallera, Matthew A. Arquette, and Douglas J. McDonald

Approach to the Sarcoma Patient
General
Soft Tissue Sarcoma
Soft tissue sarcomas
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Subjective symptoms by site of origin
The physical examination
Diagnosis and staging
Stage-directed approach to therapy
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Retroperitoneal sarcomas
Breast sarcomas
Head and neck sarcomas
Treatment of metastatic disease
Bone Sarcoma
Bone sarcomas
Presentation
Pertinent history
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General principles of local therapy
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Molecular biology
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APPROACH TO THE SARCOMA PATIENT

I. **General.** Sarcomas are malignancies of connective tissue (from the Greek *sarx* for flesh), including fatty tissue, muscle, blood vessels, and bone. Most of these tissues share a common embryologic origin, arising primarily from tissues derived from the mesoderm, although there are three notable exceptions [Ewing sarcoma, neurosarcomas, and the peripheral neuroectodermal tumors (PNETs)]. The clinical manifestations of sarcomas are dependent on the anatomic site of origin. The presenting signs and symptoms vary markedly, from a painless lump to debilitating pain. Because of the large number of neoplasms categorized as a sarcoma, the discussion of sarcomas will be divided among the soft tissue neoplasms (extremity, retroperitoneal, and visceral) and the bone sarcomas.

SOFT TISSUE SARCOMA

I. **Soft tissue sarcomas** represent a number of tumor histologies. Pathologic diagnosis follows the resemblance of these tumors to normal tissues. Despite this diversity, many of the clinical features and treatment decisions are common among various histologies.
II. **The presentation** of soft tissue sarcomas varies according to the site of origin.
   A. **Pertinent history** should include a search for risk factors, including genetic syndromes (hereditary retinoblastoma, Li–Fraumeni syndrome, neurofibromatosis, and familial adenomatous polyposis), chemical exposures (herbicides, wood preservatives, Thorotrast contrast, dioxin/Agent Orange, vinyl chloride, arsenic), and ionizing radiation. In most patients, prior risk factors cannot be identified.
   B. **Subjective symptoms by site of origin**

      1. Extremity sarcoma. Approximately half of all soft tissue sarcomas occur in the extremities. The majority are first seen as a painless primary soft tissue mass. Pain is present in less than one third of patients. Patients often report an antecedent history of trauma, but the etiologic significance of this is unclear.

      2. Retroperitoneal sarcomas account for 15% of all soft tissue sarcomas. Most patients have an abdominal mass (80%), and approximately half have abdominal pain. The pain is often vague and nonspecific. Weight loss is seen infrequently, with early satiety, nausea, and emesis occurring in fewer than 40% of patients. Neurologic symptoms, primarily paresthesia, occur in up to 30% of patients.

      3. Visceral sarcomas represent 15% of soft tissue sarcomas. Signs and symptoms relate to the viscus of origin. For example, gastric sarcomas frequently occur with dyspepsia or gastrointestinal bleeding. Rectal bleeding and tenesmus are seen with sarcomas of the rectum. Dysphagia and chest pain are common presenting symptoms of esophageal sarcomas. Painless vaginal bleeding is seen with uterine leiomyosarcomas.

   C. **The physical examination** of a patient with sarcoma should include an assessment of the size of the mass and its mobility relative to the underlying soft tissues. Site-specific neurovascular examinations also should be done. Spread to regional lymph nodes is rare in soft tissue sarcomas, but assessment for lymphadenopathy should be performed. In terms of laboratory evaluation of a patient with a sarcoma, baseline laboratory studies are usually normal.
   D. **Diagnosis and staging.** In addition to a thorough history and physical examination, the staging evaluation of patients with soft tissue sarcoma includes biopsy to establish the pathologic diagnosis and tumor grade and radiographic imaging to determine the size of the tumor and the extent of disease.
      1. **Radiographic imaging.** The studies needed for adequate staging vary depending on the site of disease. For soft tissue masses of the extremities, magnetic resonance imaging (MRI) has been regarded as the imaging modality of choice because of the contrast between tumor and muscle and between tumor and adjacent blood vessels. It further provides multiplanar definition of the tumor. For pelvic lesions, the multiplanar capability of MRI is superior. However, for retroperitoneal and abdominal sarcomas, computed tomography (CT) scans provide satisfactory anatomic definition of the tumor. CT also provides adequate imaging of the liver, the most common site of metastasis for abdominal and retroperitoneal sarcomas.

         Angiography is not usually indicated in the staging of sarcomas because MRI accurately delineates vascular involvement. In addition, nuclear medicine bone scanning has poor specificity and sensitivity in detecting bony invasion and is rarely recommended. Positron electron tomography (PET) has not become routine but may be helpful in detecting unsuspected distant metastases in patients with high-grade lesions.

         For patients with sarcoma of the extremities, most metastases (88%) will go to the lung. For small, superficial lesions, a preoperative chest radiograph may be sufficient to evaluate for lung metastases, but in patients with high-grade tumors, or tumors larger than 5 cm, a staging CT of the chest should be

performed.

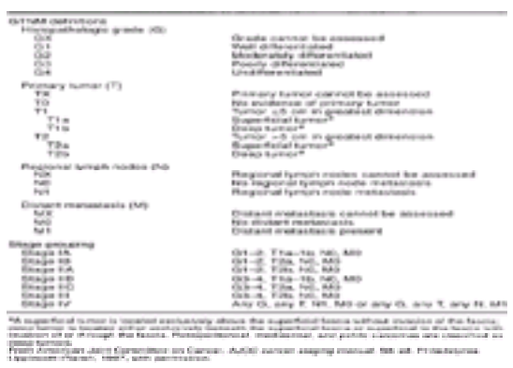
2. **Pathology. In an adult, biopsy should be obtained** of any soft tissue mass that is symptomatic or enlarging, larger than 5 cm, or has persisted beyond 4 to 6 weeks. Grossly, most sarcomas are similar, with a pale tan “fish flesh” appearance. For most extremity lesions, a longitudinal incision is required because the incisional scar must be included in the wide local excision of the mass. The incision should be centered over the mass at its most superficial location. Meticulous hemostasis should be ensured to prevent hematoma formation and possible dissemination of the tumor.
   a. **The histologic classification of soft tissue tumors is organized** according to the normal tissues they resemble. The ratio of benign to malignant tumors is approximately 100:1. Unlike carcinomas, sarcomas (malignant soft tissue tumors) do not demonstrate *in situ* changes, nor does it appear that they originate from benign soft tissue tumors (with the exception of malignant peripheral nerve sheath tumors in patients with neurofibromatosis). As can be expected from a diverse group of tumors, there can be considerable disagreement among pathologists regarding specific histologic diagnoses, which may necessitate second opinions to confirm a diagnosis. Clinical behavior is determined more by anatomic site, grade, and size than by a specific histology. Hence most soft tissue sarcomas with these features in common are treated similarly despite different histologies.
   b. **The histologic grade** of a sarcoma is the single best prognostic indicator for the development of recurrent disease. The pathologic features that determine grade include cellularity, differentiation, pleomorphism, necrosis, and number of mitoses (Table 18.1).

Low-Grade Sarcomas	High-Grade Sarcomas
Good differentiation	Poor differentiation
Hypocellular	Hypercellular
Increased stroma	Minimal stroma
Hypovascular	Hypervascular
Minimal necrosis	Much necrosis
<5 mitoses per high-power field	>5 mitoses per high-power field

From Hajdu SI, Shiu MH, Brennan MF. The role of the pathologist in the management of soft tissue sarcomas. World J Surg 1988;12:309–301, with permission.

TABLE 18.1. GUIDELINES TO THE HISTOLOGIC GRADING OF SARCOMAS

   c. **The three most common histopathologic** subtypes are the malignant fibrous histiocytoma, liposarcoma, and leiomyosarcoma. One can often correlate a location of a tumor with its histology. For example, most retroperitoneal sarcomas are liposarcomas or leiomyosarcomas. Leiomyosarcoma is the most common type of genitourinary sarcoma in the adult. Rhabdomyosarcomas arising in paratesticular tissues can be seen in young men. The three major types of uterine sarcomas are leiomyosarcomas, mesodermal mixed tumors, and endometrial stromal sarcomas.
   d. **Clinical pathologic features of specific tumor types**
      1. **Malignant fibrous histiocytoma (MFH)** is a tumor of later adult life with a peak incidence in the seventh decade. It usually is first seen as a painless mass. The most common site of involvement is the lower extremity, followed by the upper extremity, and then the retroperitoneum.
      2. **Liposarcoma** is primarily a tumor of adults with a peak incidence between ages 50 and 65 years. It may occur anywhere in the body, but the most common sites are the thigh and retroperitoneum. Several types of liposarcoma are recognized, and they have different clinical outcomes. Well-differentiated liposarcoma is a nonmetastasizing lesion. Sclerosing liposarcoma also is a low-grade lesion. Myxoid and round cell (or lipoblastic) liposarcomas are low- to intermediate-grade lesions and typically have a t(12;16)(q13-14;p11) translocation. Fibroblastic and pleomorphic liposarcomas are higher-grade lesions.
      3. **Leiomyosarcomas** may arise in any location, but more than half are located in the uterus, retroperitoneum, or intraabdominal regions. Extremity leiomyosarcomas most frequently arise in the thigh. There are reports of leiomyosarcomas arising in large vascular structures and obstructing blood flow. The most common arterial site is the pulmonary artery, where the clinical picture may mimic pulmonary embolus. Leiomyosarcomas of the inferior vena cava may mimic Budd–Chiari syndrome.
      4. **Kaposi sarcoma (see AIDS-Associated Malignancies, Chapter 6)** may occur as raised pigmented lesions on the skin. It classically affects elderly Jewish and Italian men and is fairly indolent. It usually occurs in the lower extremities. An aggressive variant occurs in younger children and is endemic in some areas of Africa. In patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), a disseminated, aggressive form of this disease may develop.
      5. **Angiosarcoma** is an aggressive malignant tumor of blood vessels affecting primarily the elderly. It may arise in any organ, but is especially seen in the head and neck region, the breast, and the liver. The skin is commonly involved. Breast angiosarcomas occur in young and middle-aged women, and liver angiosarcomas arise in adults previously exposed to thorium dioxide, insecticides, and polyvinyl chloride. This also is the most common primary malignant tumor of the myocardium. The 5-year survival is less than 20%.
      6. **Synovial sarcoma** usually occurs in young adults. The most common site is the knee. Unlike most soft tissue sarcomas, these lesions are usually painful.
      7. **Rhabdomyosarcoma** is a malignant tumor of skeletal muscle. Four categories are recognized: pleomorphic, alveolar, embryonal, and botryoid. **Pleomorphic rhabdomyosarcoma** usually occurs in the extremities of patients older than 30 years. It is highly anaplastic and may be confused with MFH pathologically. The 5-year survival is about 25%. The **alveolar variant** is a highly aggressive tumor that affects adolescents and young adults. Its histology resembles that of lung alveoli. The 5-year survival is less than 10%. **Embryonal rhabdomyosarcoma** arises primarily in the head and neck, especially the orbit. It affects infants and children, with a peak incidence at age 4 years. With this tumor, there is a high sensitivity to chemotherapeutic agents and a high cure rate with combined-modality therapy. The **botryoid variant** has been encompassed in the embryonal category. It has a gross appearance of polypoid masses and has a predilection for the genital and urinary tract. It occurs primarily in children with an average age of 7 years.
3. **Staging.** The staging system for soft tissue sarcomas incorporates histologic grade (G), size of the primary (T), nodal involvement (N), and distant metastasis (M) (Table 18.2). Grade of the tumor is the predominant feature predicting early metastatic recurrence and death. Beyond 2 years of follow-up, the size of the lesion becomes as important as the histologic grade. Outcome by stage is shown in Table 18.3.



*A superficial tumor is located entirely above the superficial fascia without invasion of the fascia. Deep tumor is located entirely below or partially beneath the superficial fascia or invades it. Fascia is the invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.
From American Joint Committee on Cancer. AJCC cancer staging manual. 5th ed. Philadelphia: Lippincott-Raven, 1997, with permission.

TABLE 18.2. AJCC STAGING SYSTEM FOR SOFT TISSUE SARCOMAS

Stage	Five-Year Survival (1991)
I	>90%
II	70%
III	20%–50%
IV	<20%

Adapted from Forscher CA, Kempe CE, Eilber FR. Soft tissue sarcomas. In: Haskell CM, ed. *Cancer treatment*. 5th ed. Philadelphia: WB Saunders, 2001:1268–1279, with permission.

TABLE 18.3. SURVIVAL RATES FOR SOFT TISSUE SARCOMA BY STAGE

III. **Stage-directed approach to therapy**

A. **Extremity soft tissue sarcomas**

1. **Surgery is the mainstay of therapy** for all soft tissue sarcomas of the extremity and trunk. Over the past 20-year period, there has been a gradual shift in the surgical management of extremity soft tissue sarcomas away from radical ablative surgery, such as amputation and compartment resection, toward limb-sparing surgery. In the past, very conservative surgical approaches in which the plane of dissection is immediately adjacent to a pseudocapsule (an area around the tumor that is composed of tumor fimbriae and normal tissue) were associated with a local recurrence rate of 37% to 63%. However, a wide local resection encompassing a rim of normal tissue around the lesion led to improvements in local control, with a local recurrence rate of 30% in the absence of adjuvant therapy. The planned resection should encompass the skin, the subcutaneous tissues, and soft tissue adjacent to the tumor, including the previous biopsy site and any associated drain sites. The tumor should be excised with a 2- to 3-cm margin of normal surrounding tissue whenever possible.

   Wide local excision alone is all that is necessary for small (T1), low-grade, soft tissue sarcomas of the extremities, with local recurrence rate of less than 10%. For T2 extremity soft tissue sarcomas or any high-grade sarcomas, limb-sparing surgery plus adjuvant radiation to improve local control has become the standard approach. When adjuvant radiation is planned, metal clips should be placed at margins of resection to facilitate radiation field planning. Currently, in most centers, more than 90% of patients are treated with limb-sparing procedures. Amputation is reserved as a last-resort option for local control, and it should be used with the knowledge that it does not affect survival when compared with limb-sparing strategies.

   There is almost no role for regional lymphadenectomy in adult patients with sarcoma because of the low (2% to 3%) prevalence of lymph node metastases. However, patients with angiosarcoma, embryonal rhabdomyosarcomas, synovial sarcoma, and epithelioid sarcomas have an increased incidence of lymph node involvement and should be examined and imaged for lymphadenopathy.

2. **Radiation therapy** alone in the treatment of unresectable or medically inoperable soft tissue sarcoma patients yields a 5-year survival rate of 25% to 40% and a local control rate of 30%. Radiation doses should be at least 65 Gy, if feasible, given the site of the lesion. After local excision, adjuvant radiation therapy (XRT) should be recommended for (a) virtually all high-grade extremity sarcomas, (b) lesions larger than 5 cm (T2), and (c) positive or equivocal surgical margins in patients for whom reexcision is impractical. A phase III NCIC study comparing adjuvant (postoperative) and neoadjuvant (preoperative) radiation demonstrated similar local control rates, metastatic outcome, and overall survival rates between the two arms. However, patients receiving preoperative radiation had a significantly higher incidence of wound complications (35% vs. 17%).

   Brachytherapy also has been used in treatment for sarcomas. Iridium 192 is the most commonly used agent. It has comparable local control rates versus adjuvant external-beam radiation therapy, although some data suggest a higher rate of wound complications and a delay in healing when the implants are afterloaded before the third postoperative day. The advantages of brachytherapy include a decrease in the patient's entire treatment to 10 to 12 days from 10 to 12 weeks, and the advantage that smaller volumes of tissue can be irradiated, which could improve functional results. However, smaller volumes may not be appropriate, depending on the tumor size and grade.

3. **Chemotherapy.** The benefit of adjuvant chemotherapy is controversial. The exciting results of systemic chemotherapy obtained in pediatric sarcomas have not translated to the adult population. A formal meta-analysis of individual data from 1,568 patients who participated in 13 trials was performed by the Sarcoma Meta-Analysis Collaboration. The analysis demonstrated a significant reduction in the risk of local or distant recurrence in patients who received adjuvant chemotherapy. There also was a decrease in the risk of distant relapse (metastasis) by 30% in treated patients. Overall survival, however, did not meet criteria for statistical significance between the control group and adjuvant chemotherapy arm, with a hazard ratio of 0.89. Outside of a clinical trial, the role of chemotherapy in soft tissue sarcomas is currently limited to the small round blue-celled tumors (i.e., rhabdomyosarcoma, PNETs), bone sarcomas, and palliation in patients with advanced disease.
4. **Local recurrence** should be treated with surgical resection whenever feasible. Adjuvant XRT is often used. For unresectable recurrence of disease, XRT is preferred.
5. **Treatment of limited pulmonary metastasis.** For patients with a limited number of pulmonary metastases, metastasectomy has been performed with some improvement in survival when compared with no surgery. Three-year survival rates range from 23% to 42% if a complete resection is performed. For unresectable “pulmonary only” disease, isolated lung perfusion, a technique to administer chemotherapeutic drugs in a way that results in a high concentration of the agent in the lung with less systemic exposure, has been attempted with equivocal results so far.

B. **Retroperitoneal sarcomas.** Only 50% of patients with retroperitoneal sarcomas are able to undergo complete surgical resection, and of these, approximately half will develop a local recurrence. This points to an important role for adjuvant therapy. Two-year local control rates of 70% have been reported with the addition of postoperative XRT. However, the doses that effect control in the extremity (more than 65 Gy) are usually associated with significant gastrointestinal (GI) toxicity.

C. **Breast sarcomas** are rare, accounting for 1% of all breast malignancies. They usually occur as a painless mass with no distinctive findings on mammography. The main treatment is surgery, with controversy over the extent of resection. The role of radiation therapy is not yet defined. The 5-year survival rate is approximately 60%.

D. **Head and neck sarcomas.** Adult head and neck sarcomas are rare, representing approximately 1% of all head and neck malignancies and 10% of all soft tissue sarcomas. Most of these tumors occur as a painless mass. Any histologic type of sarcoma could originate in the head and neck area, but there is a preponderance of angiosarcoma in this site. Sarcomas in this area are treated with multimodality therapy. Surgery is the main treatment, but achieving a wide local excision is difficult or impossible, necessitating the use of radiation therapy. Five-year survival rates vary from 29% to 74%.

E. **Treatment of metastatic disease.** The goal of therapy for patients with metastatic sarcoma is palliation and prolongation of survival. Cure is no longer a viable goal. Systemic chemotherapy is the primary modality of treatment. Radiation and surgery may be used with a goal of palliation.

1. **Numerous chemotherapy agents** have been used as single agents in soft tissue sarcomas. Doxorubicin and ifosfamide are the most active agents. In the 1980s, a number of drugs including cyclophosphamide, dactinomycin, and vincristine were used as single agents with response rates of 5% to 10%. Doxorubicin was the first significantly active agent against soft tissue sarcomas, with an objective overall response rate of approximately 25%. Continuous infusion of doxorubicin decreases the risk of cardiotoxicity and the severity of nausea while maintaining equivalent antitumor activity when compared with bolus infusion. Dacarbazine (DTIC) also has been found to have activity in soft tissue sarcomas, with a response rate of 17%. It is particularly effective in leiomyosarcomas. Ifosfamide has been found to have significant activity in sarcoma, with a response rate of 24% to 38%. Based on evidence of an increasing response rate to higher doses of ifosfamide, trials of “high-dose ifosfamide” (approximately 12 to 14 g/m ^{2}) showed higher response rates and responses after an ineffective standard-dose ifosfamide.
2. **Combination chemotherapy.** When doxorubicin was combined with dacarbazine (the AD or ADIC regimen), higher response rates were observed, with a response rate of approximately 17% to 40%. To improve the response rate further, several agents were added to the ADIC combination. A phase III trial comparing ADIC, cyclophosphamide plus ADIC (CyADIC), and dactinomycin plus ADIC (DACADIC) resulted in equivalent toxicities but no significant differences in response rates between the three arms. Furthermore, the combination of cyclophosphamide and vincristine with ADIC (the CyVADIC regimen) was no better than doxorubicin alone in a randomized trial.

   A combination of [sodium 2-]mercaptoethane sulfonate (MESNA), doxorubicin, ifosfamide, and dacarbazine (MAID) resulted in a response rate of approximately 47%, with 30% complete responses. A phase III trial comparing MAID with ADIC resulted in a higher overall response rate with MAID (32% to 17%) but significantly more myelosuppression on the MAID arm. Further, overall survival was not significantly different and appeared worse in older

patients with MAID. Combination chemotherapy has been compared with single-agent doxorubicin in eight randomized phase III trials. Some of them showed superior response rates with combination chemotherapy, but none of the trials found a significant survival advantage. Kaplan–Meier plots are superimposable within each trial and from trial to trial.

BONE SARCOMA

I. **Bone sarcomas** may be derived from any of the cells in bone, including cartilage (chondrosarcoma), bone (osteosarcoma, parosteal osteogenic sarcoma), notochord (chordoma), or unknown cells of origin (Ewing sarcoma, malignant giant cell tumor, and adamantinoma). Some sarcomas more common in soft tissue also may arise in bone, including malignant fibrous histiocytoma, fibrosarcoma, liposarcoma, and angiosarcomas.

II. **Presentation.** The clinical presentation of bone sarcomas may suggest the pathologic diagnosis before biopsy.

A. **Pertinent history** should note any history of malignancy, which may be a source of metastasis to bone or a history of RT resulting in a radiation-induced sarcoma. Rapid growth or change in a lesion favors a malignant etiology.

1. **Chronic bone lesions.** Paget disease of bone may give rise to osteosarcoma and giant cell tumors of bone. Sites of chronic osteomyelitis may produce osteosarcomas and squamous cell carcinomas. Fibrous dysplasia may rarely give rise to osteosarcoma. Chondrosarcomas may arise from preexisting benign enchondroma (solitary or multiple in Ollier disease), or exostoses (hereditary multiple exostoses).

B. **Subjective symptoms.** Localized pain and swelling are the hallmark clinical features of bone sarcomas. The pain initially is insidious but can become unremitting. Occasionally a pathologic fracture will bring the patient to medical attention. If the tumor arises in the lower extremities, the patient may have a limp. Constitutional symptoms are rare but can be observed in patients with Ewing sarcoma or patients with metastatic disease.

C. **The physical examination** may reveal a palpable mass. A joint effusion may be observed, and range of motion of the joint may be limited with stiffness or pain. Neurovascular and lymph node examinations are usually normal.

D. **Diagnosis and staging** evaluation should include biopsy and review of appropriate radiographic imaging.

1. **Radiographic imaging** should include plain films of the lesion and MRI or CT scan. Biplanar radiographs of the affected bone are helpful in determining the specific site of involvement within the bone, the pattern and extent of bony destruction, periosteal changes, and the presence of matrix mineralization within the tumor.

a. **Osteolytic (bone destroying) lesions** may be seen in metastatic carcinomas, myeloma, and primary bone tumors. Well-defined (geographic) borders of bone destruction may indicate a slower growing or less aggressive lesion, such as a low-grade chondrosarcoma. As the tumor extends beyond the area of lytic destruction, more aggressive growth may be associated with a “moth-eaten” pattern. Rapid, aggressive growth patterns may be associated with cortical destruction, a soft tissue mass, and a permeative pattern of bone destruction.

b. **Osteoblastic (bone-forming) lesions** may be associated with meta-static disease (for example, prostate, breast, pancreas, and small cell cancer of the lung) or osteosarcoma.

c. **Periosteal reactions** may be seen on plain films that give additional clues to the diagnosis. A “sunburst” pattern is associated with classic osteosarcoma. A lamellar or “onion-skin” periosteal reaction is most associated with Ewing sarcoma. Spiculated periosteal reactions are associated with rapidly growing tumors such as Ewing sarcoma. A raised periosteal reaction (Codman triangle) may be seen in a number of tumors.

d. **MRI is the imaging study of choice** for the evaluation of most bone sarcomas, allowing visualization of the relation of the tumor to the neurovascular structures, adjacent joints, and the surrounding soft tissues. MRI also can easily demonstrate the intramedullary extent of the tumor and the presence of skip metastases.

e. **CT scan** of the primary site may be considered in place of MRI to demonstrate cortical destruction more accurately and for evaluation of pelvic tumors. CT scan of the chest is preferred to image the chest, which is the most common initial site of metastasis.

f. **Radionuclide technetium 99 bone scan** imaging is important for assessing extent of tumor within bone at the primary, and the presence of skip metastases or distant bone metastases. The role of fluorodeoxyglucose (FDG)-PET imaging is not defined at this time.

2. **Laboratory features.** Anemia or leukocytosis may be present in patients with Ewing sarcoma. Elevated alkaline phosphatase and lactate dehydrogenase (LDH) levels are observed in patients with osteosarcoma, Ewing sarcoma, or Paget disease. An abnormal glucose tolerance test may be seen with chondrosarcoma.

3. **Pathology of bone sarcomas.** The classification of bone neoplasms is, like that of soft tissue sarcomas, based on the cell of origin. Primary bone sarcomas can exhibit a phenomenon of dedifferentiation, in which these neoplasms exhibit a dimorphic histologic pattern with low-grade and high-grade patterns in the tumor. Treatment is dictated by the high-grade lesion.

a. **Osteosarcoma** is the most common malignant primary bone tumor, with an annual incidence of three per million. Peaks in incidence occur in adolescents and in the elderly. Most osteosarcomas occur in the metaphyseal region, near the growth plate, of skeletally immature long bones. The distal femur, proximal tibia, and proximal humerus are most common sites.

b. **Ewing sarcoma** represents 10% to 15% of all primary malignant bone tumors. It is the second most common malignant tumor of bone in childhood and adolescence. The peak incidence is the second decade of life. It is rare in blacks. Ewing sarcoma tends to occur in the diaphysis of long bones. The most common sites are the femur, followed by the pelvis, and then the skin. Ewing sarcoma and peripheral primitive neuroectodermal tumors (PPNETs) share a common genetic origin, a translocation between chromosomes 11 and 22 or 21 and 22. When arising in bone, this tumor is recognized as Ewing sarcoma, with a soft tissue sarcoma recognized as a PPNET. Treatment of these tumors is similar, by using a combination of chemotherapy and local measures (surgery and radiation). Ewing sarcoma is one of the **small round blue cell tumors.** The differential diagnosis of these tumors includes lymphoma, neuroblastoma, retinoblastoma, and rhabdomyosarcoma.

c. **Chondrosarcoma** is the second most frequent malignant primary bone tumor, representing approximately 20% of all primary bone malignancies. It usually occurs in patients older than 40 years. It can occur in any bone, but the majority occur in the pelvis (30%), femur (20%), and the shoulder girdle (15%). The ability to perform a complete resection is the main determinant of recurrence and survival, with 5-year survival of about 50%.

d. **Adamantinoma** is an indolent, osteolytic tumor that often develops in the upper tibia. It has a 5-year survival of more than 90%.

e. **Giant cell tumor of bone,** or osteoclastoma, represents approximately 5% of all primary bone tumors. The peak incidence is in the third decade of life, with a female predilection. They are typically epiphyseal–metaphyseal tumors, with the majority in the distal femur and proximal tibia.

4. **Staging of bone sarcomas** is shown in Table 18.4. Adverse prognostic indicators include an increased LDH, an increased alkaline phosphatase, and an axial primary.

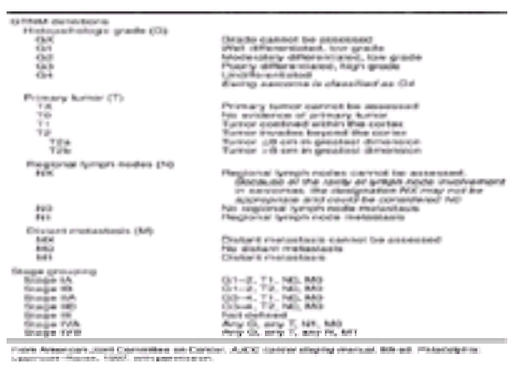


TABLE 18.4. AJCC STAGING SYSTEM FOR BONE SARCOMAS

III. **Treatment of bone sarcomas**

A. **General principles of local therapy. Surgical excision** is the mainstay of treatment for patients with low-grade bone sarcomas. For high-grade tumors, multimodality therapy is indicated. As an example, for high-grade osteosarcomas, preoperative multiagent chemotherapy is followed by surgical removal of the tumor and further adjuvant chemotherapy. It is important to distinguish high-grade osteosarcoma from a low-grade variant, parosteal osteosarcoma, which has a lower malignant potential and does not require adjuvant chemotherapy. Occasionally, parosteal osteosarcomas will become dedifferentiated and their behavior will resemble the behavior of the classic osteosarcoma.

1. **Limb-sparing surgery.** The Musculoskeletal Tumor Society recognizes wide excision, either by amputation or a limb-salvage procedure, as the recommended surgical approach for all high-grade bone sarcomas. Currently, 75% to 80% of patients may be treated with a limb-sparing surgery. This type of resection is predicated on complete tumor removal, effective skeletal reconstruction, and adequate soft tissue coverage. There are three types of limb-sparing procedures.

a. **Osteoarticular resection,** excision of tumor-bearing bone and the adjacent joint, is the most common procedure because most bone sarcomas arise in the metaphysis of long bones.

b. **Intercalary resection** is excision of tumor-bearing bone only.

c. **Whole bone resection,** excision of the entire bone and adjacent joints, is used when the tumor extends along or invades the joint. Reconstruction is usually achieved by prosthetic arthroplasty.

B. **Osteosarcoma therapy.** The 5-year survival for osteosarcoma with surgery alone is less than 20% because, although the incidence of local recurrence is low, microscopic dissemination is likely to be present in 80% of patients at the time of diagnosis. The impression of improved survival with the addition of adjuvant chemotherapy has been confirmed in randomized clinical trials and is now considered standard therapy for high-grade osteosarcoma, permitting survival as high as 80%.
   1. **Active agents** in osteosarcomas include doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate with leucovorin rescue. These agents are typically used in combination to improve response, although the optimal combination and duration of therapy remain controversial.
   2. **Preoperative chemotherapy** began as a strategy to permit limb-sparing surgery, allowing time for creation of custom-made prosthetics. Since its acceptance, other advantages have been recognized with this approach, including earlier treatment of micrometastatic disease, preventing emergence of resistant clones, and potentially allowing debulking of the primary to improve chances for limb-sparing surgery.
   3. **Histologic response to preoperative therapy** is recognized as a significant prognostic factor. Various systems have been developed for grading histologic response to chemotherapy, but greater than 90% necrosis of tumor cells is associated with the best prognosis. This recognition also has resulted in attempts to salvage poor responders by altering the postoperative chemotherapy to include alternative drugs.
   4. **Adverse prognostic indicators** also include an increased LDH, an increased alkaline phosphatase, and/or an axial primary.
   5. **Metastatic disease.** Approximately 10% to 20% of patients with osteosarcoma have evidence of metastatic disease at presentation. Some of these patients may be candidates for surgical resection of pulmonary metastases. For patients with more extensive metastatic disease, chemotherapy is used to provide control of disease and palliation of symptoms.
   6. **Radiation therapy** is not routinely used in the therapy of osteosarcoma, but may prove helpful in patients who refuse definitive resection or palliation of patients with metastatic disease.

C. **Therapy for Ewing sarcoma** and the related PPNET tumors uses a combined-modality approach.
   1. **The optimal treatment for local tumor control** is not well defined. Historically, RT has been the mainstay of local therapy, but there has been a recent trend toward surgery. No prospective randomized trials have been performed to compare the two modalities, but retrospective data suggest improvements in local control and survival when surgery is done with a complete resection of the tumor. Patients with unresectable disease or positive margins require RT to improve local control.
   2. **Chemotherapy.** Before the availability of effective chemotherapeutic agents, fewer than 10% of patients with Ewing sarcoma survived beyond 5 years, although only 15% to 35% of patients with Ewing sarcoma/PPNET have evidence of metastatic disease at presentation. This fact suggests that many patients with Ewing sarcoma had microscopic dissemination at the time of diagnosis. The First Intergroup Ewing's Sarcoma Study demonstrated an improved survival rate for patients receiving systemic therapy with VACA (vincristine, actinomycin D, cyclophosphamide, and doxorubicin). The Second Intergroup Ewing's Sarcoma Study used VACA but on an intermittent schedule and a higher dose and achieved an improved 5-year survival (73%). The addition of alternating cycles of ifosfamide and etoposide to VAC or VACA further improved survival in patients with Ewing and PPNET. Tumor response to VAC is predictive of overall outcome.
   3. **For advanced Ewing sarcoma,** cure is not a realistic goal. Palliation and prolongation of survival are more realistic expectations. Fortunately, aggressive combination chemotherapy and RT can still lead to prolonged progression-free survival.

D. **The role of chemotherapy in other high-grade bone sarcomas** is less well defined, but should be considered in the treatment approach to these malignancies. Examples may include mesenchymal chondrosarcoma, high-grade MFH, and dedifferentiated sarcomas.

BACKGROUND

I. **Epidemiology.**

In the United States, the incidence of soft tissue sarcomas is approximately 6,000 cases per year, and the incidence of sarcomas of bone is approximately 2,100 per year. It comprises 1% of adult malignancies and 7% of pediatric malignancies.

II. **Risk factors**

Most cases of sarcoma are sporadic with no identifiable risk factors. However, a number of predisposing factors have been recognized.

A. **Radiation.** Sarcomas have been found to originate in or near tissues that have received prior external-beam RT. These radiation-induced sarcomas generally occur at least 3 years after RT was delivered and often develop decades later. The majority of these lesions are high grade, and they are typically osteosarcomas, malignant fibrous histiocytomas, and angiosarcomas.

B. **Exposure to certain chemicals** has also been found to lead to the development of sarcomas. For example, colloidal thorium dioxide (Thorotrast) has been found to cause hepatic angiosarcomas. Other agents that have been linked to sarcomas include phenoxy herbicide exposure in forestry workers, dioxin exposure, and arsenic. Further, alkylating chemotherapy agents such as cyclophosphamide, melphalan, and the nitrosoureas that are used in childhood cancers have been associated with the development of sarcomas in adulthood.

C. **Genetic conditions** include several syndromes associated with sarcomas. For example, patients with neurofibromatosis type I have a 10% risk of developing a neurofibrosarcoma. Patients with the Li–Fraumeni syndrome, due to p53 mutations, are at an increased risk for sarcomas, breast cancer, lung cancer, and adrenocortical tumors. Other associations include familial retinoblastoma and the development of osteosarcoma, Gardner syndrome and the development of fibrosarcoma, and the link between rhabdomyosarcoma and tuberous sclerosis or the basal cell nevus syndrome.

D. **Other risks associated with sarcomas** include Stewart–Treves syndrome, which is the development of a lymphangiosarcoma in a lymphedematous arm after mastectomy. There is also the association between Kaposi sarcoma and HIV disease as well as the link between Paget disease of bone and the development of osteosarcoma or fibrosarcoma.

III. **Molecular biology.** Several cytogenetic abnormalities are characteristic of certain sarcomas. The following is a list of tumors and their karyotypic mutations.

PPNET and Ewing sarcoma: t(11;22)
Synovial sarcoma: t(X;18)
Clear cell sarcoma: t(12;22)
Alveolar rhabdomyosarcoma: t(2;13)
Embryonal rhabdomyosarcoma: trisomy 2q
Myxoid liposarcoma: t(12;16)
Uterine leiomyosarcoma: t(12;14)
Extraskeletal myxoid chondrosarcoma: t(9;22)

IV. **Future directions** in the treatment of sarcomas include the search for more effective chemotherapy agents and combinations, and targeted therapies that will exploit the genetic features of these tumors. Increasingly, the role of combined-modality approaches incorporating chemotherapy is being explored in treating these tumors. The limited progress in adult sarcomas should be a factor encouraging the support and entry of patients into clinical trials.

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CHAPTER 19. MALIGNANT MELANOMA AND SKIN CANCER

J. Daniel Cuevas and Eric Whitman

Malignant melanoma
Presentation
Workup and staging
Therapy and prognosis
Complications
Follow-up
Special considerations
Background
Current focus of research
Squamous cell carcinoma of the skin
Presentation
Workup and staging
Therapy
Prognosis
Follow-up and prevention
Background
Current focus of research
Other nonmelanoma skin carcinomas
Basal cell carcinoma
Merkel cell carcinoma

I. Malignant melanoma

A. Presentation

1. **Any new skin lesion or changes in a preexisting skin lesion** should be thoroughly evaluated. This evaluation should include assessment of risk factors, history of the evolution of the lesion, complete physical examination, exhaustive skin evaluation, lymph node assessment, laboratory and imaging tests, and a biopsy.

   Occasionally patients are first seen with metastatic disease and symptoms related to the site of metastasis.

2. **Subjective**
   a. **Skin lesions.** Frequently patients visit their physician after the appearance of a new skin lesion or changes in preexisting pigmented skin lesions. The lesion may change in color (variegated, lighter, or darker), size, or develop associated symptoms (itching, ulceration, or bleeding).
   b. **Metastasis.** Melanoma derives from a developmentally migratory neural crest cell, and hence it is prone to metastasize widely and to unusual sites. Frequent sites of clinically evident metastasis include skin and lymph nodes in 59% of patients, lungs in 36%, liver in 20%, bone in 17%, and other sites, 8%. It frequently metastasizes to different organs simultaneously and symptoms depend on melanoma sites.
3. **Objective.** In evaluation of the pigmented skin lesion, the “ABCDs” for differentiating melanomas from benign lesions are helpful.
   A: asymmetry; melanoma lesions are commonly asymmetric.
   B: border irregularity; melanoma lesions commonly have irregular borders.
   C: color; melanoma have variegated lesions (different color shades in the same lesion).
   D: diameter; lesions that increase in size or are larger than 6 mm in diameter should be carefully evaluated for the presence of melanoma. Other changes in skin lesions such as bluish coloration, itching, bleeding, ulceration, or changes in a preexisting mole should prompt a careful evaluation for melanoma.
   E: elevation of a lesion.

   Any skin lesion with one of these attributes is suggestive of melanoma. Such lesions should be evaluated by a dermatologist. A comprehensive skin examination also is critical in evaluating and monitoring patients with melanoma. Careful examination of axillae, scalp, interdigital webs and soles, genitalia, and oral cavity is essential.

   The differential diagnosis of a pigmented skin lesion includes benign nevi, hemangioma, seborrheic keratoses, pigmented nonmelanoma skin cancer, and atypical nevi. Benign nevi are usually well-defined lesions with a smooth surface and uniform pigmentation, and may be hair bearing. Hemangiomas are the most common soft tissue tumors present at birth and frequently regress spontaneously, occasionally requiring intralesional treatment. Seborrheic keratosis is a verrucous plaque or papule that is frequently seen on the face, neck, or trunk, and occurs in chronically sun-exposed areas. Pigmented nonmelanoma of the skin cancer may appear as a nodule with erythema in chronically sun-exposed areas of the skin. Atypical moles also are called atypical moles or dysplastic nevi and frequently are irregularly shaped large lesions with different degrees of discoloration. Some atypical nevi may develop into a melanoma even after removal of a major portion.

B. Workup and staging

1. **Excisional biopsy.** Suspected melanoma lesions should not be observed. A complete excision with clinically negative margins is always desirable. An incisional biopsy or punch biopsy may be performed if the lesion is located in a cosmetically compromising area. Shave biopsies should be avoided because they compromise the pathologist's ability to stage the cancer adequately. Frozen-section analysis is not recommended for the diagnosis of melanoma.
2. **Histologic classification.** Five types of primary melanoma have been described and appear to have slightly different biologic behavior.
   a. **Superficial spreading melanoma (SSM)** is the most common type of melanoma. It represents about 70 % of all cutaneous melanomas. Slow progression occurs, usually over years before rapid growth and diagnosis. SSM frequently arises from a nevus and spreads in a radial fashion (horizontal spread).
   b. **Nodular melanoma (NM)** is the second most common type of melanoma. It represents approximately 10% to 15% of all cutaneous melanomas. It has a more aggressive presentation than SSM, commonly arises in uninvolved skin, and spreads in a vertical fashion (invasive potential).
   c. **Lentigo maligna melanoma (LMM)** represents approximately less than 10% of cutaneous melanomas. It is seen in the elderly in sun-exposed areas such as the head, neck, and upper extremities.
   d. **Acral–lentiginous melanoma (ALM)** frequently occurs in patients with pigmented skin, and it may occur on palms, soles, nail beds, and mucous membranes.
   e. **Desmoplastic melanoma (DM)** is rare, occurs in the elderly as a thick indurated plaque or nodule, is frequently amelanotic, and is related to neurotropic melanoma.
3. **Lymph node evaluation.** Clinical and pathological evaluation (when indicated) of the lymph nodes will assist the treating physician in assessing the stage of the melanoma, prognosis, and treatment options.
4. **Current staging of melanoma.** Involvement of regional lymph nodes is the most important predictive factor, in the absence of metastasis. The other important prognostic factors are the thickness of the primary lesion, measured in millimeters (i.e., Breslow thickness), and the presence of pathologic ulceration. Breslow's depth is a method that measures the thickness of the primary tumor from the top of the granular layer of the epidermis to the deepest tumor cell at the base of the lesion.

   Several methods have been used for staging melanoma. The most commonly used method is the American Joint Commission for Cancer (AJCC) Cancer Staging (Table 19.1 and Table 19.2). New staging systems are under consideration for adoption within the next few years [American Joint Committee on Cancer, American Cancer Society, American College of Surgeons. *AJCC cancer staging handbook.* 5th ed. Philadelphia: Lippincott-Raven, 1998].

T Classification	Thickness	Other
T_is		Atypical melanocytic hyperplasia, severe melanocytic dysplasia (Clark level I)
T1	≤0.75 mm	Invades the papillary dermis (Clark level II)
T2a	0.75–1.5 mm	Invades the papillary–reticular dermal surface (Clark level III)
T3a	1.5–3.00 mm	1.5–3.00 mm, invades reticularis dermis
T3b		(Clark level IV) 3.00–4.00 mm
T4a	>4.00 mm	>4.00 mm and/or invades the subcutaneous tissue (Clark level V)
T4b		Satellite(s) within 2 cm of primary tumor
N Classification	**Lymph Nodes**	**Other**
N1a	≤3 cm in greatest dimension	
N2a	>3 cm in greatest	>3 cm in greatest dimension
N2b	dimension and/or	In-transit metastasis
N2c	in-transit metastasis	Both N2a and N2b
M Classification	**Location**	**Other**
M1	Distant metastasis	
M1a	Metastasis to skin or soft tissue or lymph nodes beyond regional	
M1b	Visceral metastasis	

TABLE 19.1. AJCC TNM CLASSIFCATION

Stage	T	N	M
I	T1–T2	N0	M0
II	T3	N0	M0
III	T4	N0	M0
	Any T	N1	M0
	Any T	N2	M0
IV	Any T	Any N	M1

TABLE 19.2. AJCC TNM STAGING FOR MELANOMA

5. **Recommendations for staging.** After complete history and physical examination including skin evaluation, further workup should include complete blood count (CBC), chemistry profile and lactate dehydrogenase (LDH), and posteroanterior (PA) and lateral chest radiograph. In patients with stage I melanoma, further workup is unnecessary in the absence of symptoms or abnormal laboratory results. In patients with high-risk primary lesions (stage II and III) or suspected distant disease, computed tomographic (CT) scans, magnetic resonance imaging (MRI), and positron emission tomography (PET) may be helpful, depending on the clinical situation.

C. **Therapy and prognosis**

1. **Therapy for primary lesion.** Early diagnosis of cutaneous melanoma may lead to removal of curable tumors. Excision of the primary lesion with adequate margins is of critical importance. Shave biopsies or cryosurgery are contraindicated. Adequate margins of excision are necessary in the management of melanoma. For lesions that are less than 1.00 mm thick, an adequate margin is 1 cm. For lesions that are thicker than 1.00 mm, a margin of 2 cm should be adequate (Karakousis C, Balch C, Urist M, et al. Local recurrence of malignant melanoma: long term results of a surgical trial. Society of Surgical Oncology 48th Annual Symposium Abstract, 1995). The margins should always be negative microscopically. If there is evidence of residual melanoma cells or melanocytic hyperplasia at the margins, reexcision is indicated. Patients in whom the margins are adequately managed and who have stage I and II disease have a 5-year survival rate of 90% and 70%, respectively.

   The risk of regional and distant metastasis correlates with tumor thickness. Lesions that are less than 0.76 mm thick have a risk of regional recurrence and distant disease of less than 3%. Lesions that are between 0.76 and 1.50 mm thick have a risk of regional recurrence and distant disease of 25% and 8%, respectively. Lesions that are between 1.50 and 4.00 mm thick have a risk of regional recurrence and distant disease of 57% and 15%, respectively. Lesions that are thicker than 4.00 mm have a risk of regional nodal disease and distant metastasis of 62% and 72%, respectively (DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology.* Philadelphia: Lippincott-Raven, 1997:1947–2011).

2. **Evaluation of lymph node metastases.** Different trials have demonstrated the lack of survival benefit of elective lymph node dissection, and this has stimulated the development of new procedures that can assess the lymph node basin and have less morbidity. Sentinel lymph node (SLN) biopsy is now recommended for patients with clinically negative lymph nodes (see later), and lymph node dissection is reserved for patients with clinically involved lymph nodes (therapeutic node dissection; *CA Cancer J Clin* 2000;50:215–236).

   The first node or nodes to which the primary melanoma drains are called SLNs. The SLNs are by definition those nodes at highest risk for metastatic disease. Multiple studies have confirmed the feasibility of identifying the SLN with a combination of isosulfan blue (Lymphazurin blue) dye and technetium 99m radionuclide injected intradermally at the primary site. Biopsy and appropriate histopathologic examination of SLNs provides essential staging information in patients at significant risk for regional nodal metastatic disease. Data suggest that SLNs can be identified with success in more than 80% of lymphatic basins dissected. Approximately 21% of the SLNs have metastases (*Arch Surg* 1992;127:392–399).

   The current indications for SLN biopsy, ideally performed at the same time as wide local excision, are (a) Breslow thickness greater than 0.75 mm, (b) pathologic ulceration, and (c) Breslow thickness less than 0.75 mm and either Clark level IV (Table 19.1) or vertical growth phase.

3. **Adjuvant therapy.** Adjuvant therapy with interferon significantly increased median relapse-free survival by 9 months and resulted in a 42% improvement in the 5-year relapse-free survival rate compared with observation. Overall, patients with stage III have a 5-year survival rate of 50% (*J Clin Oncol* 1996;14:7–17; *J Clin Oncol* 2000;18:2444–2458; *J Clin Oncol* 1996;14:1–2).

   Interferon-a2b has been approved for adjuvant therapy in patients with thick melanomas (larger than 4 mm; T4) and in patients with positive lymph nodes (N1 to 2). The treatment consists of interferon a2b, 20 million IU/m^2 i.v. every day, 5 days per week for 4 weeks, followed by 10 million IU/m^2 3 times per week for 48 weeks.

4. **Treatment of metastatic disease.** There are no generally accepted, clinically affective, treatments for stage IV melanoma. Therefore all patients with metastatic melanoma should be encouraged to participate in clinical trials. Available options for management of metastatic melanoma include single-agent chemotherapy, combination-chemotherapy regimens, immunotherapy, and biochemotherapy.

   Single-agent dacarbazine (DTIC) has an objective response rate (RR) between 15% and 20%, and it is currently approved for the treatment of advanced melanoma. DTIC as a single agent is commonly prescribed at doses between 850 and 1,000 mg/m^2 i.v., on day 1, repeated every 3 to 4 weeks. Other single agents commonly used include cisplatin, carboplatin, paclitaxel, and vincristine, with RRs ranging from 12% to 23% (DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology.* Philadelphia: Lippincott-Raven, 1997:1947–2011). Temazolamide, an imidazotetrazinone derivative analogue of DTIC, has demonstrated activity in patients with metastatic melanoma with a 21% overall RR. Because temazolamide crosses the blood–brain barrier, it has been used in patients with brain metastasis with variable success.

   Combination-chemotherapy regimens have neither a higher RR nor a survival benefit when compared with DTIC in prospective randomized trials. Frequently used regimens include CVD (cisplatin, vinblastine, and DTIC), with RRs ranging from 30% to 40%, with a median duration of response of about 9 months, and the Darmouth regimen (cisplatin, dacarbazine, carmustine, and tamoxifen), with RRs ranging from 19% to 55%, with a median survival time from randomization of 7 months (*Cancer Treat Rep* 1984;68:1403–1405).

   Biologic agents such as interferon-a2b and interleukin-2 (IL-2) have been extensively studied in advanced melanoma. Interferon-a2b, when used as a single agent in metastatic melanoma, produces a 15% RR (*Curr Opin Oncol* 1996;8:167–174). IL-2 has resulted in durable and complete responses in up

to 8% in a group of highly selected patients with metastatic disease (*J Clin Oncol* 1999;17:2105–2116). Unfortunately, IL-2 given at high doses is an extremely toxic regimen. The combination of interferon-a and IL-2 has not resulted in higher RRs than either agent alone in patients with metastatic disease.

Trials using biochemotherapy combining CVD, interferon a2b, and IL-2 have demonstrated conflicting results, with generally higher response rates but uncertain survival benefit (*Proc Am Soc Clin Oncol* 1997;16: 490a; *J Clin Oncol* 1999;17:968–975). In a randomized trial of 65 patients with 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU), DTIC, *cis*-diaminedichloroplatinum (CDDP), tamoxifen ± IL-2, and interferon showed that chemotherapy resulted in a 27% RR with eight partial responses, whereas the biochemotherapy with IL-2 and interferon resulted in 23% RR with one complete response (CR) and seven partial responses (PRs), with no difference in duration of response, disease-free survival, or overall survival (*Proc Am Soc Clin Oncol* 1997;16:490). A more recent trial by European Organization for Research and Treatment of Cancer (EORTC) compared IL-2 and interferon with or without CDDP in patients with metastatic melanoma. The RR was similar in both arms of the study. There was a slight advantage in progression-free survival in the combination arm, but no difference in overall survival (*J Clin Oncol* 1997;15:2579–2588). A National Cancer Institute (NCI) trial compared CDDP, DTIC, and tamoxifen with high-dose IL-2 plus interferon plus CDDP, DTIC, and tamoxifen in 102 patients. The chemotherapy arm demonstrated a response in 18 of the 52 patients treated in this arm. The biochemotherapy arm demonstrated a response in 25 of the 50 patients treated. The trial was stopped early because of a survival advantage to the chemotherapy-alone arm (*J Clin Oncol* 1999;12:968–975). Large-scale randomized clinical trials are addressing the use of biochemotherapy.

In general, for patients with good performance status and minimal or no medical problems, aggressive regimens should be considered, preferentially under a protocol. For debilitated individuals with multiple medical problems, single-agent chemotherapy or lower-dose immunotherapy can be considered. Providing best supportive care remains an option for these individuals.

5. **Management of metastasis.** Brain metastasis confers a poor prognosis. The treatment options depend on the number and location of the lesions. Steroids may reduce the accompanying swelling and provide palliation. For asymptomatic patients with a solitary central nervous system (CNS) lesion, or for patients without major neurologic impairment, surgical resection or gamma knife radiation should be considered. Patients who had previously responded to systemic immunotherapy and now relapsed with intracranial disease appear to have a significant benefit after resection. The benefits of craniotomy include palliation of symptomatic patients and potential for prolonged disease-free survival in the brain.

   Radiation therapy is the treatment of choice for patients with unresectable brain metastasis.

D. **Complications**

1. **Complications of the disease.** Metastatic melanoma has a median survival between 6 and 9 months. Frequent sites of metastasis include the skin, lungs, liver, brain, and bone. Removal of a single metastatic lesion remains controversial. There is not a randomized trial to support the use of metastatectomy. Nonetheless, a subgroup of patients appears to benefit from this surgical procedure. Metastatectomy should be considered when metastatic disease is limited to a single site that is amenable to complete resection and in the absence of locoregional disease.

   Patients with symptomatic skin metastasis not responding to systemic therapy may be considered for surgery or radiation therapy. Pain and ominous skin breakdown are relative indications for radiotherapy.

2. **Complications of the therapy**
   a. **Interferon-a.** Interferon-a is a highly purified glycoprotein that may be administered subcutaneously, intramuscularly, intravenously, or intralesionally. In melanoma, it is frequently used subcutaneously and/or intravenously. Influenza-like illness frequently follows the administration of interferon. The manifestations include headache, fever, chills, nausea, vomiting, diarrhea, and myalgias. Myelosuppression and neurotoxicity (somnolence, confusion, behavioral changes, and seizures) also may develop. Occasionally asymptomatic elevation of liver-function tests occurs. Cardiac toxicity and renal insufficiency also have been reported.
   b. **Interleukin-2.** The treatment of melanoma requires high doses of IL-2. Side effects include transient lymphopenia, neutropenia, hypersensitivity reactions, vascular leak syndrome, hyperbilirubinemia, behavioral changes, erythema, and hypothermia. Inpatient management is needed because of the toxicity profile of high-dose IL-2. Frequently patients require blood pressure support.
   c. **Biochemotherapy.** Combinations of chemotherapeutic agents with interferon-a and IL-2 are more toxic than chemotherapy regimens alone. An intergroup trial is comparing chemotherapy (CVD) and biochemotherapy (CVD, interferon, and interleukin).

E. **Follow-up**

For patients with carcinoma *in situ,* the recommended follow-up schedule should include yearly visits.

For patients with lesions that are smaller than 1.00 mm in thickness, recommended follow-up is visits every 6 months for the first 2 years after diagnosis and every year thereafter.

For patients with lesions that are between 1.00 to 4.00 mm in thickness, recommended follow-up is visits every 4 months for the first 3 years after diagnosis and every 6 months thereafter.

For patients with lesions thicker than 4.00 mm, recommended follow-up is visits every 3 months for the first 3 years after diagnosis and every 6 to 12 months thereafter.

For patients with lymph node involvement and metastatic disease, recommended follow-up is visits every 3 months for the first 3 years after diagnosis, every 4 months on the fourth and fifth year after diagnosis, and every 6 to 12 months thereafter.

F. **Special considerations**

Noncutaneous melanomas deserve special consideration because the site of the tumor affects the treatment approach of the primary lesion and the lymph nodes.

Mucosal melanomas compose approximately 4% of all melanomas. They occur more frequently in Asians and blacks, and usually have a poorer prognosis. Staging mucosal melanomas is clinical. Excision of the primary lesion may not necessarily be radical because of esthetic and functional deformity. Frequently this type of melanoma initially has lymph node involvement. Metastatic disease is not curable, and it is treated like metastatic cutaneous melanoma, although biologically it appears to be a different disease.

Ocular melanomas are frequently localized and arise from the choroid and ciliary body. The treatment options for patients with small ocular melanomas include observation, local treatment, and enucleating. Observation should be considered in elderly patients or severely ill patients or for tumors in patient's useful remaining eye, especially if the tumor is growing slowly. Specific local treatment alternatives include photocoagulation, local resection (local sclerochorioretinal resection, iridocyclectomy), and radiation therapy (external-beam radiation with photons, or photons, stereotactic radiosurgery, brachytherapy, and hyperthermia). Locally advanced tumors or fast-growing tumors may require enucleation. Occasionally ocular melanomas metastasize hematogenously to the liver, requiring systemic chemotherapy.

Patients with metastatic melanoma with unknown primary site constitute about 1% to 10% of all cases of melanoma. Approximately two thirds initially have lymph node involvement, and one third have distant metastasis. Careful examination of the eyes, scalp, and perineum should be performed, looking for primary lesions. A careful history should include prior treatment of nevi, and previous biopsies should be reevaluated. The survival for this group of patients is similar to that of patients with metastatic cutaneous melanoma.

G. **Background**

1. **Epidemiology of melanoma.** It is estimated that approximately 53,600 cases of melanoma will be diagnosed, and 7,400 individuals will die in the year 2002 from melanoma in the United States. Both the incidence and death rates of melanoma are increasing in most countries. The mortality rate from melanoma has increased approximately 2% yearly since 1960 (*CA Cancer J Clin* 2000;50:215–236).
2. **Etiology and risk factors.** The risk of developing melanoma of the skin is similar in men and women. Women are more likely to develop melanoma of the

extremities, and men are more likely to develop melanoma of the trunk. Patients with a history of melanoma are at risk of developing another primary melanoma or multiple other primary melanomas. The major risks for developing cutaneous melanoma are sun exposure and genetic predisposition.

Many risk factors appear to be associated with developing skin melanoma (Table 19.3).

Changes in pigmented lesion
History of xeroderma pigmentosum
Prior melanoma history
Family history of melanoma
Multiple common nevi
Atypical nevi
Lentigo maligna
Red or blond hair
Immunosuppression
Tendency to freckle
Poor suntanning ability
Excessive sun exposure and sunburns during childhood

TABLE 19.3. RISK FACTORS FOR THE DEVELOPMENT OF MELANOMA

3. **Molecular biology and genetic alterations.** Several genes may be involved in the biology of melanoma. Probably the most important is p16/CDKN24, located in chromosome 9p21. This gene encodes proteins that function by blocking the cell-cycle progression and are cyclin-dependent kinase inhibitors. Mutations in the p16 gene have been demonstrated in melanoma in up to 25% of the specimens and in other tumors such as leukemia, lymphomas, head and neck cancer, and pancreas (*Mol Med* 1997;3:5–20; *Science* 1994;264:436–440). Another gene that may be involved in small percentage of familial melanoma patients is CDK4, which encodes a protein on the pRb cell-cycle control pathway. Additionally, alterations in chromosomes 7 and 11 have been described in patients with metastatic melanoma.

   Melanoma appears to be an immunologically active tumor. MAGE-1 is a melanoma tumor-associated antigen that binds to human leukocyte antigen (HLA)-A1 and is recognized by cytotoxic T cells; it has been shown to cause tumor regression in animal and human models. Tyrosinase and MART-1 are two other melanoma tumor–associated antigens that bind to HLA-A2 and also have been extensively studied in different models (*Prin Pract Oncol Updates* 1996;10:1–20).

4. **Pathogenesis.** A progression model has been proposed to define different steps for the development of melanoma. The progression from each step to the next is associated with specific biologic and molecular changes. Initially, for the formation of a nevus, the communication between melanocytes and keratinocytes may be disrupted, allowing the melanocytes to escape regulatory control of keratinocytes. At this stage, there is no apparent chromosomal aberration. Progression from a nevus to a dysplastic nevus or to a radial-growth melanoma may involve a chromosomal alteration. There is evidence of cytologic atypia, and a local immune response is observed. The progression to a vertical growth phase is characterized by presence of angiogenesis, uncontrolled proliferation, and decreased host response. The final step of metastatic melanoma is characterized by genetic instability and growth factor independence.

H. **Current focus of research**

1. **Proposed staging system.** Different staging systems have been proposed over the last few years and include clinical and molecular characteristics of the melanoma lesions. A new staging system may be approved in the near future, reflecting independent prognostic factors frequently used in clinical trials and the outcomes of different melanoma treatment modalities. The proposed staging system will include (a) the presence of ulceration and thickness of the primary lesion in the T category; (b) the number rather than size of lymph nodes and description of nodal microscopic disease in the N category; (c) the site of metastatic involvement and the presence of elevated LDH in the M category; and (d) the stage III will include satellite metastasis around a primary melanoma and in-transit metastasis (*J Clin Oncol* 2001;19:3622–3634; *J Clin Oncol* 2001;19:3635–3648).
2. **Vaccines and gene therapy.** Vaccines are now been studied for the treatment of melanoma. The strategies include immunization with whole melanoma cells, melanoma cell lysates, purified antigens, and recombinant vaccines. Melanoma vaccines may have a role in the adjuvant setting, and trials are currently ongoing.

   Monoclonal antibody therapy has been studied either alone (directed to the ganglioside system) or in conjugates to various compounds (with radionuclides, toxins, or cytokines) as possible therapy for metastatic melanoma.

   Gene-therapy approaches primarily focused on enhancing immunogenicity of melanoma are currently under investigation. All patients with melanoma should be encouraged to participate in clinical trials.

II. **Squamous cell carcinoma of the skin**

A. **Presentation**

Many nonmelanoma skin cancers such as SCCs and basal cell carcinomas (BCCs) manifest with classic clinical findings consisting of nodularity and erythema, but definite diagnosis can be made only by biopsy. The most common precursors of nonmucosal SCC are actinic keratosis and the presence of SCC *in situ,* also known as Bowen disease. Actinic keratosis usually arises in middle-aged and fair-skinned individuals as an erythematous hyperkeratotic papule or scaly papules in sun-exposed areas.

B. **Workup and staging**

A high index of suspicion is required. Shave, curette, or skin biopsies are adequate for the diagnosis of SCC. Complete cutaneous examination should be performed as well as palpation of draining lymph nodes. To date, radiologic evaluations with radiographs, MRI or CT has no role in uncomplicated SCC.

C. **Therapy**

The treatment goals are to control the disease, optimize surgical–cosmetic outcome, and minimize side effects. The therapy for invasive SCC depends on different factors such as the histopathologic type, the anatomic location, the size of the tumor, whether it is a primary or a recurrent lesion, and the medical condition of the patient. Most small lesions require only surgical excision, curettage, or cryosurgery. Tumor recurrence may result from inadequate margins of resections. Cryosurgery and radiation should be considered in patients who are poor surgical candidates or because of the localization of the lesion; cosmetic results may be inadequate. Alternatively, Moh micrographic surgery (review of multiple microscopic sections of fresh or fixed lesions) can be used in patients with lesions located in areas at high risk of recurrence (face and scar tissue).

Chemotherapy is not routinely used in the adjuvant setting but is occasionally used in patients with advanced SCC. Platinum-containing regimens are occasionally used in this setting.

Intralesional chemotherapy and immunotherapy has been used in a selected group of patients with limited surgical options. Intralesional interferon-a has resulted in cure in some patients; unfortunately the recurrence rate is higher than that with conventional therapies. Intralesional 5-fluoruoracil and bleomycin have been used with limited success in patients with large lesions or inoperable SCC. Alternatively, radiation therapy may be useful in patients who are debilitated or with high surgical risks, resulting in 5-year cure rates exceeding 90%.

D. **Prognosis**

SCC has higher metastatic potential than BCC. The incidence of metastasis is approximately 2% in sun-damaged areas and approximately 40% in non–sun-damaged skin areas. The most frequent site of metastasis is the lymph nodes. In approximately 50% of individuals with lymph node metastasis, distant disease will develop, and they will die of their metastatic skin cancer. For SCC, the TNM staging is based on the clinical examination of the lesion and

the regional lymph nodes.

E. **Follow-up and prevention**

Prudent follow-up of patients with history of SCC is meaningful not only to determine metastatic and recurrent disease but also to watch for new primary lesions. It has been recommended to monitor patients with SCC every 3 months for the first year after treatment, every 6 months during the second year, and annually thereafter. Evaluations should include a thorough skin examination.

F. **Background**

1. **Risk factors.** Actinic skin damage plays a major role as a carcinogenic factor. Approximately 90% of cancers of the skin develop in areas of the skin previously exposed to sun. In patients with history of chronic skin damage (burns, scars, irradiation, and fistulas), metastatic disease appears in excess of 40%. Certain hereditary conditions like xeroderma pigmentosum and basal cell nevus syndrome have a higher risk of developing into nonmelanoma skin cancers. Immunosuppression also is a risk factor for developing SCC, particularly in organ-transplant recipients.
2. **Molecular biology.** The biologic behavior of SCCs depends on invasiveness and depth of the neoplasm and the degree of cellular differentiation. Deeper lesions tend to recur if not appropriately treated. SCC *in situ* has a minimal risk for metastasis. Poorly differentiated lesions show increased risk or recurrence and have greater metastatic potential to regional lymph nodes.
3. **Pathogenesis.** Ultraviolet light exposure (UVL), genetic mutations, immunosuppression, and infections appear to be major factors in the pathogenesis of both SCC and BCC. Exposure to UVL, particularly rays in the UVB spectrum, may interfere with the antigen-processing capability of Langerhans cells and T cells. It also appears that UVL may introduce mutations in the p53 gene. Xeroderma pigmentosum and oculocutaneous albinism also have been associated with the development of SCC. Immunosuppression also appears to play a role in the development of SCC, particularly in sun-exposed skin areas. Human immunodeficiency virus (HIV) infection may have an association with SCC.

G. **Current focus of research**

The use of systemic photosensitizing agents with noniodizing radiation known as photodynamic therapy for selective tumor degradation is under current investigation and appears promising.

III. **Other nonmelanoma skin carcinomas**

A. **Basal cell carcinoma**

BCC frequently arises from damaged skin as either a nodular, superficial, sclerosing, or cystic lesion. BCC is the most common skin cancer and fortunately has low metastatic potential.

Precursor lesions are not seen in BCC. The most important risk factor for developing nonmelanoma skin cancer is intense sun exposure in susceptible individuals. BCCs and SCCs that develop in areas not exposed to the sun tend to have an aggressive behavior and higher risk of metastasis. Commonly patients have multiple BCC or SCC primary lesions.

BCC is commonly treated in the same fashion as SCC. Cure rates after simple excision exceed 90%. Recurrent or large BCCs are best treated with Mohs micrography surgery for assessment of intraoperative margins.

Most of the patients with BCCs are cured after initial excision or destruction of the lesion. Metastasis is extremely rare. Metastasis may occur more than 10 years after removal of the primary tumor. The most frequent site of metastasis is the lymph nodes. The treatment for nodal metastasis is surgical. Radiation therapy and chemotherapy are used to treat patients with diffuse metastatic disease. The prognosis for patients with metastatic disease is poor.

As in patients with SCC, patients with BCC should be monitored closely with total skin examination at regular intervals.

B. **Merkel cell carcinoma**

Merkel cell carcinoma (MCC) is a neuroendocrine cell tumor with high aggressiveness potential. It frequently involves the head and neck areas, although other sites can be affected. The pathogenesis is unknown. Metastases to the lymph nodes are detected in 20% of cases at presentation and in 50% of patients during the course of their disease. Metastases may involve the skin, lymph nodes, lungs, liver, and brain.

Patients with MCC warrant extensive staging workup and aggressive therapy. The initial workup should include extensive skin examination, complete blood counts; chemistry profile, and if indicated, CT scanning of chest, abdomen, and pelvis. CT of the head and neck may be necessary.

MCC spreads initially to lymph nodes and then progresses to distant metastatic disease. For patients with local disease, wide local excision with SLN biopsy may be sufficient. Patients who have regional metastatic disease or positive SLN may benefit from lymph node dissection. Adjuvant radiation therapy is recommended for patients with regional disease and may be recommended for some patients with local disease.

Patients with recurrent disease may be treated with reexcision for optimal surgical outcome. They also may be treated with radiation therapy if surgery is cosmetically or medically prohibited.

Chemotherapy may be used in recurrent disease, but it is reserved mostly for patients with metastatic disease. Commonly used regimens include cyclophosphamide (Cytoxan), vincristine, and doxorubicin, and cisplatin in combination with etoposide. The combination of carboplatin and etoposide also has been used. Response rates may vary from 50% to 70%, depending on the stage of the disease.

The 3-year survival rate for patients with locally advanced and metastatic MCC is 35% and 17%, respectively. Patients with MCC should be followed closely for potential recurrences and metastatic disease.

CHAPTER 20. TESTICULAR CANCER AND GERM CELL TUMORS

Burton M. Needles and J. Daniel Cuevas

Introduction
Etiology and risk factors
Workup and staging
Practical approach to a new testicular mass
Pathologic classification of testicular tumors
Tumor markers
Staging and imaging of testicular cancer
Management of retroperitoneal lymph nodes: staging and treatment
Sperm banking
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Definition of good risk testicular cancer: nonseminomatous germ cell tumors
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Complications and other clinical problems
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Suggested Readings

I. Introduction

A. Etiology and risk factors

1. **Presentation.** The most common symptom of testicular cancer is the appearance of a painless testicular mass. In fewer than 50% of patients, the testicular mass is painful and may be the consequence of bleeding or infarction in the tumor. The presence of acute pain may suggest testicular torsion or epididymitis or orchitis. Hydrocele also has been associated with approximately 20% of germ cell tumors (GCTs). Gynecomastia as the first sign of testicular cancer is seen in approximately 10% of patients, whereas infertility as the initial symptom is seen in 3% of patients. Other symptoms such as back pain, emesis, constipation, and hemoptysis are seen in patients with extensive retroperitoneal lymphadenopathy or pulmonary metastasis. Patients with testicular cancer rarely initially have inguinal lymphadenopathy, except when they have received surgery to the scrotal area.
2. **Physical examination.** A thorough physical examination is essential in patients with suspected testicular cancer. This examination should include evaluation of the external genitalia and scrotum, palpation of each testis by bimanual technique, examination of lymph nodes, with particular attention to the supraclavicular areas, and breast examination. If the examination reveals a suggestive scrotal mass, transillumination or ultrasound should be performed. A solid testicular mass that does not transilluminate should be considered a neoplasm until proven otherwise.

II. Workup and staging

A. Practical approach to a new testicular mass

Management with antibiotics for infection is a reasonable initial approach. However, if symptoms or signs of infection fail to resolve in 2 to 4 weeks, ultrasound evaluation is indicated with urologic referral. The differential diagnosis includes epididymitis, orchitis, and testicular torsion. Other entities include hernia, hydrocele, spermatocele, hematoma, and paratesticular mass. A firm intratesticular mass strongly suggests malignancy.

Ultrasonography is recommended to evaluate the scrotal anatomy, to differentiate a testicular mass from an extratesticular mass, and to identify lesions that may not be palpable on physical examination. Tumor markers [a-fetoprotein (AFP), b-human chorionic gonadotropin (BHCG)] should be obtained to assist in the evaluation of a testicular mass. A testicular biopsy is contraindicated. Radical inguinal orchiectomy is the standard procedure for diagnosis.

B. Pathologic classification of testicular tumors

1. **Germ cell tumors.** The large majority (95%) of primary testis tumors originate from germ cells. More than half of testis tumors contain more than one tumor type, and metastatic disease may be of a histology different from that of the primary tumor. It is important that careful sectioning of the primary tumor be done to assess histologies. GCTs are classified for clinical purposes into two major groups: seminomas or nonseminomatous GCTs (NSGCTs). About 40% of GCTs are seminomas, 35% are NSGCTs, and 15% are mixed seminomas and NSGCTs. Mixed tumors are treated as NSGCTs. Three rare tumor types also should be distinguished: spermatocytic, seminomas, yolk sac (YSTs), and teratomas. These tumors biologically and clinically are distinct from other GCTs. The pathology must be carefully reviewed with the pathologist and should include a gross and microscopic evaluation, extent, tumor invasion, and blood vessel and lymphatic permeation, in conjunction with known tumor-marker elevations.

   GCTs contain five basic cell types: seminoma, embryonal carcinoma, YST, choriocarcinoma, and teratoma. More than half of all diagnosed GCTs have more than one cell type. Spermatocytic seminoma is seen only in the testis; polyembryoma is seen in mixed GCTs.

   In more than 90% of patients, the histology of the metastases is the same as that of the primary tumor; however, a small volume in the primary can be capable of metastasizing. Often a “burned out” primary or scar may be found in the primary tumor. The pathology must be carefully reviewed with the pathologist and should include gross and microscopic evaluation, extent, tumor invasion, blood vessel and lymphatic permeation, in conjunction with known tumor marker elevations.

   a. **Intratubular malignant cell tumors (carcinoma *in situ*) and precursor lesions.** Intratubular malignant germ cells occur singly but usually form a single file at the periphery of the tubules. Seminiferous tubules may be filled with cells. There is usually no spermatogenesis. Cells may extend to the rete testis along the seminiferous tubules and invade the testicular parenchyma or vascular and lymphatic spaces. They are frequently associated with GCTs, except for spermatocytic seminomas, YSTs, and childhood tumors.

      The cells are significant when they are seen in a testicular biopsy done during an infertility evaluation in a maldescended testis or when a contralateral testis contains a malignant GCT. Progression of carcinoma *in situ* (CIS) to an invasive tumor occurs in 3 to 5 years in patients who have this histology when undergoing an infertility workup.

   b. **Seminomas.** Seminomas are the most common testicular tumor. They may be classified as typical or atypical spermatocytic. Atypical seminomas may have features suggesting nonseminoma. Seminomas constitute 35% to 75% of GCTs. They are found generally in the fourth and fifth decade but may occur in younger patients. Of seminomas, 24% contain syncytiotrophoblasts. In seminoma and nonseminoma testicular GCTs, syncytiotrophoblasts, whether singly or within choriocarcinoma, are the source of human chorionic gonadotropin (HCG). Occasionally seminomas may have frequent mitoses, and these are classified as seminoma with a high mitotic index or anaplastic seminoma. Some reports have claimed a poorer prognosis for anaplastic seminoma. In these cases, lymphangitic infiltration also may be present. Spermatocytic seminomas, although often classified as a type of seminoma, are different in clinical and pathologic presentation. They are the most common testicular GCT in men older than 40 years. They are the most common testicular GCT in the elderly (older than 65 years), but are rare, constituting about 3% of all testicular tumors. These tumors may be associated with sarcomatous elements that may metastasize. Spermatocytic seminomas are generally benign.
   c. **Nonseminomas**
      1. **Testicular germ cell tumors.** These are present in 40% of all testicular tumors. They occur most often in the third decade, and occasionally in the latter part of the second decade of life.

In general, pure embryonal carcinomas do not produce the tumor marker AFP, although individual cells may stain positive for this marker. An elevation usually indicates the presence of yolk sac elements. Pure embryonal carcinomas do not usually produce HCG. However, syncytiotrophoblasts may be present, and these may produce the HCG sometimes seen in embryonal carcinomas.

Therefore a normal AFP or HCG level does not necessarily mean an absence of metastases.

2. **Yolk sac tumor.** In pure form it is seen in infants and children. It is rare as a pure form in adults, but often seen as a component of a mixed GCT. Yolk sac tumors are the main source of AFP.
3. **Trophoblastic tumors.** These tumors occur in three forms: pure, mixed with foci of choriocarcinoma found in association with another cell type, and a third form known as placental site trophoblastic tumor. Pure choriocarcinoma is extremely rare and associated with very high levels of HCG, but not AFP. Mixed trophoblastic tumors contain foci of choriocarcinoma in association with other GCTs.

   Depending on the volume of choriocarcinoma elements, the serum level of HCG may vary. These areas may be associated with hemorrhage. Associated syncytiotrophoblasts seen in a mixed tumor should not lead to a classification of choriocarcinoma. Placental-site trophoblastic tumors are most often seen in children and often are associated with teratomas.

4. **Teratomas.** These tumors have elements from one or more germ layers in various stages of maturation. Pure teratomas compose about 3% of adult testicular GCTs. They are most frequent in the first, second, and third decades. In the adult, mature and immature teratomas have malignant potential. Microscopically, teratomas are divided into three subgroups: mature teratoma, immature teratoma, and teratoma with malignant areas. Mature teratoma contains well-differentiated tissues.

   Ectodermal elements are reflected in squamous epithelium, keratinization, or neural tissue. Endodermal structures are reflected by gastrointestinal or respiratory tissue and other mucous glands. Mesodermal elements are reflected as cartilage, bone, and muscle tissues. In the adult, mature teratomas can metastasize, especially if there is vascular or lymphatic invasion, and may represent chemotherapy failure. Immature teratomas are characterized by primitive tissues, not well differentiated. Teratomas with malignant areas contain tissues that appear to have malignant characteristics such as sarcoma. In 19% of mature and immature teratomas, AFP can be demonstrated. Carcinoembryonic antigen (CEA) also may be seen.

5. **Tumors of more than one histologic type.** About 60% of testicular GCTs consist of mixed histology in any combination. The most frequent combination is embryonal carcinoma, YST, teratoma, and syncytiotrophoblasts. Pathologists will often designate the tumor on the basis of its most malignant component. If an elevated AFP level is seen in the setting of embryonal carcinoma, a search for yolk sac elements or teratoma can be done with AFP staining.
6. **Other testicular tumors.** About 5% of testicular tumors are of nongerminal origin. Testicular tumors in men older than 50 years most commonly are lymphomas. Other rare tumors include Leydig cell tumors, which produce steroid hormones, Sertoli cell tumors, sarcomas, and embryonal rhabdomyosarcomas of the paratesticular tissues.
7. **Occult testicular tumor.** From 5% to 10% of testicular GCTs initially have metastatic disease. The testis may have a small nonsymptomatic tumor, CIS, or scar or residual of a “burned out” testicular tumor detected only on ultrasound.
8. **Histology of metastases.** In 90% of cases, the metastasis has the same histology as the primary tumor. In the remaining cases, either there was error in sampling the primary tumor or the metastasis differentiated into another histologic subtype. In a number of patients who have embryonal carcinoma of a mixed tumor, the metastases may show only mature teratoma after chemotherapy. Possible explanations include the following: the embryonal carcinoma may have matured to teratoma, treatment may have induced maturation of embryonal carcinoma to teratoma, or the chemotherapy may have eliminated the sensitive elements, but did not affect the teratoma, which is most usually the case.

d. **Other testicular tumors.** About 5% of testicular tumors are of nongerminal origin. Testicular tumors in men older than 50 years most commonly are lymphomas. Other rare tumors include Leydig cell tumors, which produce steroid hormones, Sertoli cell tumors, sarcomas, and embryonal rhabdomyosarcomas of the paratesticular tissues.

D. **Tumor markers**

Three tumor markers have been established in testicular GCTs. They are a-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH). AFP and HCG are commonly used, and elevation of one or both is seen in 80% of metastatic nonseminomatous tumors of the testis. The primary tumor may exhibit a different pattern of elevation of markers than does the metastasis.

Serum tumor markers are seen in up to 90% of GCTs. Most seminomas do not have elevated levels of tumor markers at diagnosis or relapse, although bHCG may be elevated. Elevation of AFP implies an NSGCT.

1. **bHCG** elevation indicates either nonseminomatous elements or syncytiotrophoblasts. Elevated bHCG indicates an increase in tumor volume, not necessarily aggressiveness, and persistence after surgery implies metastatic disease. In general the presence of an elevated AFP level is thought to mean that nonseminomatous elements exist; however, several cases of pure seminoma with borderline elevation of AFP or molecular studies showing AFP messenger RNA (mRNA) in minute quantities have been described in pure seminoma. bHCG is elevated in about 60% of nonseminomatous GCTs; the half-life is 24 to 36 hours. Syncytiotrophoblasts are the cells producing HCG. The absolute elevation before treatment and rate of decline with treatment are of prognostic value.
2. **AFP** is elevated in about 50% of nonseminomatous GCTs. The half-life is 3.5 to 6 days. Endodermal sinus tumors give positive immunohistochemical staining; teratoma and embryonal cell, less commonly. AFP can be elevated is hepatocellular disease.
3. **Half-life of AFP** of more than 7 days, or of bHCG, more than 3 days after administering chemotherapy, is associated with a worse prognosis.
4. **Placental alkaline phosphatase (PAP).** Of seminomas, 90% are positive with immunohistochemical staining. The value of serum levels is not proven.
5. **LDH** is related to bulk and extent of disease, and several large multivariate analyses found it to be an independent prognostic variable.
6. **False-positive values** may result from tumor lysis. AFP elevation may be due to liver damage from chemotherapy. HCG elevation may cross-react with pituitary hormones; hypogonadal patients may have false-positive HCG; the b subunit generally is specific for HCG and excludes this, however. A tumor in the contralateral testis must be considered as a possible source of marker elevation.
7. **Schedule for follow-up of markers.** For those patients under surveillance for stage I disease, markers are measured weekly until normal, and then monthly for the first year, every 2 months for the second, every 3 months for the third year, and then every 6 months. A similar schedule can be used after completion of therapy.

   During treatments, markers should be checked before each cycle of treatment, and ideally in the middle of each cycle.

E. **Staging and imaging of testicular cancer**
   1. **Imaging studies**
      a. Scrotal ultrasound examination is required during the initial physical examination of a testicular mass. Color Doppler ultrasound may provide even more useful information regarding blood flow.
      b. Computed tomography (CT) scanning. This is currently the imaging of choice in evaluating the retroperitoneum. There is a significant false-negative rate of approximately 40%. The cut-off for lymph node size affects the sensitivity and specificity of the test. With a cut-off of 5 mm, the negative predictive value is 79%, but specificity is only 44%. With 15 mm, the negative predictive value is 63%, but specificity is 76%. The best results determining accuracy of CT after retroperitoneal lymph node dissection give 70% to 80% accuracy, 50% to 70% sensitivity, and 80% to 85% specificity.

         With a normal abdominal CT scan, only had 4% of patients will have a positive CT scan of the chest, whereas with an abnormal abdominal CT, the chance of chest metastases is about 40%. If the initial chest radiograph is abnormal, a CT scan of the chest should be obtained; however, an initial CT of the chest is recommended by many oncologists.
   2. **Laboratory tests.** Tests frequently obtained to determine the extent and prognosis of the disease include complete blood count and differential (CBC), and a chemistry profile including LDH and tumor markers (bHCG and AFP).
   3. **Staging systems.** Multiple staging systems are currently in use for the clinical treatment of GCT patients. The traditional staging system used defines stage I disease limited to the testis; stage II disease, limited to retroperitoneal nodes (II-A disease, smaller than 2 cm; II-B disease, 2 to 5 cm; II-C disease 5 cm or more in transverse diameter); stage III, supradiaphragmatic or visceral involvement (Table 20.1).

Clinical	Pathologic
I. Disease confined to the testicle (i. After noninvasive staging, negative markers	I. Disease confined to testicle after noninvasive staging and RPLND
II. Abnormalities noted in retroperitoneal lymph nodes measured by noninvasive staging	II. Retroperitoneal lymph node involvement by tumor
II_A <2 cm or elevated markers alone	II_A <2 cm or fewer than five nodes with microscopic disease or combination
II_B 2–5 cm	II_B 2–5 cm or >5 cm with microscopic disease
II_C >5 cm	II_C >5 cm, resectable II_D >5 cm, nonresectable
III. Abnormalities noted by noninvasive staging in lymph nodes above the diaphragm or in any organ	III. Disease noted in lymph nodes above the diaphragm in any organ

RPLND, retroperitoneal lymph node; NSGCT, nonseminomatous germ cell tumor.

TABLE 20.1. CLINICAL AND PATHOLOGIC CLASSIFCATION OF NSGCT

A system including tumor markers, node involvement, and metastatic disease has been developed by the group at Indiana University. This staging system classifies according to different prognostic categories (Table 20.2). The TNM classification for testicular cancer now includes an “S” category for tumor markers. In addition, T2 now includes vascular/lymphatic invasion in the primary tumor (Table 20.3). All patients with advanced disease requiring chemotherapy as initial treatment should be classified according to their risk status—the International Germ Cell Cancer Consensus Group classification is used (Table 20.3). The Indiana staging system uses minimal, moderate, and advanced disease. The International Germ Cell Cancer Classification–defined prognostic groups, Sloan–Kettering System, and the Medical Research Council staging system are all used to assess patients by risk category.

Minimal
1. Elevated marker levels only
2. Palpable cervical nodes
3. Unresectable, nonpalpable retroperitoneal disease
4. Fewer than five pulmonary metastases per lung field and largest <2 cm (± nonpalpable retroperitoneal disease)
Moderate
5. Palpable abdominal mass only
6. Moderate pulmonary metastases: 5–10 metastases per lung field and largest <3 cm, or solitary pulmonary metastasis of any size >2 cm (± nonpalpable retroperitoneal disease)
Advanced
7. Advanced pulmonary metastases: >10 pulmonary metastases per lung field, or multiple pulmonary metastases with largest >3 cm (± nonpalpable retroperitoneal disease), or primary mediastinal nonseminomatous germ cell tumor
8. Palpable abdominal mass + supradiaphragmatic disease
9. Liver, bone, or central nervous system metastasis

Minimal or moderate, good risk; advanced, poor risk.

TABLE 20.2. INDIANA UNIVERSITY STAGING SYSTEM FOR DISSEMINATED DISEASE

TABLE 20.3. TESTICULAR CANCER STAGING SYSTEM OF THE AMERICAN JOINT COMMITTEE ON CANCER AND THE INTERNATIONAL UNION AGAINST CANCER

F. **Management of retroperitoneal lymph nodes: staging and treatment.**

Retroperitoneal lymph node dissection (RPLND) is frequently used as part of the treatment in patients with nonseminomatous GCTs in staging and therapeutic management. Predictably, nonseminoma GCTs spread to the retroperitoneal lymph nodes. Either a transthoracic or transabdominal approach is used, with a surgical mortality less than 1%. In patients undergoing bilateral RPLND, retrograde ejaculation and subsequent infertility may develop. A nerve-sparing procedure is now performed to avoid these complications. Two types of nerve-sparing procedures are done. RPLND with nerve dissection results in 90% of patients with normal postoperative ejaculatory function, and RPLND with nerve avoiding results in 51% to 88% preservation of ejaculatory function.

G. **Sperm banking**

In approximately 50% of patients, oligospermia or azoospermia is seen at or after 2 years of treatment. Because testicular cancer commonly occurs in young patients who frequently have not conceived any children, sperm banking can be offered, before initiation of therapy.

III. **Prognosis**

A. **Prognostic factors in clinical stage I disease.** Included in the prognosis is an assessment of the primary tumor. The local extent of the tumor is assessed to determine if the tumor is confined to the testis (T1) or whether there is invasion beyond the tunica albuginea or into the epididymis (T2), or whether there is evidence of vascular or lymphatic invasion. Prognostic factors in NSGCT that are indicative of a potential for metastatic disease (and have implications for surveillance protocols) include the presence of either lymphatic or vascular invasion or both. Also important is the histology of the primary tumor. The presence of malignant teratoma or undifferentiated malignant teratoma (MTU) increases the potential for metastasis, and the presence of YST in the primary tumor decreases the likelihood of progression.

Unequivocal prognostic factors for clinical stage I seminoma have not been identified. In seminoma, tumors with increased metastases and diminished lymphocytic infiltration may behave more aggressively.

However, if classic seminoma and seminomas with high mitotic index are compared stage by stage, survival is similar.

1. **In nonseminomatous tumors,** choriocarcinoma has the worst prognosis, followed by embryonal carcinoma. In tumors of more than one cell type (mixed tumors), the presence of embryonal carcinoma has prognostic significance. The percentage of embryonal carcinoma may predict pathologic stage II disease. The presence of vascular or lymphatic invasion combined with the percentage of embryonal carcinoma may predict the probability of metastatic potential in clinical stage I patients. Assessment of prognosis based on histopathology must include verification in the pathology report; the classification of all histologic subtypes to correlate with tumor markers; the percentage of each histologic subtype, especially the amount of embryonal carcinoma and the vascular and lymphatic invasion; and the presence or absence of yolk sac elements.

B. **Prognostic factors in clinical stage II disease.** The size and number of lymph nodes found in a RPLND have important prognostic implications. Most

studies have shown that fewer than six positive nodes and a size of 2 cm or less is associated with a 35% or less incidence of relapse. Patients with more than six nodes or nodes larger than 2 cm have a recurrence rate of at least 50%. For seminoma, the size of RPLNs is of prognostic importance regarding the incidence of radiation failure. There is general agreement that tumor greater than 10 cm is significant, whereas others believe 5 cm or greater is significant.

C. **Definition of good risk testicular cancer: nonseminomatous germ cell tumors.** Identification of subsets of patients at good risk versus poor risk is important in selection of therapy. In the United States, the two commonly used staging systems include that of Indiana University and a system used at Memorial Sloan Kettering.

The Indiana system (Table 20.1) separates metastatic patients into three groups: good prognosis (minimal or moderate disease) and poor prognosis (advanced disease). Of patients with minimal or moderate disease in the Indiana system, 90% or more treated with *cis*-platinum–based chemotherapy are cured. Patients in the advanced-disease category have about a 50% failure rate.

At Sloan Kettering, a multivariate analysis or prognostic factor in patients with NSGCT treated with chemotherapy resulted in LDH and HCG being identified as independent variables in addition to the total number of metastatic sites. The size of metastatic disease and the pretreatment level of AFP were not found to be significant independent variables. A mathematical formula using the logarithm of pretreatment LDH and HCG alone with the total number of metastatic sites (TOTMET) was developed. With this equation, a value greater than 0.5 correlates with a good outcome, whereas a value less than 0.5 denotes a poor response (poor risk). Subsequently a mediastinal primary tumor, pure seminomatous histology, metastases to nonpulmonary visceral sites (bone, liver, brain), and the pretreatment values of LDH and HCG were found to have independent significance for response and disease-free survival. Other prognostic models have been used, including the level of AFP (greater than 1,000 KU/L) or HCG (more than 10,000 IU/L), and tumor marker doubling time, after adjustment for clearance.

The Royal Marsden Hospital classifies patients by small volume disease and with large volume disease with low serum tumor markers. The European Organization for Research and treatment of cancer (EORTC) incorporates the Royal Marsden criteria, and good risk was defined as lymph node metastases smaller than 5 cm, lung metastases smaller than 2 cm, AFP less than 1,000 mg/mL, and HCG less than 10,000 ng/mL.

Because of the differences in criteria, a consensus was developed by the International Germ Cell Cancer Collaborative Group. This system provides agreement on the use of pretreatment LDH, AFP, and HCG as prognostic factors, as well as metastases to organs other than lung or poor-risk patients, and site of primary (mediastinal vs. testis vs. retroperitoneal). A new staging system was developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC; Table 20.3). Good-risk patients are those in stage II-C and stage III seminoma without M,b metastases, and stage III-A, II-C, and some with stage II-B nonseminomatous tumors. In summary, good-risk patients are defined as having absence of a mediastinal nonseminomatous tumor, no liver, bone, or brain metastases, HCG less than 1,000 ng/mL, AFP less than 1,000 ng/mL, and LDH less than 1.5 times the upper institutional normal value. Patients with no unfavorable factors are considered to have a good prognosis (90% cure rate). Those with one unfavorable factor are considered to be of intermediate prognosis (60% cure rate), and those with more than one unfavorable factor are considered to have a poor prognosis (20% to 40% cure rate).

IV. Therapy

A. Testicular seminoma

1. Treatment options for patients with stage I seminoma (tumor confined to the testis). These options include surveillance, radiation therapy, and chemotherapy.
   a. **Surveillance.** Unfortunately, there is no agreement on which patients with stage I disease are most likely to have microscopic stage II disease. There are no risk factors for stratification. Lack of tumor marker elevation and the long natural history of untreated seminoma requiring longer follow-up than that for nonseminomatous tumors create difficulties. Although most relapses will occur within 2 years, scans should be done for 3 to 4 years, and follow-up, for at least 10 years. These factors complicate surveillance. Fifteen percent to 30% of patients will develop stage II or III disease within 3 to 4 years and receive salvage radiation. About 80% receive salvage radiation to the retroperitoneum; 20% receive chemotherapy. Patients with stage I seminoma treated with inguinal orchiectomy without radiation to the paraaortic lymph nodes require a strict follow-up program. A complete physical examination, evaluation of tumor markers (bHCG and AFP), and chest radiograph should be performed at monthly intervals for the first year, every other month the second year, every 3 months after the third year, and then less frequently. CT of the abdomen is needed every 3 months for the first year, every 4 months for the second year, and every 6 months beginning in the third year. After the fifth year, visits and evaluation are on a yearly basis.
   b. **Radiation therapy (hockey stick).** The radiation field usually consists of 25 Gy over 3 to 3.5 weeks and includes the paraaortic lymph nodes extending from T10 to L5 and the ipsilateral hemipelvis. The overall survival is 100%, because those few patients who relapse will be salvaged with chemotherapy. About 5% of patients can be expected to relapse outside the radiation treatment volume, with most relapses occurring within 18 months of diagnosis of the primary. In the 1990s, new radiation protocols were developed that limit treatment to the paraaortic lymph nodes, because these nodes are in the first echelon of spread before pelvic node involvement.

      There has been an approximate 2% pelvic relapse. Radiation toxicity is relatively low and includes dose-related gastrointestinal morbidity, impaired fertility, and possibly late malignancies. The impact of postorchiectomy radiation on fertility is related to the dose scattered to the remaining testis, and the extent of pretreatment impairment of spermatogenesis. Patients with testis tumors may have azoospermia in 15% to 20%, oligospermia in approximately 30%, and impairment of motility in almost 50% of those with normal sperm counts. Therefore evaluating the effects of radiation is difficult. The proportion of the increased risk for second malignancy related to the radiation is difficult to define (in some series, a relative risk of 1.3) and could be related to a genetic predisposition.
2. **Treatment options for stage II seminoma**
   a. Stage II seminoma can be divided into bulky and nonbulky disease, but there is lack of agreement as to definition. Generally 5 cm has been accepted as the cut-off point. Only 10% to 20% of patients with seminoma have stage II disease. Radiation therapy consists of low-dose radiation to the involved lymph node areas and ipsilateral pelvis, followed by a boost of radiation to known sites of involvement. Generally 35 Gy is administered to the gross nodal disease. Relapse rates are slightly higher than those for stage I disease, but 5-year survival is about 90%, and relapsed patients are salvaged with platinum-based therapy.
3. **Treatment of stage II (bulky) and III (supradiaphragmatic lymph node) or IV (parenchymal disease).** These patients require chemotherapy similar to that recommended for nonseminomatous GCTs. Because radiation alone yields only a 65% disease-free survival, with only 31% successfully salvaged, platinum-based therapy is recommended: three cycles of BEP [bleomycin, etoposide, and cisplatin (Platinol)] or four cycles of EP (etoposide and cisplatin). Prophylactic mediastinal radiation is no longer used because of the increased cardiac risk, increased toxicity with salvage chemotherapy, and overall survival considerations.
4. **Management of residual disease.** This is controversial. Most residual masses resolve, and the probability of disease in masses smaller than 3 cm is low. The observation that local failure is increased in postchemotherapy residual masses 3 cm or larger has prompted many to recommend surgical removal or adjuvant radiation. This policy, however, is not universally accepted. A practical approach would be very close follow-up with serial CT scans, because the overwhelming majority of patients will still have nonviable fibrotic tissue. Gallium scans have high false-negative rates; positron emission tomography (PET) scanning is still investigational.
5. **Follow-up.** Generally patients, regardless of treatment, should have follow-up every 3 months during the first 2 years, 4-month intervals in the third year, then 6-month intervals from the fourth year through the sixth year, and then annually. Chest radiographs should be monitored, and tumor markers for the first 3 years are recommended for patients with stage II disease. CT scans must be monitored until there has been resolution of retroperitoneal disease. Patients who have relapse after radiotherapy are usually treated with chemotherapy, except for an isolated inguinal relapse. Chemotherapy usually consists of *cis*-platinum, etoposide, and VP-16.
6. **Management of stage III and IV seminoma.** About 70% of patients who relapse after radiation for seminoma can obtain long-term disease-free survival with chemotherapy. The lower response rates in untreated patients is usually explained by the myelosuppression associated in previously irradiated patients. Although the optimal chemotherapy regimen for the initial therapy of patients with advanced seminoma remains in doubt, generally four cycles of bleomycin, etoposide, and *cis*-platinum are recommended.

B. Testicular nonseminomatous germ cell tumors

1. **Stage I: surveillance.** Management and prognosis of clinical stage I disease patients with clinical stage I (T1 through 4, N0) require inguinal orchiectomy, as previously described for patients with seminoma. Patients may opt for observation and close surveillance or RPLND. Relapses are uncommon after 5-year follow-up. With observation, approximately 25% of patients will relapse and require subsequent chemotherapy and surgery. Adverse prognostic factors for observation include advanced T stage, vascular or lymphatic invasion, features of embryonal carcinoma, and absence of YST. The presence of three of these four factors gave a 46% risk of relapse on surveillance, 21% for two factors, and 16% for one factor. Occult metastatic disease exists in 30% to 40% of clinically staged stage I patients. Therefore, 70% of those observed are spared surgery. Most can be salvaged with chemotherapy. This approach requires diligent follow-up. Patients with high risk for retroperitoneal disease may be offered two cycles of cisplatin-based chemotherapy; fewer than 5% of patients will relapse and would avoid RPLND. Unfortunately, patients will be exposed to the risks inherent to chemotherapy and its side effects

such as myelosuppression, neuropathy, and risk of developing leukemia. In the United States, this approach is still debated. Although the overall results with surveillance are good, problems exist. Only two thirds of patients have elevated tumor markers at relapse. Therefore, the limitations of CT scanning to evaluate the retroperitoneum should be taken into account. The appropriate frequency of CT scanning is not clear. CT scans are recommended every 4 months during the first year, every 4 to 6 months during the second year, and then only as needed for symptoms. Generally, a CT scan at 5 years is recommended. Compliance also is a major concern in surveillance.

2. **Management and prognosis of clinically stage II-A or minimal II-B disease (without elevated tumor markers).** Patients with clinically stage II-A or B (nonbulky disease) are managed with RPLND and/or chemotherapy; if patients are proven to have pathologic stage II disease, then adjuvant chemotherapy with three cycles of BEP is recommended. If any node is 2 cm or larger in diameter, with six or more involved nodes, or if there is extranodal extension, chemotherapy is recommended. Patients with no lymph node larger 2 cm; five or fewer involved lymph nodes, and no extranodal extension may be observed, because the relapse rate is low (20% to 25%). In patients who underwent RPLND and have an incomplete lymph node dissection or have persistently elevated or increasing tumor markers, three cycles of BEP also are recommended.

   Currently no treatment program has been proven superior to BEP. It is the standard for good-risk and poor-risk patients. Bleomycin is essential in the treatment of good-risk patients if only three cycles of chemotherapy are given. Bleomycin may be omitted from the fourth cycle if four cycles are given.

   It is important that dosage and schedule be followed without dose reduction or delay. It is clear that a reduction of *cis*-platinum dose gives inferior results. Carboplatinum at the standard dose is inferior to *cis*-platinum.

3. **Management and prognosis of clinically stage II-C disease.** Patients with clinically stage II-C (bulky abdominal disease or palpable mass) or retroperitoneal metastases of 3 cm or larger should be considered for chemotherapy with three cycles of BEP or four cycles of EP, which must be followed by debulking surgery when there is residual tumor.
4. **Management and prognosis of clinical stage III (metastatic) or advanced disease requiring chemotherapy.** These patients should be classified according to the International Germ Cell Collaborative Group Consensus Conference as having either good- or poor-prognosis disease (Table 20.2).
   a. **General.** Primary chemotherapy is indicated for patients with S2 or S3 markers (may include some II-A and -B disease), all patients classified as I-S, II-C, III, and extragonadal primary tumors.
   b. **Good-risk patients:** II-C, III, or extragonadal seminoma, nonseminomatous GCTs with S0 or S1 markers and absence of nonpulmonary or visceral metastases. Treatment is four cycles of EP or three cycles of BEP. In patients with a good prognosis, clinical trials have shown that three courses of BEP are equivalent to four courses. If three courses of chemotherapy are given, the omission of bleomycin gives inferior results, and carboplatinum plus etoposide with or without bleomycin is inferior to either EP or BEP.
   c. **Intermediate/poor-risk patients:** seminoma with nonpulmonary visceral metastasis or nonseminomatous GCT with S2 markers. Nonseminomatous GCTs with either nonpulmonary visceral metastasis or S3 disease, and mediastinal nonseminomatous GCTs are poor risk. Treatment is four cycles of BEP. The use of high-dose *cis*-platinum or the substitution of ifosfamide for bleomycin does not improve results. Recent phase II data indicate high-dose therapy as part of initial therapy may result in improved survival. Fewer than 50% of poor-prognosis patients are cured. Current clinical trials for patients with poor prognosis include high-dose therapy with peripheral blood stem cell support.
5. **Management of postchemotherapy masses:** all residual sites should be resected. In the retroperitoneum, 45% to 50% of residual masses will be necrotic/fibrous, and 35% to 40%, teratoma. No further therapy is required. From 10% to 20% will still show viable GCT; two more cycles of EP are recommended.
6. **Management of recurrent disease after initial therapy.** Patients with testicular tumors who continue with elevated tumor markers after optimal therapy should be considered to have residual disease and the need for further chemotherapy with two additional cycles of BEP. Approximately one third of patients with advanced disease will not achieve complete remission or relapse after initial therapy. These patients will require salvage chemotherapy and frequently receive VIP (etoposide, ifosfamide, and Platinol) or VelP (vinblastine, ifosfamide, and Platinol). This group has about a 30% to 40% chance of achieving complete remission after markers normalize. Residual masses should be resected. High-dose therapy is indicated in the management of patients who failed to achieve an initial complete remission and for management of patients who relapse after a second complete remission. Approximately 15% to 30% of patients will be cured. Postchemotherapy surgery is usually needed.

C. **Complications and other clinical problems**

Complications from therapy may be related to the surgical procedures, to radiation, or to chemotherapy. Transinguinal orchiectomy is a safe procedure and consists of removal of the testis, the spermatic cord, ligation of the vas deferens, and ligation of the testicular vessels. Transscrotal orchiectomy is not desirable because of the risk of tumor seeding along the skin and lymph nodes. RPLND can be performed either retroperitoneally or transperitoneally with a thoracoabdominal approach. This approach decreases the risk of postoperative small bowel obstruction, although it is technically difficult. Nerve-sparing surgical procedures will preserve the ipsilateral sympathetic nerve trunk and bilateral branches below the level of the inferior mesenteric artery, thus maintaining normal ejaculation and avoiding the complication of retrograde ejaculation seen in 10% of patients. Complications of radiation include nausea, vomiting, and diarrhea, which are easily controlled with medications. The risk of developing second malignancies in the remaining testicle has decreased by using smaller treatment volumes of radiation. Fertility problems related to radiation are unusual, but azoospermia may occur. Complications from chemotherapy include pulmonary fibrosis and dysfunction with the use of bleomycin, and renal insufficiency and ototoxicity with the use of Platinol. The role of chemotherapy and radiation is unclear in the developing of secondary malignancies. In approximately 2% of patients, a second primary testicular cancer develops. Patients with testicular cancer may be at increased risk of developing other carcinomas such as melanomas, gastrointestinal or genitourinary tumors, and acute leukemias. Exposure to etoposide has been linked to developing secondary acute leukemias (0.1% to 0.2%), which are resistant to treatment. Bolus bleomycin has been associated with Raynaud phenomenon in 6% to 7% of patients. Patients with GCTs appear to have a higher incidence of sarcoidosis.

V. Background and epidemiology

GCTs of the testis are the most common cancer in men between the ages of 15 and 35 years. The incidence is increasing worldwide. The introduction of chemotherapy in the early 1970s resulted in a decreased mortality. The age distribution of white men has a small peak at about age 2 years, and then declines. After age 15 years, rates climb rapidly and peak in young adults, followed by a second decline and then a slow increase or leveling off after about age 65 years. Childhood testicular cancers are generally germ cell histology, with the young adult peak at about age 25 to 29 years, and seminoma with a peak at ages 35 to 39 years. After age 65 years, testicular tumors are generally non–germ cell, primarily lymphomas. In the United States, in African Americans, the age peaks are the same, but the incidence is lower.

Testicular cancer should be suspected in male patients younger than 35 years who have a testicular mass. There were 6,900 new cases of testicular cancer, and approximately 300 deaths for the year 2000. Since the advent of *cis*-platinum–based chemotherapy, the 5-year survival for all patients with GCTs is approximately 95%. Even patients with advanced stage are cured in 80% of cases. The most common site of presentation is the testis (90%), followed by extragonadal locations (10%). The extragonadal sites include RPLNs, mediastinum, and central nervous system.

Several risk factors have been associated with the development of testicular cancer, but the only specific risk factor is maldescended testis. Cryptorchidism has been associated with increased risk of developing testicular cancer and is the only known predisposing risk factor. All abdominal cryptorchid testes should be surgically removed, whereas inguinal cryptorchid testes can be observed. Surgical correction of the undescended testis before age 5 years decreases the risk of cancer. Nevertheless, 25% of patients with cryptorchidism will develop cancer in the normally descended testis. Approximately 2% of patients with a history of testicular cancer will develop a second primary in the opposite testis. Patients with testicular feminization syndromes have an increased risk of developing cancer of the testicles. Patients with Klinefelter syndrome and Down syndrome are at increased risk for developing GCTs. Several other risk factors such as mumps orchitis seem likely to be risk factors, but are less well established. Testicular tumors account for 1% of all cancers in male patients.

VI. Current focus of research

Clearly most patients with testicular cancer are cured with cisplatin-based chemotherapy regimens even after relapse. Research efforts are directed toward developing regimens for salvage purposes. High-dose chemotherapy with stem cell rescue has been frequently used in the salvage setting in patients with cisplatin-sensitive tumors. Taxanes and gemcitabine are now used in protocols as part of combination chemotherapy with encouraging results. Ifosfamide has been incorporated into cisplatin regimens for patients with relapsed disease.

VII. Extragonadal germ cell tumors

An extragonadal GCT (EGGCT) is defined as a tumor histologically associated with gonadal origin but found outside the testis, without a detectable testicular

mass. This group may include teratomas.

In the mediastinum, these tumors are generally located in the anterior–superior region. Generally these EGGCTs refer to the mediastinum and exclude an abdominal or retroperitoneal location, which often has an occult or burned-out primary gonadal origin. These tumors occur mostly in young men, with a midline location, and may have elevated AFP or HCG. Often isochrome 12p karyotypic abnormality is demonstrated. These tumors often are sensitive to *cis*-platinum–based therapy.

Patients with EGGCTs often have greater tumor bulk than with primary testicular tumors, and have a distinctly worse prognosis.

A. **Histology.** These tumors probably originate from primordial germ cells and consist of seminoma (germinoma, dysgerminoma), and nonseminoma–endodermal sinus (yolk sac), embryonal, choriocarcinoma, mature and immature teratomas.
   1. **Seminoma subtypes** are curable with radiation and *cis*-platinum–based therapy and have a better prognosis.
   2. **Teratomas.** Mature teratoma comprise mature or well-differentiated elements derived from one of the three germinal layers. Even mature teratomas can grow and metastasize, and therefore, staging and surgical treatment are needed. Immature teratomas have a higher incidence of malignant transformation.
B. **Location:** generally anterior–superior mediastinum. Usually patients are first seen at an advanced stage with local symptoms, such as superior vena cava syndrome, tracheal compression, etc. These tumors can be locally invasive or have distant metastases.
   1. **Central nervous system (CNS) disease** may occur in the absence of retroperitoneal or nodal disease. A midline CNS tumor may be a distinct subset.
C. **Prognostic factors based on histology.** The prognosis for GCTs may depend on several pathologic features: cell type, presence of vascular or lymphatic invasion, and pathologic stage.
   1. **Seminoma.** Tumors with increased mitoses and diminished lymphangitic infiltration may behave more aggressively. However, if one compares classic seminomas and seminomas with high mitotic index stage by stage, survival is similar.
   2. **Nonseminomatous tumors.** Choriocarcinoma has the worst prognosis, followed by embryonal carcinoma. In tumors of more than one cell type (mixed tumors), the presence of embryonal carcinoma has prognostic significance. The percentage of embryonal carcinoma may predict pathologic stage II disease. The presence of vascular or lymphatic invasion combined with the percentage of embryonal carcinoma may predict the probability of metastatic potential in clinical stage I patients. Assessment of prognosis based on histopathology must include verification in the pathology report of the classification of all histologic subtypes to correlate with tumor markers; the percentage of each histologic subtype, especially the amount of embryonal carcinoma and the vascular and lymphatic invasion; and the presence or absence of yolk sac elements.

      In Europe, staging systems from the EORTC and the Medical Research Council (Table 20.3) Working Party on Testicular Tumors are used. Periaortic nodes larger than 5 cm, more than three lung metastases with one or more metastasis being bulky (larger than 2 cm), liver or bone metastasis, number of sites, age older than 30 years, AFP greater than 500 KU/L, and HCG greater than 1,000 IU/L are used to distinguish good- from poor-risk patients. Other indicators used include mediastinal mass larger than 5 cm, more than 20 lung metastases, older age, and absence of embryonal cell component in the primary tumor are used to separate good-risk from poor-risk patients.

      The International Germ Cell Tumor Collaborative Group (Table 20.4) uses pretreatment levels of LDH, HCG, and AFP, site of primary tumor (mediastinal vs. testis or retroperitoneal), and nonpulmonary visceral metastases.

BEP
Bleomycin, 30 IU bolus days 2, 9, and 16
Etoposide (VP-16), 100 mg/m^2 i.v. daily × 5 days
Cis-platinum, 20 mg/m^2 i.v. daily × 5 days
21-day cycles
VIP
Etoposide (VP-16), 75 mg/m^2 i.v. daily × 5 days
Ifosfamide, 1,200 mg/m^2 i.v. daily × 5 days
Cis-platinum, 20 mg/m^2 i.v. daily × 5 days
EP
Cis-platinum, 20 mg/m^2 daily × 5 days
Etoposide (VP-16), 100 mg/m^2 daily × 5 days

TABLE 20.4. COMBINATION CHEMOTHERAPY REGIMENS

The International Germ Cell Tumor Collaborative Group defines good-risk patients as having absence of a mediastinal nonseminomatous tumor; no liver, bone, or brain metastases; HCG less than 1,000 ng/mL; AFP less than 1,000 ng/mL; and LDH less than 1.5 times the upper institutional normal value.

Patients with no unfavorable factors are considered to have a good prognosis (90% cure rate); those with one unfavorable factor are considered to have an intermediate prognosis (60% cure rate); and those with more than one unfavorable factor are considered to have a poor prognosis (20% to 40% cure rate).

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CHAPTER 21A. KIDNEY CANCER

Michael Naughton, Burton M. Needles, and Chandru Sundaram

Presentation
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Objective
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I. Presentation

A. Subjective

Renal cell carcinoma has been referred to as the internists' tumor because of its protean clinical manifestations. Despite a number of interesting clinical syndromes and paraneoplastic syndromes associated with this disease, many of these cancers remain asymptomatic until bulky metastatic disease produces symptoms, leading to diagnosis. The diagnosis of small asymptomatic tumors has increased rapidly in the past several decades, likely because of an increase in utilization of imaging procedures, such as computed tomography (CT) scans.

The most common presenting symptoms of renal cell carcinoma (RCC) are anemia (20% to 40%), cachexia, fatigue, weight loss (33% each), and fever (30%). Less commonly, patients may be first seen with erythrocytosis, related to increased erythropoietin production, or elevated liver-function tests (LFTs) in the absence of metastatic disease (Stauffer syndrome). The classic triad of symptoms (flank pain, hematuria, and a flank mass) is seen in fewer than 10% of patients and usually heralds the presence of metastatic disease. Almost 50% of patients will have gross hematuria at some time in the disease course.

B. Objective

Hematuria is the most common objective finding in RCC. The presence of a flank mass is not uncommon, being present in up to 45% of patients in some series. A variety of laboratory abnormalities can be seen, including anemia, erythrocytosis, hypercalcemia, and elevated LFTs. An uncommon but interesting physical finding associated with kidney cancer is a varicocele that does not subside in the supine position.

II. Evaluation and staging

As described in the introduction section, a large number of RCCs are diagnosed serendipitously when seen on imaging studies obtained for another indication, or because of symptoms related to metastatic disease. A smaller number of patients have symptoms related to local disease, such as hematuria or flank pain related to the stretching of the renal capsule. In this section, we focus on the evaluation of a renal mass and the appropriate staging evaluation after an RCC has been diagnosed.

III. Evaluation of a renal mass

A. Radiology

The evaluation of a renal mass, noted either incidentally or during evaluation of related symptoms, should proceed according to a rational algorithm. It should be noted that there is great reluctance to perform a biopsy of a renal mass. There is good reason for this reluctance. Several authors have reported the seeding of needle tracts, and although the risk of such occurrence appears to be low, even a small chance of making a curable lesion incurable is unacceptable. In addition, the risk of false-negative biopsy results due to sampling error limits the utility of percutaneous biopsies.

The first step in evaluating a renal mass is determining whether it is solid or cystic. The best imaging modality to answer this question is ultrasound. If the lesion is cystic, no further evaluation is necessary. If the lesion is solid, or cystic with solid components, a CT scan should be performed. A CT scan should help to differentiate benign solid renal masses, such as angiomyolipomas and oncocytomas, from RCC. If a solid renal mass cannot be confirmed to be benign based on CT appearance, excision is indicated.

Newer imaging modalities, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) have not yet proven to be of sufficient sensitivity and specificity to alter this algorithm. Despite the high resolution and ability to detect vascular enhancement achieved by MRI, no difference was seen in the ability to detect RCCs by MRI in comparison to contrast-enhanced CT. The role of MRI in the evaluation of renal masses is probably limited to patients who cannot tolerate contrast-enhanced CT because of contrast allergy or impaired renal function. Although PET scans are a promising adjunctive imaging modality, there is as yet insufficient experience with this modality to define a role in the diagnosis of renal masses.

B. Pathology

Cancers of the kidney can generally be broken down into cancers of the renal parenchyma (80%) and cancers of the renal pelvis. Cancers of the renal parenchyma are generally adenocarcinomas (RCCs), and those of the renal pelvis are generally transitional cell tumors. This chapter focuses on cancers of the renal parenchyma. Histologically RCCs are classified into clear cell type (75% to 85%), chromophilic type (12% to 14%), chromophobic type (5%), and collecting duct type (1%).

C. Staging

Once an RCC is diagnosed, treatment planning must be based on preoperative or clinical staging. The keys to staging RCC, like those for most other malignancies, are to define the local extent of disease and to determine whether there is distant spread of disease. The approach to staging RCCs outlined here is depicted in Fig. 21.1.

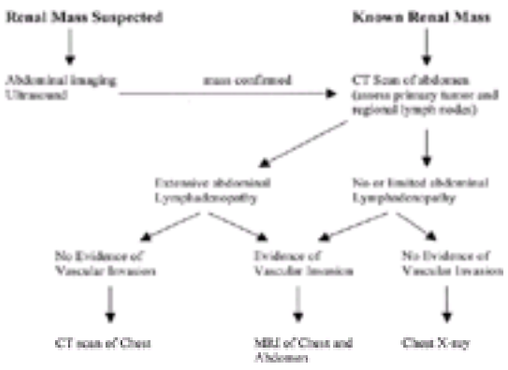

FIG. 21.1. Approach to staging evaluation of renal cell carcinoma.

The principal tool for determining the local extent of disease is the abdominal CT scan. The size of the lesion, the degree of invasion, the presence of lymphadenopathy, and the presence of vascular invasion are the essential pieces of information for determining T and N stage (Table 21.1). CT scanning is currently the most effective tool for correctly assessing these issues. In a comparison of CT scans with pathologic stage in 100 patients with RCC, Johnson et al. found that CT scans had a 46% sensitivity for perinephric invasion, 78% for venous invasion, 83% for adenopathy, and 60% for adjacent organ invasion. Overall, 91% of patients were correctly staged by CT scan. There are certain limitations of CT scans for staging. Lymph node status is generally determined by size criteria, with lymph nodes larger than 1 cm thought to be involved, whereas those smaller than 1 cm are not thought to be involved by tumor. CT scans are notoriously poor for determining tumor extension to the liver. This determination is based on obliteration of fat planes between the two organs, and intraoperative findings frequently do not correlate with CT in this regard.

TABLE 21.1. AJCC STAGING OF RENAL CELL CARCINOMA (FROM THE AJCC CANCER STAGING MANUAL, FIFTH EDITION)

CT scans are of limited value in identifying tumor thrombus. The presence or absence of tumor thrombus significantly affects surgical planning. The presence of thrombus is not a contraindication to surgery, but will affect the surgical approach. Modern CT-scanning techniques have improved the sensitivity and specificity for detection of tumor thrombus, but MRI scans with gadolinium enhancement do appear to provide superior assessment of the extent of thrombus, as well as discriminating bland thrombus from tumor thrombus. Obtaining a preoperative MRI is probably not necessary in all patients, but in patients with evidence of venous extension on CT scan, it is an important part of the preoperative evaluation.

In addition to determining the T and N stages, metastatic disease must be ruled out before proceeding with surgery. The most common sites of metastatic spread of RCCs are the adrenal glands, liver, lung, and bone. An abdominal CT scan obtained to evaluate the primary tumor is usually sufficient to evaluate the adrenal glands and liver. In the case of elevated LFTs without liver metastases on CT scan, it may be worthwhile to obtain an MRI of the abdomen before attempted surgical resection. As mentioned earlier, abnormal LFTs may be a manifestation of Stauffer syndrome, but basing this diagnosis on CT findings alone may lead to attempted resection in the presence of liver metastases.

A chest radiograph is generally considered sufficient to rule out pulmonary metastases. A chest CT scan should be obtained if a complex surgical resection, such as extensive thrombectomy, is being considered. The presence of enlarged retroperitoneal lymph nodes on abdominal imaging also warrants a staging chest CT.

A bone scan is indicated if there is bone pain or laboratory evidence suggestive of possible bony metastases (elevated calcium or alkaline phosphatase).

IV. Treatment

A. Early disease (T1 or T2, N0)

The treatment of localized, that is, nonmetastatic RCC is primarily surgery. In general, a radical nephrectomy is performed. Partial nephrectomy, or nephron-sparing surgery, is performed in certain situations, such as bilateral RCC, RCC in a solitary kidney, and in patients at risk for future insults to the nondiseased kidney. The nephron-sparing approach seems to offer satisfactory outcomes with respect to disease recurrence, especially for low-stage tumors.

Radical nephrectomy includes *en bloc* resection of the kidney and the perinephric fat outside Gerota capsule. Ipsilateral adrenalectomy is performed for large, upper-pole tumors. Removing a clinically uninvolved adrenal gland with small tumors, or mid- or lower-pole primaries, is more controversial. Resection of the regional lymph nodes at the time of radical nephrectomy also is controversial. Lymph node resection certainly provides more accurate staging than does clinical staging alone. It also may be that removing involved lymph nodes improves the outcome in node-positive disease, but no clear data support this belief.

Radical nephrectomy can be performed from a number of approaches. Incisions can be midline upper abdominal, flank, subcostal, or thoracoabdominal. The selection of incision depends on which approach is likely to provide adequate exposure.

Partial nephrectomy is indicated if a radical nephrectomy would lead to the immediate need for dialysis. Partial nephrectomy also is considered in patients with small (smaller than 4 cm) tumors that are clearly localized. A number of operative techniques are used to perform partial nephrectomies, including segmental polar nephrectomy, wedge resection, and major transverse resection.

Laparoscopic radical nephrectomy also is gaining popularity because of diminished operative morbidity and shortened hospital stays. The first laparoscopic nephrectomy was performed in 1990 for benign disease. Since then, this technique has been applied to both benign and malignant disease. Early reports indicate that laparoscopic nephrectomy is safe, and at least for short-term follow-up, provides outcomes similar to those of radical nephrectomy. Laparoscopic nephrectomy is associated with less postoperative pain, shorter hospital stays, and shorter convalescence time. This approach is a reasonable option for patients at centers with expertise with this procedure. As with most operative techniques, complications associated with this procedure decline

dramatically as operators gain experience with the technique.

B. **Locally advanced disease (T3 or T4, N1 or N2)**

In approximately half of patients, RCC is first seen as locally advanced disease (T3 to T4), presenting a number of therapeutic challenges. Involvement of the inferior vena cava (IVC) by direct extension of tumor down the renal vein (T3) is not an uncommon scenario. Resection of these tumors involves specialized surgical approaches determined by the superior extension of the tumor thrombus. Tumors involving the IVC, even up to the right atrium, are technically resectable, and these tumors may still be cured with surgery alone. Ten-year survival rates of up to 40% have been reported for patients undergoing tumor thrombectomy.

Renal artery embolization has been used in a variety of circumstances. In locally advanced disease, embolization of the renal artery may be used to attempt to shrink large tumors, or to diminish the extent of IVC thrombus. The efficacy of embolization in these settings is unclear. Embolization also may be used to diminish perioperative blood loss, or as a palliative intervention for hematuria. Embolization can be complicated by a postinfarction syndrome. This syndrome is characterized by pain, fever, nausea, and vomiting. The syndrome may last several days after embolization.

Locally invasive disease, that is, direct extension of primary tumors into adjacent organs such as the liver, pancreas, or colon, sometimes occurs in the absence of metastatic disease (T4). The mainstay of treatment is this setting is again surgical. Few patients with extension to adjacent organs are cured with surgery. Their quality of life may be improved if a complete resection can be performed, allowing local control of the tumor and tumor-related symptoms. Resection may be considered in patients with a good performance status, with few competing morbidities, and tumors that can be completely resected. Survival at 1 year is unusual in this group of patients.

C. **Adjuvant therapy**

At this time, there is no proven role for adjuvant therapy in the treatment of RCC. Postoperative radiation was evaluated in a randomized trial and was not found to be effective. Interferon-a has been evaluated in this setting and was not found to be effective. The use of high- and intermediate-dose interleukin-2 (IL-2) is still being evaluated.

D. **Metastatic disease**

Approximately 33% of patients with RCC are first seen with metastatic disease, and in up to 50% of patients treated with surgery for local disease, metastatic disease eventually develops. Metastatic disease is generally treated with systemic therapy, although surgery and radiation do have roles in the treatment of metastatic RCC.

E. **Solitary metastasis**

RCCs first seen with a solitary metastasis represent a relatively unique situation. Patients whose solitary site of metastatic disease can be completely resected have between 35% and 60% chance of surviving 5 years. Radiation therapy (XRT) often is delivered after surgery. Despite this favorable outcome, it is unclear whether the improved survival is a result of surgical intervention or of the indolent nature of the tumor.

A number of patient and disease characteristics predict for survival after resection of metastatic disease in RCC. Features favoring long-term survival include a disease-free interval of longer than 12 months (55% vs. 9% overall survival), solitary versus multiple sites of metastases (54% vs. 29% 5-year survival), and age younger than 60 years (49% vs. 35% 5-year survival). Survival is longer after resection of lung metastases than of brain metastases. Anecdotal evidence suggests that patients may derive benefit from resection for a second or third recurrence. For patients with a solitary metastatic site that cannot be resected, XRT can be considered. Radiation also is effective for relieving symptoms from metastatic lesions, with approximately 66% of patients receiving symptomatic benefit, and 50% achieving objective tumor regressions.

F. **Multiple metastases**

RCCs frequently have multiple metastatic lesions, with lung and bone being the most frequently affected sites. The treatment of metastatic RCC is generally systemic therapy, with local modalities used for palliative purposes. Immunotherapy is the basis of most of the systemic treatment regimens of RCC, whereas more conventional chemotherapy agents have little activity in this disease.

G. **Immunotherapy**

Standard cytotoxic chemotherapeutic agents have been uniformly disappointing in the treatment of RCC. Immunotherapy, which refers to treatment with agents that stimulate the patient's own immune system to combat the cancer, has shown some limited success in the treatment of RCC. The primary agents studied are IL-2 and interferon-a (IFN-a). IL-2 works through the activation of cytotoxic T-cell subgroups and stimulation of cytokine release. A number of clinical trials have documented modest but reproducible response rates to IFN-a and IL-2 in RCC.

H. **Interleukin-2 in renal cell carcinoma**

IL-2 was initially studied as a high-dose, intravenous regimen (600,000 IU/kg i.v. bolus every 8 hours for a total of 28 doses. This regimen resulted in an overall response rate of 14%, with 5% complete responses. Complete responders had a significant chance of long-term survival. Since this finding, a number of studies have looked at doses, schedules, and routes of administration of IL-2. The response rates in these studies vary from none to 40%. The dose-limiting toxicities of IL-2 are generally hypotension and a vascular-leak syndrome. In general, during high-dose therapy with IL-2, doses are skipped rather than reduced for toxicity. A significant portion of patients treated with this regimen will require hemodynamic support with vasopressors. In the initial National Cancer Institute (NCI) study, a 4% mortality rate was observed. This mortality rate has been significantly reduced as experience with the regimen and supportive care improved, but this regimen should be delivered in a monitored setting by physicians well versed in the regimen.

Several studies have reported the use of subcutaneous IL-2 given on an outpatient basis. These studies have demonstrated response rates similar to those seen in high-dose i.v. regimens, with greatly reduced toxicity. The most commonly used regimens advocate IL-2, 15 to 20 million units given s.c. for the first 5 days, with lower doses (approximately 10 million units) given on days 1 to 5 of subsequent weeks.

I. **Interferon-a in renal cell carcinoma**

IFN-a has been widely studied in phase II studies, using different preparations and dosing schemes. Published response rates have been in the 15% to 20% range. The optimal dosing and schedule of IFN-a has not been determined, but 5 to 10 million IU/m^2 given s.c. 3 to 5 days per week is the generally accepted dosing.

J. **The combination of interleukin-2 and interferon-a**

The combination of IL-2 and IFN-a has been evaluated in a number of studies with inconclusive results. At least one randomized study showed improved response rates and survival with the combination of the two cytokines compared with either used alone. Negrier et al. reported the results of a three-arm randomized study comparing IL-2, IFN-a, or the combination (*N Engl J Med* 1998;338:1272–1278). Response rates were significantly higher (18.6% vs. 6.5% and 7.5%) for the combination compared with IL-2 and IFN-a, respectively. Event-free survival at 1 year was 20% in the combination arm, compared with 15% and 12% in the single-agent arms ($p = 0.01$). Overall survival was not different between treatment groups. Toxicity was most pronounced in the combination arm. The relatively small improvement in event-free survival is generally not thought to justify the toxicity of this regimen. The very low response rates in the single-agent arms also were disappointing.

K. **Immunochemotherapy**

Another randomized study recently compared the combination of IL-2 and IFN-a with the same combination given with continuous-infusion 5-fluorouracil (*J Clin Oncol* 2000;24:4009–4015). In this study, the response rate to IL-2 and IFN-a was 1.4%, and in the group that received IL-2 and IFN-a and 5-fluorouracil, the response rate was 8.2%. This difference was not statistically significant, and the survival at 1 year was not different between the groups. This result was disappointing, not only because it failed to show any improvement with the addition of 5-fluorouracil, but also because the response in the "standard arm" was so low.

L. Current standard of systemic therapy for renal cell carcinoma

At this time it is probably not possible to draw definitive conclusions regarding the role of immunotherapy in RCC. It appears that there is a subset of patients that derives benefit from these types of therapies. Patients with good performance status and disease limited to the lungs or lymph nodes are reasonable candidates for a trial of immunotherapy. For patients with metastatic RCC, enrollment in a clinical trial whenever possible is appropriate. Best supportive care alone remains a viable treatment alternative.

M. Radical nephrectomy in metastatic renal cell carcinoma

There remains interest in removing the primary tumor in patients with metastatic RCC. This is derived from reports of regression of metastatic disease after removal of the primary tumor. In theory, removing the primary tumor may provide an immunologic impetus that leads to response in the metastatic disease. The Southwest Oncology Group reported a large randomized trial in which nephrectomy plus systemic interferon immunotherapy was compared with immunotherapy alone (interferon) for patients with advanced RCC. A statistically significant survival benefit was seen in favor of the nephrectomy arm (12 months vs. 8.5 months). It seems reasonable for the moment to view a combination of nephrectomy and immunotherapy as a new standard of care, although it is possible that even newer cytokines will improve results. Patients with a good performance status who are being considered for systemic therapy should therefore be considered for nephrectomy as well.

V. Complications

A. Of the disease

The complications of RCC may be related to local progression of disease or metastatic spread. Local progression of disease often leads to pain and hematuria. RCC frequently metastasizes to lung and bone. Bone pain and pathologic fractures are relatively common. Shortness of breath, cough, hemoptysis, and malignant pleural effusions all occur relatively frequently.

B. Of therapy

Serious complications occur in approximately 20% of patients undergoing radical nephrectomy, and the mortality rate associated with this procedure is approximately 2%. Common complications include perioperative myocardial infarction, cerebrovascular accident, pulmonary embolism, and pneumonia. Early mobilization and incentive spirometry may help reduce the incidence of some of these complications.

Intraoperative injuries to the liver, spleen, pancreas, and bowel may occur. These should be recognized and repaired in the operating room. A pancreatic fistula can develop as a result of an unrecognized injury to the pancreas.

Pneumothorax, retroperitoneal bleeding, and wound infection also can occur.

As described earlier, laparoscopic nephrectomy is associated with less postoperative pain, shorter hospital stays, and shorter overall convalescence.

The complications of systemic therapy are related to agents and doses used. IL-2 regimens are generally more toxic than IFN-a regimens. Combinations regimens are more toxic than single-agent regimens. The common toxicities of high-dose IL-2 include hypotension requiring vasopressors, fever, and decreased performance status.

VI. Natural history

RCC is well known for its unpredictable behavior. Spontaneous regressions of metastatic disease have bee reported more often than for any other solid tumor. Late recurrences also are seen. These cases represent extremes, however, and the majority of RCCs follow relatively predictable patterns.

Pathologic stage is the most important determinant of prognosis. Five-year survival rates are approximately 75% for stage I, 60% for stage II, 40% for stage III, and 10% for stage IV. The median survival of patients with metastatic disease is in the range of 14 months.

VII. Background

A. Epidemiology

Approximately 30,000 cases of RCC occur in the United States each year, resulting in 12,000 deaths. There is a slight (1.5:1) male predominance, and RCC is more common among urban than among rural populations. The incidence increases with increasing age, although cases have been reported at essentially all ages.

The incidence of RCC has increased gradually over the past two decades. It is unclear whether this represents a true increase in the incidence of disease or increased diagnosis related to the use of CT scans and MRIs of the abdomen on a more routine basis.

B. Identifiable risk factors

Several risk factors have been identified for kidney cancer. Cigarette smoking has been associated with kidney cancer in case–control studies, and cohort studies have demonstrated a clear association with a dose–response relation. Obesity is associated with RCC, with increasing risk with increasing body mass index. Hypertension and the use of antihypertensive agents are considered risk factors for RCC. Renal cell cancers have no clear relation to occupational exposures.

By far the majority of RCCs are sporadic, but three distinct family syndromes have been described.

The von Hippel–Lindau (VHL) syndrome carries a high risk of clear cell RCC. This disorder is caused by germline mutations of the tumor-suppressor VHL gene located on chromosome 3p. Familial occurrence of clear cell carcinomas in the absence of VHL syndrome has been associated with balanced translocations of 3p. Hereditary papillary RCC is related to mutations of the protooncogene met on chromosome 7q.

C. Molecular pathology

Studies of the molecular pathology of RCC have focused on genetic alterations. Mutations of the VHL gene (3p) are closely associated with clear cell RCC, whereas mutations of met (7q) are associated with papillary RCC (*J Urol* 1999;162:1246–1258).

D. Pathogenesis

The VHL gene has been found to be mutated in a high percentage of patients with clear cell RCC, and have also been noted in patients with granular and sarcomatoid RCC. Such mutations are not seen in patients with papillary RCC. It is thought that acquired mutations of the gene may contribute to the development on nonpapillary RCC.

VIII. Future directions

Much of the ongoing research in RCC is focusing on immunotherapy approaches to this disease.

The role of *ex vivo* activated lymphocytes, either lymphocyte-activated killer cells (LAKs) cells or tumor-infiltrating lymphocytes (TILs), has been evaluated. Both of these methods are cumbersome, expensive, and potentially toxic. They have not as yet been found to produce higher response rates or more durable responses than either IL-2 or IFN-a.

Another approach to immunotherapy is allogeneic stem cell transplantation. The theory is to achieve a graft-versus-tumor effect, as seen in leukemia. In general, a nonmyeloablative induction regimen is used, followed by infusion of donor stem cells from a human leukocyte antigen (HLA)-matched sibling. One small study from the National Heart, Lung, and Blood Institute reported 10 responses in 19 patients treated in this manner. Two patients died of treatment complications. Regression from metastases occurred late, often after discontinuation of cyclosporins used to suppress graft-versus-host reaction, being consistent with graft-versus-tumor effect. In the three complete responders, responses lasted 27, 25, and 16 months (*N Engl J Med* 2000;343:750–758). It is not clear whether case selection and nature of metastases influenced results. This approach also remains experimental, but offers promise for the future of the treatment of metastatic RCC.

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CHAPTER 21B. CANCER OF THE BLADDER

Michael Naughton and Burton M. Needles

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I. Presentation

A. Subjective

The most common presenting symptom of bladder cancer is hematuria in 80% to 90% of patients. Gross hematuria obviously warrants a thorough evaluation of the genitourinary system. When gross hematuria is painless and total (present during the entirety of the urinary stream), it especially causes concern for bleeding from the bladder or upper tracts. In a study of 1,000 patients with total, gross, painless hematuria, 15% were found to have bladder cancer (*JAMA* 1957;153:783). Irritative urinary symptoms are relatively common at presentation, including frequency, urgency, and dysuria. The combination of these symptoms with hematuria is very suggestive and warrants full urologic evaluation. Depending on the location of their tumors, patients may have symptoms of bladder-outlet obstruction or ureteral obstruction. A small subset, 5% to 10% of patients, have symptoms related to metastatic disease.

B. Objective

Physical findings may be conspicuously absent in early bladder cancer. With more advanced disease, a pelvic mass may become palpable. Lower extremity edema also may develop with advanced disease.

Hematuria, either microscopic or gross, will usually be present. It may, however, be intermittent.

II. Workup and staging

A. Workup

Evaluation of gross hematuria should include a urine culture, cytologic evaluation of the urine, imaging of the kidneys and upper urinary tracts, and cystoscopy. Microscopic hematuria potentially presents more difficult diagnostic decision making. Microscopic hematuria is an extremely common finding, and most cases of microscopic hematuria are nonneoplastic in origin. The question becomes how to evaluate the finding adequately without putting the majority of patients through unnecessary diagnostic tests. The initial evaluation of urine that tests positive for blood on a dipstick is microscopic evaluation to confirm the presence of red cells. Again, culture and cytology should be performed. Bladder cancer is generally diagnosed with cystoscopy. At cystoscopy, the gross appearance of the cancer can be assessed (focal vs. multiple, flat vs. papillary or nodular), and biopsies can be obtained. If a bladder tumor was anticipated before cystoscopy, and appropriate anesthesia arranged, the evaluation can proceed to transurethral resection (TUR) of the bladder tumor and examination under anesthesia (EUA). If anesthesia was not arranged before cystoscopy, then this takes place in two stages, cystoscopy with biopsy followed by TUR and EUA. EUA allows bimanual palpation of the bladder wall. Induration of the bladder wall without a palpable mass likely portends a better-prognosis tumor, whereas the presence of a palpable mass likely indicates gross extravesical tumor. TUR provides a more sensitive method for defining the depth of invasion. Ideally, a full-thickness bladder wall specimen would be obtained to allow definitive staging. Specimens should be obtained with clear indications of the superficial and deep aspects of the biopsy. Small papillary tumors that appear to be superficial may be resected completely, without resecting deep into the detrusor muscle. Larger tumors, especially nodular or solid masses, require deeper resection done in layers. Resection to the depth of the perivesical fat can be performed in attempts to resect completely the muscle-invasive tumors.

B. Pathology

1. **Staging.** In the 1940s, Jewett and Strong noted a relation between the depth of invasion into the muscle wall of bladder tumors and survival. This observation lead to the first staging system for bladder cancer, the Jewett system. The staging of bladder cancer has since been modified to correlate with the tumor, node, metastasis (TNM) system used by the American Joint Committee on Cancer (AJCC). The TNM system (Table 21.2) is still largely based on the depth of tumor invasion into the muscular wall of the bladder, and the most important information regarding clinical stage comes from results of transurethral biopsies or resection specimens. Treatment and prognosis are to a large extent defined by T stage. Patients with Ta or T1 disease are generally treated with transurethral resection, whereas patients with muscle-invasive or T2 disease generally require cystectomy or radical radiation. Bladder cancers are initially staged clinically; if cystectomy is performed, they are staged pathologically.

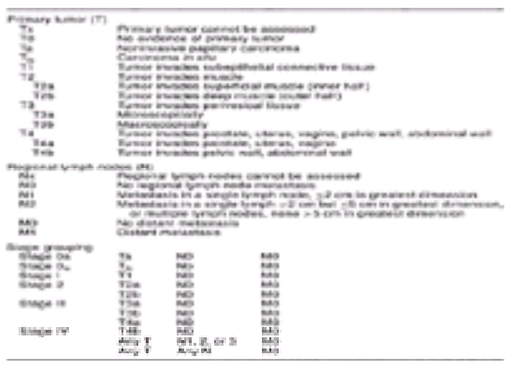

TABLE 21.2. AJCC STAGING OF BLADDER CANCER (1997)

There are two main prognostic groups. Superficial tumors occur at the level of the bladder mucosa and include carcinoma *in situ* (CIS; T_{is}), papillary

lesions (Ta), and those that invade (but not through) the lamina propria (T1). T2, T3, and T4 tumors that penetrate the muscularis propria are more aggressive and have a strong tendency to metastasize.

Determining the T stage of bladder tumors by TUR has its limitations. The correlation between TUR and cystectomy staging is in the range of 60%. The single most important determination made by TUR is whether muscle invasion is present. Superficial, that is non–muscle-invasive tumors, are treated much differently than muscle-invasive tumors. Even this determination can be challenging. The **muscularis mucosae,** a muscular layer that is sometimes seen in the lamina propria, can be confused with the **muscluaris propria** or detrusor muscle.

In addition to the depth of invasion, information regarding gross appearance, grade, and the presence of **CIS** can be determined at cystoscopy. Papillary tumors are more likely to be superficial and may be completely resected without deep muscle resection. Solid or nodular tumors are more likely to be muscle invasive, and will likely require deeper resection. High-grade tumors are more likely to be muscle invasive, and cystectomy studies have documented a 95% rate of muscle invasion for high-grade tumors. The presence of CIS is generally thought to portend a worse prognosis, and CIS is generally characterized as high grade. The risk of invasion increases when tumors are found to be multifocal. Lymphatic or vascular invasion also is associated with increased risk for metastasis.

For patients without invasion into the **muscularis propria,** the risk of nodal or systemic metastases is quite low, and further staging studies are generally not indicated. For patients with muscle-invasive disease, more complete staging is indicated before determination of the treatment plan. In general, a CT scan or MRI of the abdomen is obtained to help define the local extension of the tumor, the presence or absence of nodal metastases, and the presence or absence of other abdominal metastases. CT and MRI both have relatively high specificity (greater than 90%) for the presence of nodal metastases when size criteria are used, but also relatively poor sensitivity (approximately 50%). A chest radiograph is generally sufficient to exclude pulmonary metastases, and a bone scan should be obtained to rule out bone metastases.

III. Therapy and prognosis

The therapy and prognosis of bladder cancer is dependent on the stage of disease at presentation. Treatment options and prognosis can best be described according to the clinical presentation: superficial, muscle invasive, or metastatic.

IV. Superficial bladder cancer

The majority of bladder cancers, in the neighborhood of 75%, are superficial at presentation. Treatment of superficial bladder tumors consists of resection (TUR), intravesical chemotherapy or immunotherapy, and in very selected cases, cystectomy. Most superficial tumors can be completely resected by TUR. The most important determinations to be made in regard to these tumors are the risk for recurrence and the risk for progression to muscle-invasive disease. Most patients with superficial bladder tumors will experience recurrence within 5 years of diagnosis. Approximately 30% of these patients will progress to muscle-invasive disease. For patients at high risk of recurrence or progression, intravesical therapy may be added to TUR to reduce these risks. For patients with refractory superficial disease or extremely high risk for progression, cystectomy may be considered.

The risk of progression is related to the initial tumor stage. Most patients with Ta disease will recur with superficial disease. Patients with T1 disease and T_{is}, especially multifocal T_{is}, are at much greater risk for progression to muscle-invasive disease. Grade also affects the likelihood of progression. Ta disease that is grade 2 or 3 has a significant (20%) risk of progression, whereas Ta grade 1 disease has a negligible risk of progression (Table 21.3).

Stage	Recurrence at 1 yr	3 yr	5 yr	Rate of Progression to Muscle Invasion
Ta G1	25%	50%	65%	Rare
Ta G2,3	35%	65%	85%	20%
T_{is}, local	25%	50%	65%	20%
T_{is}, multicentric	50%	75%	100%	50–80%
T1	50%	80%	90%	50%

TABLE 21.3. APPROXIMATE RISK OF RECURRENCE AND PROGRESSION OF SUPERFICIAL BLADDER CANCER BY STAGE

Determining the risk of progression plays a role in defining treatment. As stated earlier and depicted in Table 21.2, most patients with superficial bladder cancer will experience recurrence. Therefore, it is recommended that patients undergo repeated cystoscopy 3 months after their initial resection. Recurrent tumors are resected and evaluated for evidence of progression, in terms of both invasiveness and grade. For patients at high risk for recurrence and/or progression, consideration must be given to intravesical therapy.

The indications for intravesical therapy have not been clearly defined. Some general guidelines have been proposed. At Memorial Sloan-Kettering Cancer Center, the indications for prophylaxis have included four or more recurrences in 1 year, tumor involvement of more than 40% of the bladder surface, diffuse T_{is}, and T1 disease. Intravesical therapy has been shown to reduce the likelihood of recurrence and the rate of progression to muscle-invasive disease.

A number of agents have been used for intravesical therapy, including chemotherapeutic and immunologic agents. Chemotherapy agents used have included mitomycin-c, doxorubicin, epirubicin, and thiotepa. All have been found to reduce recurrence rates by 15% to 20%. None has been shown to prevent progression to muscle-invasive disease or alter overall survival.

Immunotherapies used for this purpose have included primarily bacille Calmette-Guérin (BCG) and IFN-a. BCG is thought to be the most active agent for preventing recurrence and progression of superficial bladder cancer. Randomized studies have shown BCG to be superior to thiotepa, doxorubicin, and epirubicin. Mitomycin-c has shown equivalent and inferior results to BCG in randomized studies. A number of treatment regimens with BCG have been used. The most standard is probably a regimen evaluated by the Southwest Oncology Group (SWOG). They found a regimen of 6 weekly instillations followed by instillations for 3 consecutive weeks at every 3 months for 3 years to be superior to a 6-week induction regimen. The mechanism of action of BCG is not well understood, but there is evidence that the bacillus attaches to the bladder cells and evokes an immune response, or perhaps nonspecific immune stimulation or an alteration of suppressor/helper T-cell ratios in the bladder. BCG has been shown to reduce the rate of recurrence and to prolong the disease-free state, but may not affect the ultimate rate of progression to invasive cancer. Patients may experience flu-like symptoms. A granulomatous infection can occur at various sites including liver, lung, prostate, and kidney. BCG sepsis can be life threatening. If dissemination is documented, 6 months of antituberculous therapy is needed.

A small number of patients with superficial bladder cancer will require cystectomy for effective management. Patients with recurrent high-grade papillary tumors or CIS, tumors that have progressed to muscle invasion, and tumors involving the prostatic stroma or ducts should be considered for cystectomy. Cystectomy results in high rates of cure for patients with superficial cancer who require this aggressive treatment.

V. Muscle-invasive disease

The standard treatment for muscle-invasive bladder cancer is radical cystectomy. Over recent years, interest in bladder-sparing approaches for muscle-invasive disease has grown. Such approaches include aggressive TUR, with or without intravesical therapy, radiation, and/or chemotherapy. These approaches are still considered investigational.

A. **Radical cystectomy**

Early series using radical cystectomy for the treatment of bladder cancer reported disappointing results. This was due in a large part to very high rates of operative mortality. As the care of operative patients has improved over the past several decades, the mortality rate associated with this procedure has been reduced to less than 5%, and radical cystectomy with pelvic lymph node dissection (PLND) is considered the standard of care for muscle-invasive bladder cancer. Modern series report 5-year survival rates in the ranges of 60% to 80% for stage II disease, and 30% to 60% for stage III disease.

In male patients, radical cystectomy involves the *en bloc* removal of the bladder, prostate, seminal vesicles, proximal vas deferens, proximal urethra, and a margin of adipose tissue, and peritoneum. In female patients, the procedure involves the *en bloc* removal of the bladder, urethra, uterus, fallopian tubes, ovaries, anterior vaginal wall, and surrounding fascia.

After removal of the bladder, a route for elimination of urine must be created. This is accomplished either with a noncontinent urinary diversion, usually an ileal conduit, or with a continent urinary diversion. An ileal conduit is created by connecting the ureters to a segment of ileum, and the segment of ileum to the abdominal wall. A number of surgical approaches have been designed for the creation of continent diversions. These include approaches that use the abdominal wall, orthotopic bladders, and the rectum as sites of drainage. All forms of urinary diversion entail a number of potential complications including metabolic and electrolyte disturbances, pyelonephritis, urinary calculi, and altered drug metabolism. The continent diversions generally entail longer operations and increase the risk of complications. They should be considered for patients with a reasonable life expectancy and the ability to catheterize themselves.

B. **Radiation therapy**

In many countries, external-beam radiation is considered standard therapy for muscle-invasive bladder cancer. This is not the case in the United States. The ability to perform radical cystectomy and PLND with greatly reduced morbidity and mortality has made this a procedure with an acceptable risk profile for most patients with muscle-invasive bladder cancer. For patients who are not thought to be candidates for radical surgery, XRT would be an alternative.

Radiation has been evaluated in both the pre- and postoperative settings. Several randomized trials of preoperative radiation therapy have failed to demonstrate significant improvement in outcomes and have shown significant increases in gastrointestinal (GI) toxicity. Postoperative radiation also has been evaluated and not found to improve survival over surgery alone. Pre- and postoperative radiation are generally not indicated, unless they are incorporated into a multimodality bladder-sparing approach, as described later.

C. **Chemotherapy**

Chemotherapy has been evaluated in the neoadjuvant and adjuvant settings. The commonly used chemotherapy regimens in the treatment of transitional cell carcinoma (TCCA) of the bladder are discussed in more detail in the section on metastatic disease. In general, regimens containing cisplatin have been found to be the most efficacious in this disease, and most of the regimens evaluated in these settings have included cisplatin.

The role of neoadjuvant chemotherapy remains controversial in bladder cancer. One trial, the Nordic 1 Trial, randomized patients with muscle-invasive disease or high-grade T1 tumors to two cycles of cisplatin (70 mg/m^2) and doxorubicin (30 mg/m^2) or no chemotherapy before radiation and cystectomy. This trial included 304 patients and demonstrated a significantly improved 5-year survival for the chemotherapy group for patients with muscle-invasive disease (*Scand J Urol Nephrol* 1993;27:355). This subgroup analysis was not confirmed in a subsequent trial. A larger randomized trial compared three cycles of cisplatin, methotrexate, and vinblastine (CMV) before radiation or surgery, versus no chemotherapy. This trial enrolled 976 patients and demonstrated a small (5.5%) but not statistically significant difference in 3-year survival (*Lancet* 1999;354:1650). The SWOG reported a survival benefit in a trial of neoadjuvant MVAC [methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatinum] plus radical cystectomy versus radical cystectomy alone in patients with locally advanced bladder cancer (t2-4a). Of patients treated with chemotherapy, 38% had no disease at surgery. Median survival was 6.2 years for the chemotherapy group versus 3.8 years for cystectomy alone (*Proc ASCO* 2001;20:3).

Despite these promising results, neoadjuvant chemotherapy is not considered standard in the treatment of bladder cancer. A number of criticisms applied to the SWOG trial may put this into perspective. This trial was designed with the power to demonstrate a significant improvement in survival by using a one-sided significance test with $p = 0.05$. If a two-sided test is applied, the result is no longer significant. In addition, the 95% confidence interval for the reported data includes 1, implying no difference between the treatment arms. This trial includes approximately 10% of the patients reported in randomized trials of neoadjuvant therapy in bladder cancer. The other trials, including trials using combination chemotherapy, have not revealed any benefit from neoadjuvant chemotherapy. Finally, the probable benefit of adjuvant therapy must be considered. If chemotherapy is given in the adjuvant setting, patients with early-stage disease may be spared unnecessary chemotherapy. A large international randomized trial is under way to attempt to answer this question. Suffice it to say, neoadjuvant therapy of bladder cancer remains a controversial issue.

Adjuvant chemotherapy also has been evaluated in a number of trials, but this issue also remains controversial. Three completed randomized studies have suggested a survival benefit to adjuvant chemotherapy. One trial, from the University of Southern California, compared four cycles of cyclophosphamide, doxorubicin, and cisplatin (CISCA) with surgery alone. A difference in median survival of 51 versus 29 months, favoring the chemotherapy group, was seen, but this was not statistically significant ($p = 0.062$), and only 91 patients were randomized in this trial. A second trial using methotrexate, vinblastine, epirubicin, and cisplatin (M-VEC) was terminated early because of a higher rate of relapse in the no-treatment group at an interim analysis. This study eventually reported a survival difference, but this is difficult to interpret, because relapsing patients in the no-treatment arm did not receive chemotherapy at the time of relapse. A third trial randomized 50 patients to CMV or no chemotherapy, and showed no significant survival difference.

It remains unclear whether adjuvant chemotherapy improves outcomes in patients with extravesical extension or nodal involvement of their tumors. Many clinicians recommend adjuvant chemotherapy for patients at high risk of relapse. This may be justified if the poor outcomes without therapy and the reported long-term survival seen in patients with metastatic disease treated with chemotherapy are considered. Nevertheless, the benefit of this therapy is unproven, and further investigations of adjuvant chemotherapy versus chemotherapy at the time of relapse are warranted.

VI. Bladder-sparing/combined-modality approaches

Radical cystectomy is associated with an operative mortality rate of approximately 3%, and results in significant lifestyle changes. A number of approaches have been evaluated in muscle-invasive TCCA to find alternatives that would allow patients to be successfully treated for their cancer and maintain normal urinary function. For instance, patients who are found to have muscle-invasive disease on TUR, and are found to have no residual disease at repeated TUR, may not require further treatment. Patients with papillary tumors and patients with minimal muscle invasion may be successfully treated with TUR alone. This does require regular follow-up, and patients must understand that they may require cystectomy, should their disease recur.

Given the relatively high response rates to chemotherapy and radiation therapy, and the morbidity and quality-of-life issues associated with radical cystectomy, a number of centers have actively evaluated bladder-sparing approaches for the treatment of muscle-invasive bladder cancer. Trials of neoadjuvant chemotherapy have documented pathologic complete responses to the neoadjuvant therapy in a subset of patients. Radiation therapy also can result in pathologic complete responses. Using one or both of these modalities, followed by a more limited surgical procedure such as partial cystectomy or aggressive TUR, may result in equivalent outcomes to radical cystectomy.

A number of single-arm studies have demonstrated 5-year survival rates similar to those achieved with conventional treatment (approximately 50%), and a significant portion (approximately 40%) of patients surviving with an intact bladder. These-single arm studies do not necessarily demonstrate equivalence to radical cystectomy. Patients are often highly selected, and patients who do not achieve significant responses to chemotherapy may be removed from the bladder-sparing approach and undergo radical cystectomy. They do demonstrate that selected patients may be able to survive with their bladders intact, despite muscle-invasive bladder cancer.

One approach reported from Massachusetts General Hospital involves CMV chemotherapy, radiation with concurrent cisplatin, and TUR. Patients undergo aggressive TUR followed by two cycles of CMV. They then undergo repeated cystoscopy and assessment of response. They then receive radiation to a maximum of 40 Gy with concurrent cisplatin. A third cystoscopy is performed after completion of the radiation therapy, and patients without a complete response

are referred for cystectomy. Other groups have reported on similar approaches, with acceptable survival, and bladder preservation in the range of 40%.

Some patients with muscle-invasive bladder cancer may be managed without a cystectomy. Patients with small, papillary tumors and with the ability to maintain regular follow-up are reasonable candidates for bladder-sparing approaches. We hope that ongoing trials will help define the optimal combination of therapies to obtain tumor control while minimizing toxicity.

VII. Metastatic disease

Patients with locally advanced, usually thought to include T4b and N2 or N3 disease, and metastatic bladder cancer die of their disease unless they receive effective chemotherapy. These patients generally receive limited benefit from local-treatment modalities and are considered for systemic therapy.

A number of single agents have been found to produce a significant number of partial remissions. Unfortunately, these remissions tend to be brief, in the range of a few months. These findings led investigators to pursue combinations of active single agents, and these efforts have led to a number of active combinations in the treatment of bladder cancer (Table 21.4).

Regimen	Drug	Dose	Schedule	Response Rate
MVAC, every 28 days	Methotrexate	30 mg/m^2	Days 1, 15, 22	46% (12% CR)
	Vinblastine	3 mg/m^2	Days 2, 15, 22	
	Doxorubicin (Adriamycin)	30 mg/m^2	Day 2	
	Cisplatin	70 mg/m^2	Day 2	
CMV, every 21 days	Cisplatin	100 mg/m^2	Day 2	56% (28% CR)
	Methotrexate	30 mg/m^2	Days 1 and 8	
	Vinblastine	3 mg/m^2	Days 1 and 8	
GC, every 28 days	Gemcitabine	1,000 mg/m^2	Days 1, 8, and 15	49% (12% CR)
	Cisplatin	70 mg/m^2	Day 2	
ITP	Ifosfamide	1,200 mg/m^2	Days 1, 2, 3	79% (20% CR)
	Paclitaxel	200 mg/m^2	Day 1	
	Cisplatin	70 mg/m^2	Day 1	

CR, complete response.

TABLE 21.4. COMMON CHEMOTHERAPY REGIMENS FOR THE TREATMENT OF TRANSITIONAL CELL CARCINOMA

Several combination regimens have been evaluated and found to produce high response rates, with some durable responses in advanced TCCA of the bladder. The most commonly used regimens are the combination MVAC and the combination CMV. Another highly active regimen is ifosfamide, paclitaxel, and cisplatin. Both MVAC and CMV have been found to be superior to single-agent cisplatin. In a study comparing MVAC with cisplatin, the response rate of MVAC was 39% with a median survival of 12.5 months, statistically significant compared with the 12% response rate and 8.2-month median survival with cisplatin alone. MVAC has been demonstrated to be superior to CISCA. MVAC and CMV have not been directly compared.

In general, MVAC has been thought to be the standard regimen for metastatic TCCA. Some clinicians prefer CMV, and as stated earlier, the regimens have not been directly compared. MVAC has been associated with significant toxicity, including treatment-related mortality in the range of 5%. Newer agents are being studied, and paclitaxel, docetaxel, ifosfamide, and gemcitabine have all been shown to have significant activity. Combinations have resulted in response rates between 50% and 80%. The ITP regimen of ifosfamide, paclitaxel, and cisplatin was reported to have a median survival of 18 months. Recently the combination of gemcitabine and cisplatin (GC) has been found to have similar clinical activity to MVAC with significantly fewer side effects in the treatment of advanced TCCA of the bladder.

On reviewing the chemotherapy data, it is apparent that stage migration has occurred. Patients with smaller volume (e.g., node-only disease) are being treated. MVAC, when initially used in 1986, yielded a median survival of 12 months, whereas a report a decade later indicated a median survival of 18 months. Although bladder cancer is a chemosensitive tumor, one must carefully evaluate duration of response and survival data in evaluating these new drug combinations.

Unfortunately, despite high response rates, nearly all patients with advanced TCCA of the bladder die of their disease. Median survival in most series using an effective combination regimen is in the range of 12 months. Up to 20% to 30% of patients with nodal and up to 10% of patients with metastatic disease may obtain long-term remission. Most authors currently recommend six cycles of therapy for responding patients, with consideration of surgical resection of residual disease after four cycles, followed by two additional cycles.

Patients with poor performance status, or extensive bony or visceral metastases, are unlikely to achieve a complete response or long-term survival. The median survival for these patients is in the range of 6 months. For these patients, consideration could be given to using one of the many active single agents (cisplatin, gemcitabine, or paclitaxel) or no chemotherapy, as opposed to the aggressive combination regimens.

VIII. Complications of therapy

A. Surgery

The major surgical treatments for TCCA of the bladder are TUR and radical cystectomy. Each is associated with its own potential complications.

TUR is generally accomplished with a resectoscope inserted into the bladder via the urethra. A resecting loop is passed beyond the tumor, and then pulled back toward the scope with application of an electric current. The tumor is generally resected until healthy muscle can be seen at the base of the resection site. The most common complication of this procedure is perforation of the bladder. Often the perforations are minor and of limited clinical consequence. A cystogram can confirm the diagnosis, and patients are generally treated with a drainage catheter and prophylactic antibiotics.

Other complications of TUR include clot retention due to bleeding, obturator nerve injuries, and injury to the urethra or ureteral orifice. Late complications include bladder contracture.

Radical cystectomy and PLND is a major operative procedure. As described earlier, advances in operative and perioperative care have greatly reduced the mortality rate associated with this procedure. Reported mortality rates in recent series are generally less than 3%. The incidence of significant early postoperative complications is in the range of 10%, and this includes hemorrhage requiring transfusion, partial small bowel obstruction, and urine leakage. Early ambulation and the use of pneumatic compression stockings have greatly reduced the incidence of deep venous thrombosis and pulmonary embolism.

The long-term complications of this procedure are to a great extent related to the type of urinary diversion used. The most common type of diversion used at this time is the ileal conduit. In addition to common postoperative complications such as wound infections or dehiscence, urine leakage, and bowel obstruction, these patients are at risk for a number of complications specifically related to the urinary diversion. These include stomal stenosis, parastomal hernia, pyelonephritis, urinary calculi, and metabolic problems. The metabolic problems encountered depend on the type and length of bowel used in creating an anastomosis. Hypochloremic, hyponatremic, hyperkalemic, metabolic acidosis occurs in up to 40% of patients with a small bowel conduit. Drugs that are excreted unchanged in the urine and can be reabsorbed in the intestine may build up to toxic levels. This phenomenon has been described for phenytoin, among others. B_{12} and fat malabsorption may occur. Chronic acidosis may lead to osteomalacia.

B. Radiation therapy

As with surgery, radiation techniques have advanced over recent years, and this has resulted in a significant decrement in the toxicities associated with this form of treatment. Three-dimensional treatment planning has been a major advance. This has allowed higher doses of radiation to be delivered to tumors, with less radiation delivered to surrounding normal tissues. The most common complications of radiation to the bladder include irritative bowel or bladder symptoms, chronic proctitis, and reduced bladder capacity. Occasionally severe bowel obstruction or severe bladder dysfunction requiring surgical diversion

will occur.

C. **Chemotherapy**

As would be expected, the toxicities of chemotherapy are predicated by the agents and doses used. The most commonly used regimens in bladder cancer are multiagent regimens including cisplatin (MVAC, CMV, or GC). Common toxicities of these regimens include neutropenia and fever (10% to 30%) and mucositis (10% to 20%). Peripheral neuropathy, hearing loss, and renal impairment occur less frequently. Anticipated treatment-related mortality is in the range of 3% for MVAC and 1% for GC.

D. **Follow-up**

Specific follow-up recommendations depend on the clinical presentation of disease. The most specific recommendations address the care of patients with superficial bladder cancer. Given the high rate of recurrence of superficial bladder cancer, most authors recommend regular follow-up, usually with cystoscopy and urine cytology 3 months after initial diagnosis. Subsequent follow-up is determined by the findings at the 3-month evaluation (Table 21.5). Patients with a single tumor at diagnosis and no recurrence at 3 months may be followed up with annual cystoscopy. Patients with a single tumor at diagnosis and a recurrence at 3 months, or multiple tumors at diagnosis and no recurrence at 3 months should undergo cystoscopy every 3 months. Patients with multiple tumors at diagnosis and recurrence at 3 months should receive intravesical therapy. These guidelines have been validated only retrospectively. The duration of follow-up has not been defined, but given the propensity of this disease for late recurrences, many authors recommend indefinite follow-up.

Presentation	3-Month Cystoscopy	Follow-up
Single tumor	No recurrence	Annual follow-up
	Recurrence	Cystoscopy every 3 mo
Multiple tumors	No recurrence	Cystoscopy every 3 mo
	Recurrence	Intravesical therapy

Modified from Parmar MKB, Freedman CS, Kaegreave TB, et al. Prognostic factors for recurrence and follow-up policies in the treatment of superficial bladder cancer: report from the EMRC subgroup on superficial bladder cancer (Urological Working Group Party). J Urol 1989;142:284–288, with permission.

TABLE 21.5. FOLLOW-UP OF PATIENTS WITH SUPERFICIAL BLADDER CANCER

The follow-up of patients with muscle-invasive disease is less clearly defined. Certainly, patients undergoing bladder-sparing treatment require frequent cystoscopy to document response to treatment, and they will require regular follow-up after completion of treatment. Even patients treated with radical cystectomy warrant follow-up. They remain at risk for local recurrence, metastatic disease, and new tumors occurring anywhere in the remaining urothelium. Unfortunately, the follow-up evaluations are even less clearly defined in these patients.

Patients with metastatic disease are generally monitored with radiographic tests to document their response to therapy. If a complete response is obtained, regular radiographic evaluation of the areas previously involved with disease will likely be undertaken. The value of such follow-up is not proven.

IX. Background

A. Epidemiology

Bladder cancer is relatively common, with approximately 50,000 cases diagnosed in the United States in 1995. The median age at diagnosis is 65 years, and this disease is uncommon before age 40 years. It is more common in men than in women (3:1), in urban than in rural settings, and in African Americans than in whites. Superficial tumors account for 75% of disease at diagnosis, whereas muscle-invasive disease accounts for 20% to 25%. This helps to explain why 50,000 cases were diagnosed in 1995 and 10,000 deaths occurred.

B. Identifiable risk factors

The most well-defined risk factor for bladder cancer in the United States is cigarette smoking. Exposure to polycyclic aromatic hydrocarbons, including 2-naphthylamine and benzene, result in increased risk. Several occupations pose increased risk, including chimney sweeping, dry cleaning, and manufacturing preservatives. Infection with *Schistosoma haematobium,* a parasite found in many third-world countries, increases the risk of bladder cancer, and greatly increases the risk of squamous cell bladder cancer. In the United States, 90% to 95% of bladder cancers are TCCAs. In countries with endemic *S. haematobium,* squamous cell tumors compose a larger portion.

C. Molecular biology

Alterations in a numbers of oncogenes and tumor-suppressor genes have been associated with bladder cancer. Oncogenes associated with bladder cancer include p21 *ras,* c-*myc,* and c-*jun.* The tumor-suppressor genes most commonly associated with bladder caner are p53 (17p) and the retinoblastoma gene (*RB*) (13q). Overexpression of *erb*B-2 also has been associated with higher grade tumors and higher risk of recurrence (*Urol Res* 1993;21:39).

D. Pathogenesis

Bladder cancer is thought to arise because of a field defect of the urothelium, resulting in a genetically unstable urothelium. This helps explain why bladder tumors tend to recur either locally or at anatomically distinct sites. Smokers have been found to have atypia in the urothelium when examined at autopsy. There appears to be a progression of genetic changes from low-grade, noninvasive tumors to higher grade, invasive tumors. Deletions of *17p* (TP53 gene locus), *18q* (DCC gene locus), and *13q* (*RB* gene locus) are associated with invasive tumors.

X. Current focus

Bladder cancer has offered a unique opportunity for cancer researchers. These tumors are relatively accessible for obtaining tissue. In addition, the natural history of this disease, with recurrences and progression from relatively innocuous to more malignant behavior has allowed evaluation of molecular changes as tumors advance through this course.

A number of important molecular associations of bladder cancer have been described. Mutations of the p53 gene have been found to be present in up to 80% of CIS and invasive tumors at diagnosis. The p53 protein is an important transcription factor, regulating genes involved in cell-cycle control. Mutations of the p53 gene lead to aberrant cell-cycle regulation and appear to play a role in malignant transformation. Other prognostic factors include the absence of blood group antigens on the tumor cell surface, DNA ploidy, and expression of epidermal growth factor receptor. As the molecular abnormalities underlying bladder cancer are more clearly elucidated, it is likely that clinical interventions based on these findings will be developed. One area of investigation is gene transfer to correct existing gene abnormalities in the urothelium and prevent progression to invasive cancer. These strategies are in very early development.

Another major area of ongoing interest is the development of bladder-sparing approaches for muscle-invasive disease. As described earlier, a number of these strategies have been piloted. Ongoing studies should help define the optimal approach in this setting and will help more clearly to define which patients are appropriate for this strategy.

Strategies for screening and prevention in high-risk groups also are under evaluation. As molecular abnormalities are identified and their significance determined, they may be incorporated into screening strategies. Specifically, precancerous abnormalities that can be identified in shed cells of the urothelium

may help with early detection and even prevention of TCCA of the bladder.

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CHAPTER 21C. PROSTATE CANCER

Bill Blum and Joel Picus

Presentation
Subjective
Objective
Workup and staging
Laboratory testing
Imaging
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Localized disease (T1 to T3 N0 M0)
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I. Presentation

With the widespread use of prostate-specific antigen (PSA) screening, most prostate cancers (75%) are now discovered before they become advanced. PSA screening has changed the landscape of prostate cancer from advanced to localized disease at the time of diagnosis, and the goal of research is to use this lead-time advantage to achieve better overall survival and quality of life with new treatments.

A. Subjective

Patients commonly have initial symptoms of bladder-outlet obstruction. Those with metastatic disease have a wide variety of symptoms related to the sites of metastases including bone pain, neurologic dysfunction (due to spinal cord compression), and lower-extremity edema (due to lymphatic obstruction). Other presentations of metastatic prostate cancer include focal neurologic signs, shortness of breath or cough from pulmonary nodules, deep venous thrombosis due to a cancer-related hypercoagulable state, and the superior vena cava syndrome.

Because many prostate cancer patients have asymptomatic disease, there has been considerable discussion about the benefit of aggressive therapy. Understanding the natural history of the disease is paramount in recommending treatments that have significant morbidity. Multiple observational studies in cohorts of patients with untreated prostate cancer have shown variable results, but most studies demonstrated that between 30% and 50% of prostate cancer patients eventually die of their cancer. Given these findings, expectant management should be reserved for patients with low-grade histology or elderly patients with less than 10- to 15-year survival.

Because of the potential use of hormonal therapy, prostate cancer remains one of several neoplasms that physicians must rule out in the evaluation of carcinomas of unknown primary (see Chapter 23).

B. Objective

Physical examination findings can contribute to clinical staging of prostate cancer, most notably the digital rectal examination (DRE). During the DRE, one should attempt to palpate both lobes of the prostate and carefully extend the examination to the lateral borders of the prostate overlying the seminal vesicles. It is possible to detect extraprostatic extension of cancer with digital examination, but DRE commonly underestimates the extent of extraprostatic disease and may also miss up to 40% of localized cancers. As with all cancer patients, a careful comprehensive physical examination including palpation of all lymph nodes can aid in staging and direct additional workup. Particular attention should be given to the skeletal examination for point tenderness, especially if the patient complains of bone pain.

II. Workup and staging

Autopsy studies have shown that localized prostate cancer may occur in 30% of men aged 50 years and in 60% of men aged 80 years. The prevalence continues to increase as men age. PSA testing has led to the detection of cancer in a group of patients with clinically silent tumors, and defining anatomic stage and grade are critical in understanding prognosis and in formulation of a treatment plan.

A. Laboratory testing

1. **Prostate-specific antigen.** The use of PSA testing has helped to identify cases of prostate cancer that are or will become clinically significant, rather than simply identifying cases of cancer that are unlikely to be detected until autopsy. PSA is directly associated with tumor volume and clinical stage. Normal PSA ranges depend on factors such as age and race, and PSA level is affected by prostatic biopsy but not significantly by DREs.

   Elevations of PSA can predict the likelihood of organ-confined disease and influence opinions on the likelihood of a cure. PSA levels of greater than 10 µg/L are predictive of extension of prostate cancer outside of the prostatic capsule. Most patients, however, have PSA levels between 4 and 10 µg/L, and staging with PSA alone is therefore suboptimal. Some physicians advocate the use of free PSA versus bound PSA to quantify further the risk of cancer and need for biopsy; higher percentage free PSA levels are associated with more favorable histopathologic features in prostate tumors. A cutoff of 25% free PSA detects 95% of cancer while avoiding 20% of unnecessary biopsies (*Urology* 2000;55:372–376.)

2. **Complete blood count and chemistries.** Laboratory workup should include basic blood counts and comprehensive metabolic panel. Widely metastatic disease may cause anemia or thrombocytopenia because of marrow infiltration, but most patients will have normal peripheral counts and normal chemistries at the time of diagnosis. Abnormal tests should prompt investigation, especially in patients thought to have only localized disease. For example, elevated alkaline phosphatase may be due to bony metastases and, in the absence of known metastatic disease, a bone scan should be done to rule this out.

B. Imaging

CT scans and bone scan are important in the assessment of advanced disease, but they are not often indicated in the standard workup of low-risk prostate cancer because of their low sensitivity and high cost. Physicians should adopt a symptom-directed approach to the use of imaging of low-risk patients (for the definitions of high-risk and low-risk disease, see later). Patients with high-risk disease are more likely to have benefit from routine imaging, and many physicians use CT of the abdomen and bone scan as adjuncts to clinical staging in this group. Imaging in these patients may help to identify those with lymph node involvement, but sensitivity is poor even in this risk group. It has been suggested that endorectal coil MRI can be used to categorize risk further in intermediate-risk tumors by identifying seminal vesicle involvement before surgery, but favorable results found with its use have not yet been reproduced.

C. Surgery

In patients with PSA greater than 10 ng/mL, high Gleason score, and clinical stage T3 disease (intermediate or high-risk disease), pelvic lymphadenectomy should be considered to rule out metastatic disease before definitive therapy. These patients are at higher risk for lymphatic involvement, and positive findings will affect future therapy decisions, as lymph node involvement is truly metastatic disease. Most urologists perform this procedure laparoscopically

today.

D. **Staging**

One must carefully combine TNM staging, histologic grade, and PSA level to prognosticate and treat accurately. With the TNM staging system, the physician assigns a clinical T score by physical examination. Prognostic information is most accurately obtained by combining clinical T score, PSA, and histologic grade.

1. **TNM** tumor staging is more commonly used than the older Whitmore–Jewitt system (Table 21.6).

TNM	Whitmore–Jewitt	Description
TX	None	Primary tumor cannot be assessed
T0	None	No evidence of primary tumor
T1		Clinically inapparent tumor (not palpable/visible on imaging)
T1a	A1	Tumor incidental finding in ≤ 5% tissue resected
T1b	A2	Tumor incidental finding in > 5% tissue resected
T1c	B0	Nonpalpable tumor identified because of elevated PSA and biopsy
T2		Palpable tumor confined to the prostate
T2a	B1	Tumor involves one lobe
T2b	B2	Tumor involves both lobes
T3		Tumor extends through the prostatic capsule
T3a	C1	Tumor extends through the capsule, not into seminal vesicles
T3b	C2	Tumor invades seminal vesicles
T4	D1	Tumor is fixed or invades structures other than seminal vesicles
	D2	Lymph nodes above the aortic bifurcation or bonerelt tissue
	D3	Hormone refractory metastatic disease

PSA, prostate-specific antigen.

TABLE 21.6. STAGING OF PROSTATE CANCER

2. **Histologic grade** is determined with the Gleason scoring system. **Gleason score** is the grading of tumor patterns on a score of 1 to 5 (with a score of 1 for well-differentiated patterns and 5 for poorly differentiated patterns.) Gleason score is the sum of the scores for the primary and secondary patterns seen on the biopsy specimens. It is often reported as “Gleason 4+3” but also may be reported as “Gleason 7” (Table 21.7). Most men have intermediate-range Gleason scores, and it is important to recognize that Gleason scores from transrectal ultrasound (TRUS)-guided biopsies may underscore a tumor. Pathologic review from subsequent prostatectomy may increase Gleason scores; for example, a “Gleason 6” may be upgraded to a “Gleason 7.”

Gleason Sum	Tumor Pattern
2 to 4	Well differentiated
5 to 6	Intermediate
7	Intermediate, usually more aggressive
8 to 10	Poorly differentiated, aggressive

TABLE 21.7. GLEASON SEORES

3. It is the **combination of clinical stage, Gleason score, and PSA level** that allows physicians to prognosticate most accurately. Patients at highest risk for progression/relapse have PSA greater than 20, Gleason score greater than 7, and extraprostatic disease. Intermediate-risk disease is T2b, PSA 10 to 20, Gleason 7; and high-risk disease is T2c, PSA more than 20, and Gleason 8. It has been shown that histologic grade is a good predictor of the outcome. Patients with well-differentiated, moderately differentiated, and poorly differentiated tumors had 15-year death rates for untreated disease of 9%, 28%, and 51%, respectively (*JAMA* 1995; 274:626.)

III. **Treatment**

A. **Localized disease (T1 to T3 N0 M0)**

The discussion of treatment options for localized disease should include risks and benefits of surgery or radiation (either external beam or brachytherapy). The 5-year disease-free survival for both radical prostatectomy and radiation therapy is approximately 60% to 70%.

1. **Radical prostatectomy.** For most men, the treatment of choice for early-stage prostate cancer remains surgical resection. Anatomic radical prostatectomy, also known as radical retropubic prostatectomy, is the most common technique for resection currently and allows for the possibility of nerve-sparing techniques that increase the likelihood of preserving potency as well as total continence. The procedure is performed through a midline lower-abdominal incision and may involve pelvic (hypogastric and obturator) lymph node dissection. External iliac nodes are not generally removed to reduce the risk of future lower-extremity edema. Nerve-sparing techniques allow preservation of neurovascular bundles if uninvolved by tumor. Indications for removal of the neurovascular bundle and surrounding tissues are induration along the posterolateral margin of the prostate, palpable induration of the lateral pelvic fascia, and fixation of the neurovascular bundle to the prostate. **Pelvic lymphadenectomy** does not provide additional curative benefit, but may provide prognostic information. It can be especially useful in patients with high-risk or locally advanced disease in which future hormonal therapy will be an important consideration, and, likewise, it may not be indicated in low-risk patients. Most urologist perform pelvic lymphadenectomy by using laparoscopic techniques. The finding of malignant involvement of pelvic nodes should lead to medical rather than surgical therapy. Radical prostatectomy is likely curative for organ-confined prostate cancer, somewhat less likely to be so in more locally advanced tumors with capsular penetration or high Gleason score, and never curative in lymph node–positive/metastatic disease. Conventional surgery is still the standard of care for prostatectomy, but early studies of laparoscopic prostatectomy showed promise and technical feasibility with results comparable to those of conventional surgery.
2. **Radiation therapy.** Radiation therapy for the prostate is a continually evolving field as new and better technologies make it possible to deliver higher doses of targeted local radiation, sparing normal tissues, with fewer local toxicities. **External-beam radiation** is given in 1.8- to 2.0-Gy fractions over 5 weeks to a total dose of up to 50 Gy, with an additional 20 Gy boost given to a smaller field for a total of 70 Gy to the prostate. Outcomes for T1/T2 disease are similar to those seen with surgery, with 87% of patients free of local recurrence at 10 years. Pelvic lymph node analysis before definitive radiotherapy may be useful in patients at high risk for advanced disease.

   An alternative to external-beam therapy is **interstitial radiotherapy** with seed implants (brachytherapy). Under either ultrasound or CT guidance, multiple radioactive seeds (iodine or palladium) are inserted into the prostate, with care taken to radiate the entire gland. Bladder toxicity is the most common problem with this modality of treatment; GI toxicity also is seen. The ability of brachytherapy to deliver uniformly adequate doses to prostate cancers, especially in locally advanced disease, has been questioned in past years, but as techniques improve, it is difficult to compare current use with past results. Attempts to intensify intracapsular dose along with treatment of microscopic extracapsular disease have led to the combined use brachytherapy and external-beam therapy with promising results

   A major advance in radiotherapy is the use of **3D/conformal radiotherapy.** This allows treatment with an increased local dose of radiotherapy with promising early results, but complicated computer modeling limits its use to larger centers. Advanced computer modeling has led to the development of **intensely modulated radiation therapy (IMRT),** which currently is available only in highly specialized centers. This technique uses complicated tools that precisely control both the dose of radiation and the tissue targeted.

B. **Locally advanced disease (T2 to T3 N0)**

1. Surgery or radiation remains first-line therapy for locally advanced disease. Neoadjuvant therapy with hormonal blockade has been shown to decrease the rate of positive margins at surgery in these patients, but it did not affect overall survival. When extraprostatic cancer within the pelvis is detected, there is benefit to the use of hormonal blockade after surgery or radiation. However, physicians must weigh the toxicities of hormonal therapy versus the

possible benefits. There is substantial debate regarding the efficacy of **immediate hormonal blockade** versus **delayed hormonal blockade** (waiting until there is evidence of disease progression) in the management of locally advanced prostate cancer after radical prostatectomy. A number of studies with conflicting results have been performed. A small percentage of these studies have demonstrated survival benefit to the immediate-treatment group, but the majority of studies have found no survival difference. In a randomized prospective study, patients with node-positive (microscopic) disease discovered at the time of radical prostatectomy were assigned to immediate surgical or hormonal castration or to observation and castration only when metastatic disease was found (*N Engl J Med* 1999;341:1781–1788.) The group of patients who had immediate castration had a significant survival benefit. It should be noted that this study had a small sample size. In addition, patients were considered to have progressive disease only when they had measurable disease by imaging. Patients with increasing PSA were not treated until they had measurable disease, and perhaps because of this additional delay, the study found a survival difference between groups.

The MRC (Medical Research Council) study (*Br J Urol* 1997;79:235–246) also compared immediate versus delayed therapy in locally advanced disease after surgery, and although survival differences were not impressive, early treatment had **quality-of-life benefits** with decreased incidence of cord compression, ureteral obstruction, and pathologic fractures versus delayed treatment.

2. The combination of **hormone therapy with radiation** alone in locally advanced disease also has been evaluated. The benefit of adding hormone therapy in this setting continues to be a matter of debate and the subject of several ongoing clinical studies. The combination of XRT and hormonal therapy in locally advanced disease has been shown to result in superior survival when compared with XRT alone in this setting (*N Engl J Med* 1997;337:295–300). It is unclear whether these data can be extrapolated to use of higher-dose conformational radiation therapy now commonly given. A similar study, in contrast, did not show survival benefit to combined hormonal and radiotherapy. However, there was improved duration of disease-free survival and decreased local failure with combined therapy (*J Clin Oncol* 1997;15:1013–1021). The combination of hormonal therapy with brachytherapy in locally advanced disease has not yet shown convincing evidence of survival benefit.
3. **Increasing prostate-specific antigen after prostatectomy or radiation.** Asymptomatic progressive increase in PSA is a common problem in patients with prostate cancer after radiation therapy or surgery. Prognostic factors to consider in this setting are doubling time of PSA, time from definitive therapy to increase in PSA, age of the patient, and comorbidities. Many methods have been used to predict failure, and most physicians consider higher risk patients to be those with seminal vesicle involvement, aggressive histology (Gleason greater than 6), and PSA greater than 10.

   Local control after initial failure can be attempted. XRT may provide additional local control after radical prostatectomy, but it has not shown survival benefit and may be associated with higher rates of radiation-related complications. Salvage prostatectomy after XRT is rarely an option because of higher surgical complication rates. Other surgical options in this setting include cryotherapy and brachytherapy, but current studies show only negative results.

   Most men who have increasing PSA levels after initial management are given medical therapy (see next section for dosing). Ongoing trials will attempt to determine whether combined hormonal and radiotherapy is beneficial in patients with increasing PSA after definitive surgery.

C. **Metastatic disease**

1. **Initial therapy (hormone-sensitive disease).**

   Castration, either surgical or medical, remains the first-line therapy for metastatic disease, as it can often reduce PSA levels to undetectable levels. Metastatic prostate cancers may remain sensitive to the effects of hormonal blockade an average of 12 to 18 months, and some patients have disease control for more than 5 years.

   The most cost-effective approach to hormonal blockade is **bilateral orchiectomy,** but most men prefer medical blockade, given the psychological impact of the surgery.

   Luteinizing hormone–releasing hormone (LHRH) agonists are the most commonly used first-line therapies. Lupron (7.5 mg s.c. monthly) or goserelin acetate (3.6 mg s.c. monthly or 10.8 mg s.c. q3 months) effectively produce chemical castration. On the initiation of therapy, physicians must recognize the “flare” phenomenon in which a transient increase in testosterone may lead to increased bone pain or progressive disease, even cord compression, and for this reason, often antiandrogens are used in combination with LHRH agonists initially. The most common side effects of castration include hot flashes and impotence. Physicians should recognize the adverse psychological impact of impotence and discuss the use of supportive medications like sildenafil with patients. Decreased libido in these patients remains a difficult problem.

   Failure of castration to control disease, usually marked by increasing PSA, may be managed with the addition of second-line agents, most notably **antiandrogens.** Bicalutimide, 50 mg daily; nilutimide, 150 mg daily; flutamide, 250 mg 3 times a day; are all antiandrogens that block the binding of dihydrotestosterone to its receptor and may provide additional control in disease that is still sensitive to androgen withdrawal. The addition of antiandrogens to medical/surgical castration is termed complete androgen blockade (CAB) or total androgen blockade (TAB). Unfortunately, after failure of first-line hormonal therapy, metastatic disease is usually controlled only for 2 to 3 months after the addition of antiandrogens.

   One recent study demonstrated that in patients who have progressive disease, there may be no survival or quality-of-life difference between the use of flutamide, 250 mg p.o. t.i.d., versus prednisone, 5 mg p.o. q.i.d., when added to medical/surgical castration (*J Clin Oncol* 2001;19:62–71.)

   Diethylstilbestrol at doses less than 3 mg/day also has been used in this setting. Potential side effects of estrogen-containing medications include gynecomastia, loss of libido, and increased risk of thrombotic events.

   Ketoconazole at doses up to 1,200 mg/day in three divided doses in concert with hydrocortisone also may provide temporary disease control after failure of first-line therapy. Ketoconazole may reduce tumor size for patients that would benefit from rapid response, most notably patients initially seen with **cord compression.** In patients treated for hormone-refractory disease, LFTs must be monitored regularly at high doses of ketoconazole. Steroids are required to prevent addisonian crisis (hydrocortisone, 20 mg in a.m., 10 mg in p.m.).

   Withdrawal of antiandrogens after progression of disease on complete androgen blockade can result in temporarily better disease control (*J Urol* 1993;149:607–609). There does not yet appear to be any survival benefit to antiandrogen discontinuation. Similarly, some physicians advocate the intermittent use of antiandrogens.

   Intermittent therapy with gonadotropin releasing hormone (GNRH) agonists may provide disease control very similar to continuous use of GNRH agonists, while allowing periods of time without the side effects of hormonal blockade, especially sexual dysfunction. Intermittent therapy may even increase disease-free progression.

2. **Secondary therapy (hormone-refractory disease)**

   Chemotherapy has in the past been thought to be ineffective in hormone-refractory prostate cancer, but the recent development of new drugs and new combinations of drugs has given hope for effective palliation and survival benefit (Table 21.8).

TABLE 21.8. CHEMOTHERAPY

a. When possible, patients with metastatic hormone-refractory prostate cancer should be offered an opportunity to participate in clinical trials. If appropriate clinical trials are not available, the choice of therapy depends on the performance status. Patients with poor performance status may be offered oral **cyclophosphamide**-based regimens.

   Unlike some other cancers, there is not a widely held standard first line chemotherapy for patients with hormone-refractory prostate cancer who have a good performance status, but it has been suggested that the combination of mitoxantrone and hydrocortisone should be used as the standard for comparison in clinical trials.

b. **Mitoxantrone,** 14 mg/m^2 every 3 weeks, along with **hydrocortisone given orally,** 30 mg in the morning and 10 mg in the evening, has been shown to have activity in hormone-refractory disease (*J Clin Oncol* 1999;17:2506–2513). No survival benefit was detected in the study, but 38% of patients responded with at least a 50% decrease in PSA compared with only 22% in patients treated with hydrocortisone alone. Mitoxantrone-based chemotherapy also has been shown to be effective in reduction in pain and improvement of quality of life. Another study reported that the addition of mitoxantrone to prednisone provided palliative benefit (*J Clin Oncol* 1996;14:1756–1764.)
c. **Estramustine,** a combination of estradiol and nornitrogen mustard, also has activity in prostate cancer and has been used in combination with a number of other agents. Estramustine affects the function of microtubules and has been used with other agents with similar mechanisms of action including vinblastine and etoposide. Toxicities of estramustine include nausea/vomiting along with venous and arterial thrombosis due to the estrogenic effects. Because of the high risk of thrombosis, many physicians routinely provide anticoagulation for patients with warfarin, 2 mg a day, while taking estramustine, although there is not a consensus on the degree of anticoagulation required.
d. **Estramustine, 600 mg/m^2/week plus vinblastine, 4 mg/m^2** may be given for 6 consecutive weeks in every 8 weeks. This regimen has been reported to have a response rate of 30% (*J Clin Oncol* 1999;17: 3160–3166).
e. **Alternatively, estramustine, 15 mg/kg/day, plus etoposide, 50 mg/m^2/day** with both drugs given orally for 21 days has similar response rates, although toxicity is substantial. Chemotherapy cycles are repeated every 28 days.
f. **Estramustine has also been combined with docetaxel,** another drug active against the microtubular function. Docetaxel *in vitro* inactivates the antiapoptotic protein Bcl-2 by phosphorylation and has recently been shown to have activity in hormone-refractory prostate cancer. Bcl-2 upregulation may have a role in the development of androgen independence, and it is hoped that greater understanding of the mechanisms of resistant disease will yield increasingly active combinations of drugs. High doses of **estramustine, 280 mg p.o. t.i.d., on days 1 through 5 plus docetaxel, 40 to 80 mg/m^2** had a 59% response rate (*J Clin Oncol* 1999;17:958). Dexamethasone, 20 mg, is administered 12 hours before docetaxel, 6 hours before docetaxel, and 15 minutes before docetaxel in this regimen. Current studies are investigating whether estramustine dose can be reduced to 140 mg p.o. t.i.d.
g. **In addition, docetaxel** alone at 75 mg/m^2 every 21 days has significant antitumor activity, with response rate of 46% (*Semin Oncol* 1999; 26:19–23).
h. **The combination of paclitaxel (Taxol), estramustine, and carboplatin** has activity in hormone-resistant disease. This TEC regimen was associated with an overall time to progression of 21 weeks, with a median survival of 19.9 weeks. It is administered as paclitaxel, 60 to 100 mg, i.v., over 1 hour weekly; oral estramustine, 10 mg/kg daily in three divided doses 5 days a week; and carboplatin [area under the time–concentration curve (AUC), 6 mg/mL/minute] every 4 weeks. Toxicities include myelosuppression (mild), thromboembolic disease in 25% of patients, hyperglycemia, and hyperphosphatemia (*J Clin Oncol* 2001;19:44–53)

   A phase III SWOG 9916 trial under way now compares mitoxantrone (12 to 14 mg/m^2 on day 1) plus prednisone (5 mg p.o. b.i.d., days 1 to 21) versus estramustine (280 mg p.o. t.i.d., days 1 through 5) plus docetaxel (60 mg/m^2, day 2) plus dexamethasone (20 mg t.i.d., days 1 and 2).

   The role of continued hormone suppression is not firmly established in hormone-refractory disease, but most physicians prefer to continue hormonal blockade.

   Any discussion of treatment for prostate cancer should include the use of alternative medications, as they are commonly used by patients. Many herbal and alternative medicines have been used, but the most well-known preparation for prostate cancer is known as PC-SPES. It is marketed in health food stores as a nonhormonal therapy and appears to have some limited benefit in both hormone-sensitive and hormone-refractory disease. However, the effect may be hormonal, as PC-SPES has estrogenic effects of gynecomastia, loss of libido, and most important, increased risk of thrombosis. A comprehensive review of alternative medicines for prostate cancer has recently been published (*Oncol Issues* 2000;15:23–27).

IV. **Complications**

A. **Complications of therapy**

1. **Complications of surgery.** The complications of radical prostatectomy are predominantly incontinence and impotence, but nerve sparing and the retropubic approach have decreased the complication rates. In the best series, an estimated 8% of men will have stress incontinence after surgery, with only 1% to 2% requiring more than one pad daily. Larger studies, unfortunately, have shown higher complication rates. Impotence is still a major problem, and the rate of total impotence increases with advanced disease and advanced age. An estimated 50% of men who are fully potent before surgery will retain potency after the procedure, but the erections may not be of the same quality. In men younger than 50 years, some degree of potency is preserved in an estimated 91%, even if one neurovascular bundle is excised. However, in men older than 70 years, potency rates decrease to approximately 25% with excision of the neurovascular bundles (*J Urol* 1999;162:433–438). It is important to make men aware of available therapies designed to restore potency, both pharmacologic and nonpharmacologic. Sensation to the penis is preserved after radical prostatectomy (via the pudendal nerve), even while the autonomic innervation of the corpus callosum is damaged. Medications such as sildenafil may have significant effect in returning these patients to satisfactory sexual activity.
2. **Complications of radiotherapy.** Toxicities of radiation therapy most commonly involve the rectum and the bladder. An estimated 60% of patients will have moderate rectal symptoms including pain, tenesmus, or diarrhea. Others will have symptoms of cystitis, hematuria, impotence, incontinence, or difficulty with urination around the period of radiotherapy. Most of these symptoms resolve on completion of the therapy. Fewer than 1% of conventional radiotherapy patients require hospitalization for local toxicities including rectal pain, rectal/urinary bleeding, or other urinary complaints.
3. **Complications of medical therapy.** Management of chemotherapy-related problems in prostate cancer requires an understanding of the hormonal treatment. Hormonal blockade leads to impotence and decreased libido. Prolonged periods of low-testosterone states may lead to bone loss and other complications. In starting hormonal therapy, most physicians advocate the use of any of the antiandrogens to block the “flare” of tumor growth that can be seen initially with the GNRH agonists. Often this additional therapy can be stopped after 1 month.

   Chemotherapy complications that are somewhat unique to prostate cancer include the thrombotic risk of estramustine and other estrogen derivatives, and many physicians provide at least low-dose anticoagulation for these patients as prophylaxis.

4. **Complications of progressive disease.** As with many of the other cancers, cord compression is probably the most difficult of the tumor-related complications. A discussion of cord compression can be found in the chapter on oncologic emergencies (Chapter 27); high doses of ketaconazole may provide anti-tumor effects in this setting. Bone pain is the most common symptom of patients with progressive disease. Palliative radiation is useful, and some patients benefit from steroid therapy for pain relief.

V. **Follow-up**

After initially definitive management, follow-up should include PSA and DRE every 3 months for the first year, every 6 months for the second year, and yearly thereafter. PSA should decrease to zero after radical prostatectomy. With this approach, it has been suggested that a cut-off for PSA of 0.2 ng/mL should be used to define disease progression (*JAMA* 1999;281:1591–1597.)

There is no consensus on the use of standard radiographic imaging to monitor prostate cancer. Most physicians agree that the best approach is symptom guided. Once metastatic disease is found and especially after hormone-refractory disease is present, the common complications of cord compression and bone pain may require radiotherapy or surgical intervention. There is no benefit to routine bone imaging, either with plain radiographs or nuclear imaging, in the management of metastatic disease. All radiographic studies should be taken with a specific treatment in mind should there be evidence of disease.

Because of the difficulty in monitoring bony metastatic disease for response to therapy, before the administration of chemotherapy, most physicians advocate the use of CT scans. CT scans can detect soft tissue disease that can be monitored and measured for disease response, helping to make decisions regarding future use of chemotherapy. CT scans are not, however, useful in the routine follow-up of prostate cancer outside of the chemotherapy arena. A symptom-directed approach should be taken.

VI. Background

Prostate cancer remains the second leading cause of cancer death in American men. The average lifetime risk of developing invasive prostate cancer is one in six. Established risk factors are older age, African-American race, and family history of prostate cancer. The role of diet and smoking has not yet been firmly established. Vasectomy does not appear to increase risk.

VII. Current focus

Multiple genetic alterations have been associated with prostate cancer including p53. There has not yet been any single identifiable event common to all prostate cancers thought to be responsible for the final step in tumorigenesis, but ongoing research aims to identify genes and gene products that might allow earlier detection of malignancy.

At the molecular level, there does appear to be some relation between altered **bcl-2** function and the development of hormone-refractory disease, and bcl-2 is overexpressed in hormone-refractory prostate cancers. Bcl-2 has become a target for the development of new therapies including chemotherapy and antisense genetic therapy (*Urology* 1999;54:36–46.)

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CHAPTER 21D. PENILE CANCER

Steven Brandes, Joel Picus, and Marcia L. Chantler

Presentation
Signs and symptoms
Workup and staging
Imaging
Laboratory testing
Staging
Therapy and prognosis
Prognosis
Therapy
Complications
After surgery
After chemotherapy
After radiotherapy
Of the disease
Follow-up
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Epidemiology
Risk factors
Pathophysiology
Natural history
Current focus
Suggested Readings

I. Presentation

Patients typically ignore penile lesions until they reach considerable size. Patients typically delay seeking medical attention (15% to 50% of patients delay presentation longer than 1 year). On presentation, 30% to 60% of patients have enlarged/palpable inguinal nodes.

A. Signs and symptoms

1. Signs

Penile cancer [squamous cell carcinoma (SCC) of the penile skin] typically originates on the glans (48%), followed by the prepuce (21%), both prepuce and glands (9%), coronal sulcus (6%), and penile shaft (2%).

Tumor presentation is widely variable. SCC can be papillary and exophytic, flat and ulcerative, or extensively destructive. Patients typically have a long history of phimosis (more than 50%), in which tumors of the glans or prepuce can be concealed and allow tumor progression. Lesions also can be subtle, like patchy erythema or cutaneous induration. Such subtle lesions are typically CIS, and typically are subdivided into erythroplasia of Querat, a velvety, red lesion with ulcerations, localized to the glans penis or prepuce, and Bowen disease, a red plaque with encrustations that involves the remaining genitalia or perineum.

Each penile tumor should be assessed for size, location, mobility, and/or corporal body involvement. Examine the penile base and scrotum for tumor extension. Rectal and bimanual examination can help determine the presence of a pelvic mass, as well as prostatic, urethral, or perineal body tumor involvement.

Careful examination of both groins for any palpable inguinal adenopathy is essential. Nodal size, location, fixation, and involvement should be noted. Reexamine after 4 to 6 weeks of antibiotic therapy to rule out infection enlargement.

2. Symptoms

Lesions are typically painless and often secondarily infected. Lesions also can occur as itching or burning of the glans, under the prepuce, which can progress to ulceration. Chronic penile infection can result in fatigue, weight loss, and general malaise.

II. Workup and staging

A. Initial diagnosis is by local excision or biopsy of all suggestive penile lesions for pathologic evaluation. Histologic diagnosis usually does not require special stains.

The status of palpable inguinal adenopathy versus no adenopathy is assessed by careful physical examination. Both groins can be involved. From 50% to 70% of initially palpable inguinal node are inflammatory in nature. After 4 to 6 weeks of antibiotic therapy, the groins should be reexamined for persistence of adenopathy.

B. Imaging

Radiographic staging includes a chest radiograph and CT of the abdomen and pelvis. The CT assesses for the status of the pelvic, common iliac, periaortic, abdominal lymph nodes, and any other potential metastases. CT-guided biopsy of significant inguinal or pelvic adenopathy can help guide the planning of lymphadenectomy surgery or chemotherapy. MRI can be helpful in delineating penile shaft (corpora) and adjacent tissue involvement and extent.

C. Laboratory testing

Laboratory testing includes a CBC and electrolytes, including LFTs. Hypercalcemia can occasionally occur, even without evidence of bony metastases.

D. Staging

The most commonly used staging system, until recently, has been the Jackson staging for penile cancer (Table 21.9). The TNM staging system, as updated in 1987, has become the standard staging system (Table 21.10).

Stage 1 (A)	Tumor confined to the glans and/or prepuce
Stage 2 (B)	Tumor extending into the penile shaft/corpora
Stage 3 (C)	Tumors with inguinal metastases amenable to surgery
Stage 4 (D)	Tumors involving adjacent structures or inoperable inguinal metastases (fixed nodes on examination), pelvic node metastases, or distant metastases

TABLE 21.9. JACKSON STAGING OF PENILE CANCER

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of tumor
T_{is}	Carcinoma *in situ*
Ta	Noninvasive verrucous carcinoma
T1	Tumor invasion into subepithelial connective tissue
T2	Tumor invasion into corpus spongiosum and/or cavernosum
Regional Lymph Nodes (N)	
Nx	Nodes cannot be assessed
N0	No metastases
N1	Metastasis in single superficial inguinal node
N2	Metastases in multiple and/or bilateral superficial nodes
N3	Metastases in deep inguinal or pelvic nodes
Distant Metastases (M)	
Mx	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

TABLE 21.10. TNM STAGING OF PENILE CANCER

Histologically, penile SCCs demonstrate keratinization, epithelial pearl formation, and varying degrees of mitoses. Most are low grade.

III. **Therapy and prognosis**

A. **Prognosis**

Overall, 5-year cancer-specific survival is roughly 55%. Survival is directly related to tumor stage and grade. Overall, the strongest indicator for survival from penile cancer depends largely on the presence or absence of inguinal node metastases and/or pelvic node metastases. Prognosis is poor when the diagnoses is late, with deep infiltrating tumors, ilioinguinal node metastases, or pelvic node metastases.

Penile cancer is one of the few malignancies in which regional lymphadenectomy can be curative. The indications and timing for ilioinguinal and/or pelvic lymphadenectomy are controversial. Patients without palpable inguinal adenopathy have a 65% to 80% 5-year survival rate. The 5-year survival rates, however, are 20% to 50% when the palpable inguinal nodes are positive for malignancy. When inguinal node dissection is pathologically negative, survival rates approach 90%.

B. **Therapy**

1. **Carcinoma *in situ*.** Treatment begins with excisional biopsy to confirm diagnosis and depth of invasion. Local excision is used when not overly deforming or involving the meatus or urethra. Circumcision is performed for preputial lesions. Other treatments are topical 5-fluorouracil, neodymium/yttrium aluminum garnet (Nd:Yag), or CO_2 laser fulguration, or Mohs micrographic surgery.
2. **Invasive squamous cell carcinoma**
   a. **Surgical therapy**
      1. **Primary lesion.** Initial treatment consists of excision of the primary tumor. Depending on the size and location of the tumor, treatment may be circumcision, partial penectomy, or total penectomy. Local wedge resection has more than 50% local recurrence rate. In general, a 2-cm surgical margin proximal to the tumor is essential. Selected tumors confined to the prepuce can typically be treated with circumcision. Traditionally, tumors involving the glans or penile shaft require either a partial or total penectomy. In patients in whom a partial penectomy will not leave sufficient penile length to void while standing, or cannot provide a 2-cm surgical margin, then total penectomy and perineal urethrostomy is preferred.
      2. **Inguinal and pelvic lymph nodes.** Indications for inguinal and pelvic lymphadenectomy are outlined and detailed in Fig. 21.2. Of patients with clinically negative nodes at diagnosis, 20% harbor occult metastases. Because the primary tumor is commonly infected at the time of diagnosis, inguinal lymph node enlargement and lymphangiitis is common. Before inguinal lymphadenectomy, all penile cancer patients should be treated with 4 to 6 weeks of antibiotic therapy (i.e., cephalexin, for good Gram-positive coverage). After the course of antibiotics, the groins should be carefully examined for adenopathy. Low-grade tumors in which enlarged nodes normalize after antibiotic therapy are candidates for expectant management. From 30% to 50% of persistently palpable nodes will harbor metastases. When metastases are present in one groin, 50% to 60% will also have contralateral groin metastases, due to lymphatic crossover. In such cases, then, contralateral inguinal lymphadenectomy is warranted. When inguinal nodes are positive for malignancy, the iliac nodes are involved in 30% to 40% of cases.

FIG. 21.2. Management of inguinal nodes for squamous carcinoma of the penis. (Reproduced from Lynch DF Jr, Schellhammer PF. Tumors of the penis. In: Walsh PC, Retik AB, Vaughn ED, et al., eds. *Campbell's urology.* 7th ed. Philadelphia: WB Saunders, 1998:2474, with permission.)

Tumor grade correlates to survival. In a recent U.S. study, 5-year cancer-specific survival for low-grade penile cancers was 84%, and for high-grade tumors, 42%. Inguinal nodal metastases were present in one (4%) of 52 low-grade and in 43 (82%) of 52 high-grade tumors. Similar findings have been reported in recent series from Brazil and Holland.

a. **Noninvasive cancers (T_{is}, Ta, T1 N0 M0).** Grade I (low-grade), noninvasive tumors (T_{is}, T0, Ta, or T1) with palpably negative inguinal lymph nodes can be safely managed expectantly, as long as frequent and periodic groin examinations can be performed. Unreliable patients or those who cannot be monitored periodically are recommended for inguinal lymphadenectomy.
b. **Invasive cancers (T2).** Patients with moderate or poorly differentiated tumors (grade 2 or 3) or with invasion into the corpus spongiosum or corpora (stage greater than T2) are at high risk for recurrence. When the groins have no adenopathy or normalize after antibiotic therapy, such patients have up to 68% occult metastases, and thus should undergo a prophylactic modified bilateral superficial inguinal groin dissection with frozen-section analysis, as detailed by Catalona et al. A prophylactic groin dissection is performed because of potential survival benefit and the lack of effective alternative treatments. Bilateral superficial node dissections are performed because of the lymphatic crossover. If the nodes are histologically negative, no further dissection is performed, and the patient is monitored expectantly. When the nodes are positive for malignancy, the limits for the groin dissection are extended into a classic inguinal lymphadenectomy and pelvic lymphadenectomy. Deep inguinal and pelvic dissections are performed only on the side with involved superficial inguinal nodes. In patients with clinically negative inguinal nodes, there has been some debate as to the timing of surgery (delayed or immediate). For patients with T2 to 4 and no palpable nodes, there is growing support in the literature for immediate lymphadenectomy. For immediate surgery, most reports show that 5-year survival rates approach 57% to 88%. Delaying surgery until the nodes are palpable reduces 5-year survival to 8% to 38%. A lack of effective adjuvant therapies further supports immediate groin dissection. Metachronous presentation of unilateral groin adenopathy after primary tumor resection demands lymphadenectomy of the involved groin only.
c. **Adenopathy (N1 to 3, M0).** Patients with primary tumors of any stage and persistently palpable lymph nodes after a course of antibiotic therapy also

should undergo classic ilioinguinal lymphadenectomy, if potentially resectable. For unilateral palpable adenopathy, a contralateral superficial node dissection is first performed; 50% will be negative. Because lymphatic drainage is sequential, when the superficial nodes are negative and a pelvic CT scan negative, ipsilateral deep and pelvic node dissections are not necessary.

Patients with common iliac or paraaortic metastases have poor (5%) 5-year cancer-specific survival rates. Therefore, before any inguinal surgery, fine-needle biopsy or aspiration of suggestive nodes should be performed. Confirming pelvic or distant metastasis avoids unnecessary and potentially morbid lymphadenectomy surgery.

d. **Inoperable adenopathy.** Jackson stage IV disease (i.e., fixed inguinal nodes) is typically thought to be incurable and not to warrant lymphadenectomy surgery. In young patients with such penile cancer, however, heroic surgery and multimodal therapies have been advocated. Some stage IV disease also requires palliation. Lymphadenectomy is typically needed here to prevent or alleviate groin pain, infection, bleeding (by tumor invasion into the femoral vessels), or skin erosion.

f. **Surgical techniques for regional metastases**

1. **Sentinel lymph node biopsy**

   Based on the work of Cabanas, there is a postulated node or group of nodes in which inguinal metastases from penile cancer typically first occur. A negative sentinel-node biopsy was thought to indicate that formal node dissection was not necessary. However, there are numerous reports of regional metastases (10% to 50% of patients) after a negative sentinel-node biopsy. Therefore, sentinel-node biopsy is unreliable and should not be used.

2. **Lymphadenectomy**

   A clear knowledge and understanding of the lymphatic-drainage pattern of the penis is essential to determining penile cancer management. The prepuce and shaft skin drain into the superficial inguinal nodes (superficial to the fascia lata). The glans and corporal bodies drain into both the superficial and the deep inguinal nodes (deep to the fascia lata). Penile lymphatics cross-communicate, and thus drainage is bilateral to both groins. Drainage is first to the superficial inguinal nodes, which are anterior and medial to the saphenofemoral junction between Scarpa fascia and the fascia lata. The next group of drainage is the deep inguinal nodes, medial and lateral to the femoral vein and deep to the fascia lata. Subsequent drainage from the inguinal nodes is into the pelvic nodes.

   For cartoons of the differing incisions and the margins for resection for the classic inguinal and ilioinguinal lymphadenectomy, see Daeseler et al. (1948). For details of the modified superficial inguinal lymphadenectomy, see Catalona WJ (1988). In brief, in the modified version, the skin incisions are shorter, the saphenous vein preserved, transposition of sartorius muscle eliminated, and there is less node dissection laterally and inferiorly.

g. **Alternative therapies**

1. **Mohs micrographic surgery.** Surgical technique of serial resections that maximizes tissue preservation and function, best suited for small and distal tumors. Local control is excellent for tumors smaller than 1 cm and poor (50%) for tumors larger than 3 cm.
2. **Laser therapy.** KTP, Nd:YAG, argon, and CO_2 lasers have been used to treat penile cancers. CO_2 is ideal for treating CIS and superficial disease, but offers poor cancer control and high recurrence when treating T1 or T2 disease.

h. **Chemotherapy**

The role of chemotherapy in penile cancer is difficult to evaluate, as most published studies have had small numbers of patients, and patient-selection factors and extents of disease treated have varied. SCC of the penis is relatively responsive to chemotherapy; however, effective treatment combinations are yet to be defined. Single-agent therapy lacks sufficient benefit, and the results of combination regimens are often limited by small sample size and unfavorable toxicity profiles. Currently the role of chemotherapy in penile cancer remains investigational, and there are three basic clinical settings in which this treatment modality may be beneficial: in the presence of metastatic disease, in the neoadjuvant setting to render unresectable disease resectable, and in the setting of pathologically proven lymph node metastases.

Limited experiences suggest that adjuvant chemotherapy can improve long-term survival of patients with radically resected positive nodes. It also is suggested that primary chemotherapy can allow 50% of cases with fixed inguinal lymph nodes to be resectable. A combination of vincristine, bleomycin, and methotrexate has been effective as both neoadjuvant and adjuvant chemotherapy. Regimens containing cisplatin and 5-fluorouracil or cisplatin, methotrexate, and bleomycin also have been effective, with reported response rates as high as 32%.

i. **Radiotherapy.** SCC is characteristically radioresistant. For small primary lesions that are superficial, exophytic, and on the glans, in patients refusing surgical resection of the primary tumor, XRT may be effective. Prophylactic groin irradiation in patients with clinically negative inguinal nodes has not proved effective in reducing subsequent regional metastases. Irradiation makes physical examination of the groins difficult and makes any future lymphadenectomy surgically challenging and problematic for poor wound healing. After XRT, penile fibrosis is difficult to distinguish from recurrent tumor. Radiation, however, may have a palliative role for patients with unresectable tumor or in those with poor performance status precluding surgery.

IV. Complications

A. After surgery

Complications for partial and total penectomy are both psychological and physical. Such patients should receive counseling. Meatal stenosis can occur in up to 20% of partial penectomies.

Historically, classic, radical inguinal lymphadenectomy has been associated with high rates of morbidity. Complications include 30% to 50% having long-term disabling morbidity, and mortality rates up to 3%. Minor complications include mild leg swelling, lymphoceles, and seromas. Major complications typically include the debilitating problems of severe, chronic, and disabling lower-extremity and scrotal lymphedema, skin-flap necrosis, severe wound infection, and deep venous thrombosis. More contemporary series have lower and more acceptable rates of incapacitating or major complications.

Modified inguinal node dissections (after Catalona) are at low risk (17%) for major complications. This is primarily due to the preservation of the saphenous vein and smaller regions of dissection.

B. After chemotherapy

In one phase II evaluation of cisplatin, methotrexate, and bleomycin, there was a high incidence of treatment-related deaths, and a high incidence (17%) of life-threatening toxic episodes. Some of the life-threatening episodes included infections, leukopenias, and pneumonitis. Although chemotherapy in penile cancer appears to have promising results in overall improvement in survival, further emphasis in future research to decrease toxicities would be advantageous.

C. After radiotherapy

Severe penile edema and skin maceration, ulceration, and sloughing can result. Urethra fistula, stricture, or stenosis can occur. There also are reports of penile necrosis, pain, edema, and an occasional need for secondary penectomy.

D. Of the disease

Anemia, leukocytosis, hypoalbuminemia (from chronic infection of the primary and inguinal sites), azotemia (secondary to urethral obstruction), and hypercalcemia can occur.

V. Follow-up

After definitive treatment of the primary tumor, patients whose groins are being monitored expectantly should undergo groin physical examinations every 2 months for the first 2 years from diagnosis, then every 6 months for 2 years, and then annually. Equivocal examinations should be further evaluated by either

groin ultrasound, CT, or MRI.

After inguinal lymphadenectomy, patients should be followed up every 3 months for the first 2 years, then every 6 months for 2 years, and then annually.

VI. Background

A. Epidemiology

SCC of the penis is a rare disease in the United States and other developed countries, accounting for less than 1% of all male cancers. In the United States, for the year 2000, 1,100 new cases of penile cancers (0.2% of male cancers) and 300 deaths occurred from penile cancer (0.1% of male cancer-related deaths). In the United States, blacks are affected 2 times as often as whites. In some African and South American countries, penile cancer is common, accounting for up to 20% of male cancers. Penile cancer patients are typically in their 50s to 70s, with a mean age of 60 years. It is rare before age 40 years.

B. Risk factors

Risk factors for developing penile cancer are uncircumcised penis, phimosis, chronic irritation of smegma, poor hygiene, and viruses. Men with human papilloma virus (HPV) and genital herpes have a higher incidence of penile cancer. HPV strains 16 and 18 have been identified in more than 50% of penile SCC. Infant circumcision offers protection from future development of penile cancer. Adult circumcision, however, offers no protection.

C. Pathophysiology

More than 95% of penile cancers are SCCs. The remaining rare cancers are sarcomas (including Kaposi sarcoma), melanoma, basal cell carcinoma, leukemia, and lymphoma. Verrucous carcinoma (giant condyloma) is histologically benign and is characterized by aggressive local extension and tissue destruction.

Many benign penile lesions have malignant potential or close association with cancer development. Up to 30% to 40% of patients with SCC of the penis had a history of a preexisting penile lesion. Penile lesions that are thought to have a malignant potential are **balanitis xerotic obliterans (BXO),** as known as lichen sclerosis et atrophicus (white patchy lesions of the glans, prepuce, or meatus), **leukoplakia** (whitish plaques usually involving the meatus, more common in diabetics), **cutaneous horns** (rare, protuberant, hyperkeratotic lesions), **pseudoepitheliomatous micaceous,** and **keratotic balanitis.**

D. Natural history

SCC of the penis usually begins as a small lesion on the glans or prepuce. Tumor invasion is usually by direct extension and is capable of destroying adjacent tissues. Exophytic lesions tend to be better differentiated than ulcerative lesions. Ulcerative and flat lesions tend to metastasize earlier. Tumors that metastasize usually spread first to the superficial inguinal nodes, then to the deep inguinal nodes, and then to the pelvic nodes. Skip lesions do not occur. Both groins may be involved because of lymphatic drainage crossover. Distant metastases are rare and tend to involve the abdominal lymph nodes, lung, liver, bones, and brain. Death is usually secondary to inguinal involvement, which can result in skin necrosis, chronic infection, sepsis, or hemorrhage due to tumor erosion into the femoral vessels.

VII. Current focus

Locally recurrent disease can be approached surgically or with local XRT. Patients with nodal recurrences that are not controllable by local measures are candidates for phase I and II clinical trials testing new biologicals (such as cisplatin and IFN-a2B) and chemotherapeutic agents (such as intraarterial infusion chemotherapy). Other clinical trials using radiosensitizers or cytotoxic drugs are appropriate. Because of the high incidence of microscopic nodal metastases, adjunctive inguinal dissection of clinically negative nodes with penile amputation is often used. However, further studies are needed to determine if prophylactic inguinal lymphadenectomy increases survival.

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CHAPTER 22. CARCINOMA OF UNKNOWN PRIMARY SITE

Arnel M. Pallera and Alan P. Lyss

Definition
Presentation
Subjective
Objective
Diagnosis
Workup and staging
Initial assessment
Tests for certain scenarios
Pathology
Prognosis, treatment, and clinical subsets
Well-differentiated or moderately differentiated adenocarcinoma
Poorly differentiated carcinoma or poorly differentiated adenocarcinoma
Poorly differentiated neoplasm
Squamous cell carcinoma
Background
Epidemiology

I. Definition

Carcinoma of unknown primary site (CUPS) is defined as a metastatic solid tumor for which the site of origin is not suggested by a thorough history and physical examination, radiographic studies, routine blood and urine tests, and a detailed evaluation of the biopsy specimen. These patients are very heterogeneous, with a wide variety of clinical presentations and histopathologic findings.

II. Presentation

A. **Subjective.** Common sites of metastatic involvement include the lung, liver, and skeletal system. Patients with CUPS usually are first seen with symptoms related to the areas of metastases (*Cancer: principles and practice of oncology.* 6th ed. Philadelphia: Lippincott-Raven, 2001:2537–2560; *Cancer management: a multidisciplinary approach.* 4th ed. Melville: PRR, 2000:553–562). Constitutional symptoms such as anorexia, weight loss, weakness, and fatigue also are very common. The major sites of tumor involvement are shown in Table 22.1 (*J Clin Oncol* 1994;12:1272–1280).

Site of Involvement	No. of Patients	%
Lymph nodes	244	37.1
Liver	202	30.7
Bone	184	28.0
Lung	182	27.7
Pleura/pleural space	76	11.6
Brain	50	7.6
Peritoneum	39	5.9
Adrenal	36	5.5
Skin	13	2.0

Adapted from Abruzzese et al. *J Clin Oncol* 1994;12:1272–1280, with permission.
CUP, carcinoma unknown primary.

TABLE 22.1. SITES OF TUMOR INVOLVEMENT IN 657 PATIENTS WITH THE CUP SYNDROME

B. **Objective.** In terms of physical manifestations, abnormalities can frequently be found. Common findings include lymphadenopathy, pleural effusions, ascites, and hepatomegaly.

III. Diagnosis

Diagnosis, as for all other cancers, is made by biopsy of a metastatic lesion. The biopsy should be generous, because many pathologic studies may be required in an attempt to identify a primary site.

IV. Workup and staging

A. **Initial assessment.** After a biopsy has enabled us to diagnose a neoplasm, a limited clinical evaluation is indicated to search for a primary site. A generally recommended evaluation includes a complete history, physical examination, chemistry profile, complete blood count (CBC), chest radiograph, and computerized tomographic (CT) scan of the abdomen. Other investigations must be symptom directed. There are four reasons to discourage aggressive use of invasive testing to find a primary tumor site:

- The patient's quality of life can be impaired.
- A financial burden can result.
- The prognosis of most CUPS patients is unaffected by whether a primary lesion is found.
- The search is unlikely to identify a primary tumor site.

The exact source of a malignancy is determined before death in only 13% to 25% of CUPS patients. When a site is determined, carcinomas of the lung and pancreas predominate (*Arch Intern Med* 1988;148:2035–2039). In autopsy series, a primary site can be found in approximately 70% of patients (*Postgrad Med J* 2000;76:690–693).

B. **Tests for certain scenarios.** In a few important settings, the identification of a primary site can alter treatment in a very specific way, occasionally with great prognostic value. Examples are

- Young men with a poorly differentiated carcinoma should have serum a-fetoprotein (AFP) and human chorionic gonadotropin (HCG) levels measured to assess for a germ cell tumor.
- Women with axillary adenopathy should have a mammogram to identify a breast primary.
- Men with blastic bone metastasis should have a prostate-specific antigen (PSA) test performed to evaluate for prostate cancer.
- Patients with metastatic squamous cell carcinoma of the cervical lymph nodes should have a thorough search for a primary in the head and neck region, including panendoscopy (bronchoscopy, esophagoscopy, and nasopharyngoscopy).
- Patients with squamous cell carcinoma of the inguinal lymph nodes almost always have a primary site in the perineal region. Women should undergo careful examination of the vulva, vagina, and cervix. Men should have a careful inspection of the penis and scrotum. Anoscopy should be performed to exclude lesions in the anorectal area.

C. **Pathology**

1. **Light microscopy.** Certain light-microscopic features may point to a particular site or organ system of origin for a metastatic tumor, but these features are not very sensitive or specific. They should be interpreted in conjunction with other findings. Some histopathologic clues are shown in Table 22.2.

Helpful Findings	Probable Primary Site
Histopathology	
Signet ring cells	GI, ovary, breast
Psammoma bodies	Ovary, thyroid, breast
Papillary structures	Thyroid, ovary, mesothelioma
Nonacinar cell nests	Carcinoid, melanoma, paraganglioma
Rosettes and areas of ganglion cell-like differentiation	Neuroblastoma
Electron microscopy	
Lamellar surfactant bodies	Alveolar carcinoma (lung)
Cells united by desmosomes, tonofilaments	Squamous cell carcinoma
Premelanosomes, melanosomes	Melanoma
Polyribosomes, absence of intercellular junctions	Lymphoma, leukemia
Myofibrils, osteoid	Sarcoma
Long surface microvilli	Mesotheliomas (some)
Apical terminal webs	Gut epithelial cells
Acinar spaces, tight junctions, microvilli, desmosomes, junctional complex	Adenocarcinoma
Microvilli, apical mucous granules	Colon
Intracellular neolumina, prominent tonofilaments	Breast
Staghorn microvilli	Ovary
Tubulofilamentous structures of cytoplasm	Kidney

Adapted from Casciato. Cancer treatment. 5th ed. Philadelphia: WB Saunders Company, 2001:1556–1579, with permission.
GI, gastrointestinal.

TABLE 22.2. MICROSCOPIC CLUES TO TUMOR ORIGIN

Despite these limitations, routine light microscopy provides a practical classification system through which the patient can be subsequently evaluated and managed. CUPS can be classified as:

1. Well-differentiated or moderately differentiated adenocarcinoma,
2. Poorly differentiated carcinoma or adenocarcinoma,
3. Poorly differentiated neoplasm, or
4. Squamous cell carcinoma.

2. **Immunohistochemistry.** Immunoperoxidase (IP) staining is the most widely available specialized technique for the classification of neoplasms. It can be done on formalin-fixed specimens, which usually makes repeated biopsy unnecessary. Several important questions can be answered by using immunohistochemistry (Table 22.3). For example:

Tumor Type	Immunohistochemistry
Carcinoma	Epithelial stains (cytokeratin, epithelial membrane antigen)$^+$ Common leukocyte antigen (CLA), S-100, vimentin$^-$
Lymphoma	CLA$^+$
Sarcoma	Vimentin, desmin, von Willebrand antigen$^+$
Melanoma	S-100, vimentin, HMB-45$^+$ Synaptophysin, epithelial stains$^-$
Germ cell tumor	HCG, AFP, epithelial stains$^+$
Prostate cancer	PSA, epithelial stains$^+$
Breast cancer	Estrogen receptor, progesterone receptor, epithelial stains$^+$
Thyroid	Thyroglobulin$^+$ (in follicular) Calcitonin$^+$ (in medullary)
Neuroendocrine tumor	Neuron-specific enolase, chromogranin, synaptophysin, and epithelial stains$^+$

Adapted from DeVita. Cancer: *Principles and practice of oncology*. 5th ed. Philadelphia: Lippincott-Raven, 1997:2423–2443, with permission.
HCG, human chorionic gonadotropin; AFP, α-fetoprotein; PSA, prostate-specific antigen.

TABLE 22.3. IMMUNOPEROXIDASE STAINING IN THE DETERMINATION OF A TUMOR SOURCE

- The leukocyte common antigen stain can be used to distinguish lymphoma from carcinoma.
- Staining for neuron-specific enolase (NSE), chromogranin, and synaptophysin can suggest a neuroendocrine origin (e.g., carcinoid tumor, or small cell or islet cell cancers).
- Staining for PSA in a male may predict prostatic carcinoma.
- Staining for HCG or AFP can suggest a germ cell tumor.
- Positive staining for S-100, vimentin, or HMB-45 is suggestive of melanoma.
- Positive staining for vimentin, von Willebrand antigen, and desmin is suggestive of sarcoma.
- Thyroglobulin and calcitonin staining can assist in the diagnosis of particular thyroid cancer histologies.

3. **Electron microscopy.** Electron microscopy (EM) can aid in the diagnosis of some neoplasms, but is not widely available, is expensive, and requires special tissue fixation. Therefore EM should be reserved for the study of neoplasms of unclear lineage after routine light microscopy and immunohistochemistry. It provides additional information about cell lineage by looking at the subcellular level and identifying structures that correlate with particular primary sites (Table 22.2).
4. **Genetics.** Information about a primary tumor site also can be garnered from genetic analyses of the biopsy specimen. For example, chromosomal translocations such as t(14:18), t(8:14), or t(11:14) suggest lymphoma. The t(11:22) translocation has been found in peripheral primitive neuroectodermaltumor and in Ewing sarcomas, and the t(2:13) translocation has been seen in alveolar rhabdomyosarcomas. Additional examples include an isochromosome of the short arm of chromosome 12 in germ cell tumors, 3p deletion in small cell lung cancer, 1p deletion in neuroblastoma, and t(X:18) in synovial sarcoma.

V. **Prognosis, treatment, and clinical subsets**

A. **Well-differentiated or moderately differentiated adenocarcinoma.** Adenocarcinoma is the most frequent light-microscopic diagnosis, accounting for 60% of patients (50,000 annually in the United States) with CUPS. Typically, these patients are elderly and have multiple metastatic sites, of which the most common are the lymph nodes, liver, lung, and bone. The sites of involvement determine the clinical presentation.

Adenocarcinoma is diagnosed by light microscopy when the neoplastic cells are organized in glandular formations. Immunoperoxidase staining and EM are of limited value in determining a primary site, but notable exceptions include staining for PSA in men and staining for estrogen or progesterone receptors in women to help identify prostate and breast cancers, respectively. Rarely, neuroendocrine staining (NSE, chromogranin, or synaptophysin) can identify an unsuspected neuroendocrine neoplasm.

1. **Prognosis.** As a group, CUPS patients with adenocarcinoma have a poor prognosis (median survival, 3 to 4 months) (*Arch Intern Med* 1988;148:2035–2039). These patients generally have widespread metastases, are elderly, and have a poor performance status. Autopsy studies reveal that most of these tumors originate in the pancreas or lung, tumors that are poorly responsive to systemic therapy.
2. **Treatment.** Most patients with adenocarcinoma of unknown primary site (90%) do not fit into any special subgroup (*vide infra*) and should be treated with palliative intent. Radiation therapy can be given for symptomatic management of brain metastases, painful bony lesions, spinal cord compression, or superior vena cava syndrome. Surgery may be useful to palliate obstruction of the urinary or gastrointestinal tracts. Systemic chemotherapy has been used in patients who initially have good performance status, but there is little evidence of improvement in median survival. Long-term complete remissions are rare, and therefore no single chemotherapy regimen has emerged as the ideal empiric choice. The advent of new agents in recent years (e.g., taxanes, gemcitabine, and the topoisomerase I inhibitors) has resulted in renewed interest. Hainsworth et al. reported a 47% response rate and an 11-month median survival with the combination of carboplatin, paclitaxel, and oral etoposide, in CUPS patients with adenocarcinoma who were treated in a phase II study (*J Clin Oncol* 1997;15:2385–2393). Briasoulis et al. reported similar results with carboplatin and paclitaxel in patients with CUPS. Their response rate for adenocarcinoma was approximately 40%, with a median response duration of 7 months (*J Clin Oncol* 2000;18:3101–3107).
3. **Clinical subsets.**
   a. **Women with isolated axillary adenopathy.** Breast cancer should be suspected and is strongly supported if estrogen-receptor (ER) or progesterone-receptor (PR) levels are elevated. Patients with no other metastatic sites of disease may have an occult stage II breast cancer and could have potentially curable disease. Patients should receive primary therapy with either mastectomy or axillary node dissection plus irradiation of the breast, followed by adjuvant systemic therapy. Women with distant sites of metastatic cancer should have hormone receptor and HER2/ *neu* testing on the biopsy specimen, with therapy according to guidelines for metastatic breast cancer.
   b. **Women with peritoneal cancer.** Adenocarcinoma with diffuse involvement of the peritoneum is suggestive of ovarian cancer or primary peritoneal carcinoma. These women have a better prognosis, with median survivals of 12 to 31 months. Therapy should be conducted as if the patient had stage III ovarian cancer, including cytoreductive surgery, followed by postoperative platinum-based chemotherapy.
   c. **Osteoblastic bony metastases in men.** Men with adenocarcinoma of unknown primary site should have PSA levels obtained on a peripheral blood specimen and should have immunoperoxidase staining for PSA performed on the biopsy specimen. Hormonal therapy for prostate cancer should be

attempted because palliative benefit is likely.

d. **Patients with a single metastatic site.** Local treatment, with either surgical excision or radiation therapy, should be administered to the patient with clinical evidence of a single metastatic site. Prolonged survival may be achieved, especially among patients who have a solitary metastasis in a peripheral lymph node.

B. **Poorly differentiated carcinoma or poorly differentiated adenocarcinoma.** Patients with poorly differentiated carcinoma (PDC) or poorly differentiated adenocarcinoma (PDA) account for 30% of all patients with CUPS. Approximately two thirds have PDC, and about one third have PDA. These tumors had historically been combined with the well-differentiated adenocarcinomas (*vide supra*), but there are substantial differences:

- Median age is younger for PDA or PDC than for well-differentiated adenocarcinoma.
- The predominant sites of involvement are the lymph nodes, the mediastinum, and the retroperitoneum instead of visceral organs or bony sites.
- There is usually more rapid progression of symptoms for PDC or PDA patients.
- Some patient subsets with PDC or PDA are very responsive to chemotherapy and may have sustained complete remission after platinum-based chemotherapy (*Cancer: principles and practice of oncology.* 5th ed. Philadelphia: Lippincott-Raven, 1997:2423–2443).

All patients with a light-microscopic diagnosis of PDC or PDA require further pathologic study to confirm a diagnosis of carcinoma, to identify a primary site, and to search for neuroendocrine features that might imply chemosensitivity. Molecular genetic analyses and EM may be useful.

1. **Prognosis.** An analysis by Lenzi reviewed the natural history of 197 patients with PDA and 140 patients with PDC (*J Clin Oncol* 1997;15:2056–2066). The median survival of patients with PDC was found to be approximately 13 months, and for patients with PDA, the median survival was 8 months. This study by Lenzi excluded patients who were found to have an extragonadal germ cell tumor or a neuroendocrine tumor.
2. **Treatment.** If pathology studies identify a specific neoplasm (e.g., lymphoma, sarcoma), appropriate, specific therapy can be initiated. For patients in whom pathologic studies identify no specific neoplasm and for patients who do not fit into a special subset (*vide infra*), benefit may be derived from platinum-based chemotherapy. Hainsworth et al. reported a response rate of 64%, including 27% complete responses, among unselected PDC patients treated with polychemotherapy with a platinum-based regimen (*J Clin Oncol* 1992;10:912–922). Median survival was 20 months, and 13% of patients were disease free for more than 8 years. Unfortunately, Lenzi et al. did not find that chemotherapy influenced survival in PDA or PDC patients, although certain clinical characteristics were associated with a median survival of up to 40 months. *J Clin Oncol* 1994;12:1272–1280; *J Clin Oncol* 1997;15:2056–2066), including
   1. Young age,
   2. Nonsmoker,
   3. Neuroendocrine features on IP testing,
   4. Single site of metastatic involvement (fewer than three metastatic sites), and
   5. Tumor location in the mediastinum, retroperitoneum, or peripheral lymph nodes.

   In patients who lack these clinical features, decisions about chemotherapy should be individualized based on the patient's performance status and enthusiasm for an empiric trial of cytotoxic therapy.

3. **Clinical subsets**
   a. **Extragonadal germ cell cancer syndrome.** This syndrome was described in 1979 with the following features:
      1. Young (age younger than 50 years) male patients,
      2. Midline tumors (mediastinal or retroperitoneal locations),
      3. Short duration of symptoms,
      4. Elevated levels of germ-cell tumor markers, and
      5. Good response to radiation or chemotherapy.

      PDC in a young male patient with mediastinal or retroperitoneal masses should raise the clinician's suspicion of a germ cell tumor. Cytogenetic studies that show abnormalities of chromosome 12 facilitate the establishment of a diagnosis. These patients should be treated with chemotherapy directed toward a germ cell tumor.

   b. **Unsuspected gestational choriocarcinoma.** Young women with PDC, particularly if there are lung nodules, may have a metastatic gestational choriocarcinoma. A history of a recent pregnancy, spontaneous abortion, or missed menses should suggest the possibility. Serum HCG levels are nearly always elevated. Imaging of the abdomen may show an enlarged uterus. Most of these patients are curable with chemotherapy that is appropriate for gestational choriocarcinoma.
   c. **Neuroendocrine carcinoma.** With improved IP staining technology, neuroendocrine features are recognized more frequently in patients with PDC. There are two major subsets:
      - Low-grade neuroendocrine carcinomas have histologic features of a carcinoid or an islet cell tumor. They may be associated with clinical syndromes produced by the secretion of bioactive substances (e.g., carcinoid syndrome, glucagonoma syndrome, vasoactive intestinal polypeptide (VIP)oma, Zollinger–Ellison syndrome). In some of these patients, further evaluation reveals a primary site in the small intestine, rectum, pancreas, or bronchus. These tumors are usually indolent and show slow progression over several years. Management should follow guidelines established for metastatic carcinoid or islet cell tumors. Depending on the clinical situation, appropriate management may include local therapy (embolization, resection, hepatic artery ligation), observation, somatostatin analogues, or 5-fluorouracil–based or other chemotherapy.
      - High-grade poorly differentiated neuroendocrine carcinomas (e.g., extrapulmonary small cell carcinoma, anaplastic carcinoid, Merkel cell tumors, and paragangliomas) behave aggressively. They are difficult to characterize by light microscopy, but IP staining can be diagnostic. Because these tumors may be chemosensitive, patients should receive a trial of chemotherapy with a standard regimen for small cell lung cancer.
   d. **Small cell carcinoma at a metastatic site.** Patients with small cell carcinoma at a metastatic site should have a CT of the chest and fiberoptic bronchoscopy performed in an effort to identify a primary bronchogenic cancer. Extrapulmonary sites of origin have been described, including the bladder, cervix, esophagus, ovary, prostate, and salivary gland. These patients should receive chemotherapy with standard regimens for small cell lung cancer.

C. **Poorly differentiated neoplasm.** If the pathologist is confident of the cancer diagnosis but cannot determine by light microscopy how to categorize the neoplasm (e.g., carcinoma, lymphoma, sarcoma, melanoma), it is designated as a poorly differentiated neoplasm (PDN). PDN occurs in 5% of all patients with CUPS (4,000 patients annually in the United States). A precise diagnosis is important because many patients have responsive tumors. Therefore it is important to request that a generous biopsy specimen be obtained, in preference to fine-needle aspiration, so that a thorough pathologic evaluation may be conducted. Most patients with PDN on light-microscopic evaluation will have a defined lineage after specialized pathologic staining is performed. In one series, 35% to 65% of poorly differentiated neoplasms were found to be lymphoma after further pathologic study. Sarcomas and melanomas account for 10% to 20% of PDNs (*Cancer management: a multidisciplinary approach.* 4th ed. Melville: PRR, 2000:553–562). For patients with PDN for whom no specific cell type can be identified, treatment is similar to the treatment of CUPS patients with adenocarcinoma.

D. **Squamous cell carcinoma.** Squamous cell carcinoma accounts for 5% of all patients with CUPS. Light microscopy can usually elicit this pathologic diagnosis. Except for two specific subsets, these patients can usually be considered to have an occult lung primary. CT scans of the chest should be done and bronchoscopy performed if an abnormality is found on CT scanning.
   1. **Prognosis.** For patients who do not fit into any specific clinical subsets, the outlook is poor, with median survivals similar to those for lung or esophageal cancers. Altman et al. performed a large retrospective review of 1,539 patients with CUPS and found that the median survival of patients with untreated squamous cell carcinoma (148 cases) was 2.4 months (*Cancer* 1986;57:120–124). The survival of patients with this disease who were given empiric therapy was 11 months, but this analysis included patients with squamous cell carcinoma involving the cervical lymph nodes (*Cancer* 1986;57:120–124).
   2. **Treatment.** For patients with good performance status, chemotherapy regimens effective in the treatment of non–small cell lung cancer should be used.
   3. **Clinical subsets.**
      a. **Squamous cell cancer in the high cervical lymph nodes.** These patients are usually middle-aged or elderly, and they frequently use tobacco and/or alcohol. A primary tumor of the head and neck region should be suspected. Panendoscopy (nasopharyngoscopy, bronchoscopy, and esophagoscopy) should be undertaken. Recent studies suggest that positron emission tomography (PET) scanning can assist in identifying a primary tumor in the head and neck region (*Otolaryngol Head Neck Surg* 2000;123:294–301). If a source is found, therapy can be tailored to the primary tumor site and regional lymph nodes. If no primary tumor is found, radical neck dissection, radiotherapy, or both may result in long-term, disease-free survival in 30% to 70% of patients (*Cancer management: a multidisciplinary approach.* 4th ed. Melville: PRR, 2000:553–562; *Clin Otolaryngol* 1998;23:158–163; *Semin Oncol* 1993;20:273–278).
      b. **Squamous cell cancer involving the lower cervical or supraclavicular lymph nodes.** In this subgroup, the lung should be suspected to be the primary tumor site. The prognosis is not so favorable as that for patients with high cervical adenopathy. If no disease is detected inferior to the clavicle, these patients should be treated with aggressive local therapy (surgery and radiotherapy). Ten percent to 15% of these patients will obtain

long-term, disease-free survival (*Cancer: principles and practice of oncology.* 6th ed. Philadelphia: Lippincott-Raven, 2001:2537–2560).

c. **Squamous cell carcinoma involving the inguinal lymph nodes.** A primary site in the genital or anorectal area must be suspected. Therefore, careful examination of the vulva, vagina, cervix, or penis, scrotum, and anus is mandatory. If a primary tumor site in these areas can be identified, specific and curative therapy is available despite lymph node involvement. If no site is found, surgical resection with or without systemic chemotherapy and radiation to the inguinal area can produce long-term survival (*Cancer management: a multidisciplinary approach.* 4th ed. Melville: PRR, 2000:553–562).

VI. **Background**

A. **Epidemiology.** CUPS is a common clinical syndrome, accounting for approximately 5% of all oncologic diagnoses. It occurs with equal frequency in men and women, and it has the same prognosis regardless of gender. Although a wide age range exists, the incidence increases with advancing age. The median age of patients with CUPS is 56 to 60 years. Approximately 10% of patients have a history of another antecedent cancer.

CHAPTER 23. THYMOMA AND MESOTHELIOMA

Bryan F. Meyers and Richard Battafarano

Presentation of patients with thymoma
Subjective complaints
Objective findings
Workup and staging
Radiography
Biopsy
Pathology and terminology
Staging
Therapy and prognosis
Treatment of myasthenia gravis
Stage-directed therapy for thymoma
Neoadjuvant therapy
Surgery
Indications and contraindications
Surgical procedure
Radiation therapy
Chemotherapy
Summary of stage-specific therapy
Prognosis
Other thymic tumors
Conclusions
Mesothelioma
Presentation
Workup and staging
Staging
Treatment
Epidemiology
Prognosis
Clinical factors
Pathologic factors
Conclusion
Suggested Readings

I. Presentation of patients with thymoma

A. Subjective complaints

The clinical presentation for patients with thymic neoplasms can be quite variable. Many patients will be asymptomatic and healthy with a tumor that was discovered as a result of a screening chest radiograph. Some patients will have nonspecific complaints of chest pain or fullness that lead to radiographic detection of the mass. Fewer than half of the patients with thymoma will have a diagnosis of myasthenia gravis. In these cases, the diagnosis of myasthenia often leads to a computed tomography (CT) scan of the chest in search of a thymoma. The clinical presentation of myasthenic patients varies widely: there may be systemic weakness in 70% and purely ocular myasthenia in 30%. With rare exceptions, most believe that the presence of properly managed myasthenia gravis in association with a thymoma no longer has a negative impact on survival. Some authors have actually suggested that the symptoms of myasthenia gravis may lead to an earlier diagnosis of thymoma and, therefore, an improved outcome.

B. Objective findings

The age distribution of patients with thymoma is broad, with patient ages ranging from the second to the ninth decade. The age of peak incidence is 50 to 69 years for patients without myasthenia gravis and 30 to 69 years for patients with myasthenia. There is equal representation of men and women in most large series of thymomas. Physical examination will be unrewarding in patients with stage I and stage II thymoma. Advanced stages may demonstrate physical findings caused by the local effects of tumor invasion. Invasion or compression of the superior vena cava may cause the characteristic findings of facial and upper extremity swelling, whereas invasion of the innominate vein will cause predominantly left arm swelling. Phrenic nerve invasion may cause decreased breath sounds on the affected side. Invasion of the lung parenchyma and metastases to the pleural space are not typically associated with symptoms or physical findings. The physical findings associated with myasthenia gravis are wide ranging, from trivial ptosis to profound weakness and respiratory failure.

Many of the patients found to have myasthenia gravis and thymoma are asymptomatic except in the face of provocative testing such as electromyography. Titers of antibodies against the acetylcholine receptors help to define the diagnosis of myasthenia gravis but will not guide therapy in asymptomatic patients. Most retrospective series of thymomas include patients with pure red cell aplasia and or hypogammaglobulinemia, but these paraneoplastic phenomena rarely have an impact on diagnosis and management.

II. Workup and staging

A. Radiography

Although most patients with thymoma will receive a chest radiograph, the value from this test is limited. An elevated hemidiaphragm may suggest the invasion of a phrenic nerve, and the presence or absence of other abnormalities will help clarify a patient's suitability for aggressive therapy. CT of the chest will provide valuable anatomic evidence regarding the degree of local invasion of adjacent structures and the presence or absence of gross pleural metastases. There may be a role for magnetic resonance imaging (MRI) if vascular invasion is suspected. Currently there is no proven value for routine positron emission tomographic scanning for patients with thymoma.

B. Biopsy

One controversy in the management of patients with thymic neoplasms is the role of biopsy in treatment. A preoperative biopsy is not thought to be necessary in most resectable lesions detected in patients with myasthenia gravis. Patients with anterior mediastinal masses in the absence of myasthenia deserve further diagnostic consideration before resection. The sensitivity and specificity of needle biopsy is limited in this clinical scenario because of the cytologically benign appearance of many thymomas and the difficulty of establishing the diagnosis of lymphoma with a needle biopsy. Because the thymus contains both medullary and cortical tissue, and because thymomas can show differentiation of either of these types of tissues, the sampling error introduced by needle biopsy can be misleading. The use of immunohistochemical staining of aspirated material has greatly increased the diagnostic accuracy of needle biopsy for anterior mediastinal masses. Consultation with the pathologist before needle biopsy will allow realistic expectations for obtaining a diagnosis in this manner. Biopsy will be most valuable in three situations: in the setting of an advanced tumor for which neoadjuvant therapy is considered; when the possibility for resection has been excluded altogether; or when the differential diagnosis for the mass includes a lymphoma or seminoma that would not be considered for resection.

C. Pathology and terminology

The diagnosis of thymoma is reserved for tumors fitting the criteria outlined by Rosai and Levine, specifically epithelial tumors originating from the thymus gland. This diagnosis excludes lymphoma, carcinoid tumor, anaplastic carcinoma, and germ cell tumor. Well-differentiated thymic carcinoma is inconsistently included in discussions of thymomas because of conflicting published classification schemes. Thymomas occur along a wide spectrum of histopathologic degrees of malignancy. At the most benign end of the spectrum, the medullary or spindle cell thymoma behaves very much like a benign tumor, and patients

do well after complete resection. Some thymomas have microscopically malignant epithelial features and are therefore described as well-differentiated thymic carcinomas. In truth, there is little to suggest that these tumors are anything distinct from thymoma; rather they represent the malignant end of a continuous spectrum of disease (*Am J Clin Pathol* 1999;111:826–833). Conversely, other carcinomas originating within the thymus may appear distinctly different from thymoma and behave much more aggressively. These neoplasms include squamous cell carcinoma, adenoid cystic carcinoma, and poorly differentiated thymic carcinoma.

D. **Staging**

The staging of thymomas is inconsistent, as there have been many attempts to identify distinct subgroups of patients based on survival and freedom from recurrence. Historically, the classification of thymomas as “benign” or “malignant” was left to the surgeon, and this determination was based on the presence or absence of gross invasion through the capsule at the time of surgery. However, tumors with gross invasion of surrounding structures often lack **histologic** criteria of malignancy. The most commonly used classification, and the one used at Washington University, is that proposed by Masaoka in which four clinical stages are created, based on the degree of invasiveness of the tumor (*Cancer* 1981;48:2485–2492). The basis of the Masaoka system (Table 23.1) is clinical (findings at surgery, radiography), although the substaging of patients with clinical stage II is based in part on the pathologic determination of microscopic invasion into the thymic capsule by the tumor. A classification scheme that focuses less on anatomic staging and more on histopathologic criteria is that of Müller-Hermelink et al. (*Am J Clin Pathol* 1999;112:299–303). This system classifies thymomas across a spectrum that includes medullary thymoma, mixed thymoma, cortical thymoma, organoid thymoma, and well-differentiated thymic carcinoma. Other classification schemes incorporate the degree of completeness of surgical resection (GETT system) (*J Thorac Cardiovasc Surg* 1996;112:376–384) or incorporate the information from both the histopathologic description and the anatomic staging (Pescarmoma classification) to stratify patients according to predicted survival and freedom from recurrence (Table 23.2, Table 23.3 and Table 23.4).

Stage	Substage	Description
I		Complete encapsulation of the tumor
II	a	Microscopic transcapsular invasion into fat or pleura[a]
	b	Macroscopic transcapsular invasion into fat or pleura
III		Macroscopic invasion into pericardium, great vessels, lung
IV	a	Pleural or pericardial metastases
	b	Lymphatic or hematogenous metastases

Adapted from Masaoka et al. *Cancer* 1981;48:2485–2492, with permission.
[a]While the actual Masaoka system described macroscopic invasion as stage II–I and microscopic invasion as stage II–2, the version shown above is the most widely accepted.

TABLE 23.1. MASAOKA STAGING SYSTEM FOR THYMOMA

Stage	Substage	Description
I	IA	Encapsulated tumor, totally resected
	IB	Macroscopically encapsulated, but surgeon suspects mediastinal adhesions and potential capsular invasion
II		Invasive tumor, totally resected
III	IIIA	Invasive tumor, subtotally resected
	IIIB	Invasive tumor, biopsy performed
IV	IVA	Supraclavicular metastases or distant pleural implants
	IVB	Distant metastases

GETT proposal in Regnard JF, et al. *J Thorac Cardiovasc Surg* 1996;112:376–384, with permission.

TABLE 23.2. GETT (FRENCH STUDY GROUP ON THYMIC TUMORS) STAGING SYSTEM

			Pescarmona Classification		
General	GETT	Masaoka	Medullary	Mixed	Cortical
Benign	Ia, Ib	I	Best	Best	Intermediate
Invasive	II	II	Best	Intermediate	Intermediate
Malignant	IIa, IIb	III	Intermediate	Worst	Worst
Malignant	IIIa	IVa	—	—	Worst
Malignant	IIIb	IVb	—	—	Worst

TABLE 23.3. COMPARISON OF COMMON STAGING SYSTEMS FOR THYMOMA

Masaoka stage: Lower versus higher
Tumor size: <11 cm versus >11 cm
Tumor histology: Spindle cell or lymphocytic predominant versus epithelial predominant or thymic carcinoma
Extent of resection: Complete resection versus partial resection or biopsy

Adapted from Blumberg et al. *Ann Thorac Surg* 1996;60:908–914, with permission.

TABLE 23.4. INDEPENDENT PREDICTORS OF SURVIVAL AND FREEDOM FROM RECURRENCE AFTER THYMOMA RESECTION

III. **Therapy and prognosis**

A. **Treatment of myasthenia gravis**

Patients with known or suspected myasthenia gravis should be evaluated by a neurologist, and any evidence of systemic weakness due to myasthenia gravis should be treated aggressively with plasmapheresis. Such therapy minimizes weakness and avoids the need for perioperative steroid therapy in a patient who must heal a sternotomy. Patients will typically be transferred to the neurology service where a large-bore central line will be placed to allow plasma

exchanges. Three to six exchanges will be performed with the anticipation that the maximal effect will be experienced 1 to 3 weeks after commencement of the plasma exchanges.

B. **Stage-directed therapy for thymoma**

Treatment of thymoma is very much determined by clinical and pathologic staging. Patients clinically staged I and II are offered surgical resection without any induction therapy before surgery. Postresection pathologic stage II patients will be considered for adjuvant radiotherapy as discussed in detail later. Stage III patients will be considered for either surgery alone or induction chemotherapy followed by surgery. In both of these strategies, postresection adjuvant radiotherapy is advised. Finally, stage IV patients will usually have combined radiation and chemotherapy without a surgical resection. An exception to this would be the patient in whom pleural metastases are detected after the sternotomy has been performed. In these patients, an attempt at maximal resection of all gross disease will be made to debulk tumor in advance of chemotherapy and radiation.

C. **Neoadjuvant therapy**

Neoadjuvant therapy in the broadest sense is applicable in two situations: aggressive treatment of associated myasthenia gravis to decrease the morbidity and mortality of resection, and chemotherapy or chemoradiotherapy to increase the likelihood of a complete resection in a patient with known or suspected thymoma of stage II or higher.

Neoadjuvant chemotherapy strategies have been reported by some groups to have beneficial effects on patients with stage III and IV thymoma. One such strategy, including cisplatin, epirubicin/doxorubicin, and etoposide before and after resection has resulted in dramatic improvements in survival for higher stage (Masaoka III and IV) patients when compared with historic controls. There is difficulty in accurately staging patients before resection, and this will often require anterior mediastinotomy and thoracoscopy. The accumulated experience with neoadjuvant chemotherapy is too recent to allow a full understanding of the ideal patients and the appropriate chemotherapeutic agents.

IV. **Surgery**

A. **Indications and contraindications**

The indications for surgical resection include the presence of a known or suspected thymoma that is operable, based on preoperative patient health, and potentially resectable, according to clinical radiographic staging. Contraindications include known distant metastases, excessive comorbidity with other systemic diseases, fulminant myasthenia gravis crises, and limited life expectancy.

B. **Surgical procedure**

The standard technique for resection of thymoma is median sternotomy with complete resection of the tumor and all additional thymic tissue. The sternum is divided, and both pleural spaces are opened widely to allow careful exploration of both pleura and careful identification of both phrenic nerves. In a completely encapsulated tumor (Masaoka I), the complete resection can be achieved without resection of the pericardium, but when there is any doubt about pericardial involvement, every effort should be made to achieve a complete resection. Complete surgical resection will be possible via median sternotomy in most patients. Anterior thoracotomy may be considered for patients with an eccentric tumor primarily located lateral to the lateral border of the sternum. In a small number of patients, bilateral anterior thoracotomy with transverse sternotomy (the clamshell incision) will be necessary to resect the primary tumor and debulk or resect bilateral pleural metastases.

The extent of surgery in stage III patients will vary according to the site of adjacent organ invasion. In a recent report, there were 30 sites of local organ invasion in 25 patients who were deemed stage III. Of these 25 patients, 22 had extensive resections including attached lung, pericardium, vena cava, innominate vein, and phrenic nerve. (*Ann Thorac Surg* 1997;64:1585–1591). Two patients had nonradical and incomplete resections with tumor left invading the aorta and main pulmonary artery. One patient responded to neoadjuvant therapy and avoided a chest wall resection because of the response. The decision to resect a phrenic nerve involved with tumor depends on the respiratory status of the patient and the degree of function in the nerve before surgery. A nerve that is already functionless can be resected without consequence, and a functioning nerve in a patient with good reserve can be resected if it will allow a complete resection. It is better to debulk tumor and spare a functioning nerve in patients with poor respiratory reserve or in patients who will otherwise have an incomplete resection because of unresectable disease elsewhere. There are some advocates of a less invasive approach for stage I thymomas with video-assisted thoracoscopic techniques. These authors cited the safety and efficacy of video-assisted thymectomy, but the number of such patients is too small, and follow-up is too short to support a claim of equivalency.

C. **Radiation therapy**

Radiation therapy is typically considered after operation in two settings: for patients with stage III or IV tumors who have undergone either an incomplete resection or a biopsy without plans for resection, and for patients deemed Masaoka stage II, III, or IV who have had a complete resection. Most institutions agree that the disease-free survival after a resection of a stage I thymoma is long enough to make adjuvant radiotherapy unnecessary. For instance, Massachusetts General Hospital reported a 22% rate of recurrence after resected stage II thymomas, but no recurrence after resected stage I thymomas. The authors concluded that radiation therapy is needed after stage II resections. Other investigators have demonstrated a lower recurrence rate for completely resected stage II tumors and advise that adjuvant radiotherapy for such patients is controversial. In stage IV disease, or in any stage tumor that is incompletely resected, postoperative radiation therapy alone is less likely to change survival, because patients' advanced disease generally recurs both locally and systemically. For that reason, such patients are generally treated with chemotherapy rather than with primary radiotherapy.

D. **Chemotherapy**

Primary chemotherapy is generally considered after a biopsy in inoperable disease or after an incomplete resection. In these cases, the chemotherapy may be intended as the sole therapy, but many patients will experience a radiographic improvement to such an extent that resection will become a possibility, and 5-year survival as high as 50% may result in such salvaged patients. Chemotherapy also has a role in treating recurrent disease after previous attempts at curative therapy. In up to 30% of patients with complete surgical resections, the disease will recur, and data suggest that response rates to multidrug, cisplatin-based therapy will be as high as 50% to 90%. A retrospective review of 37 patients receiving combination chemotherapy consisting of cisplatin, doxorubicin, vincristine, and cyclophosphamide described a 91% response rate, with 16 of the 37 patients described as complete responses. The median survival of complete responders had not been reached after 24 months of follow-up. Other authors reported excellent results after surgical resection of recurrent disease, with 90% survival 2 years after the repeated resection. The role of adjuvant chemotherapy is poorly defined, and treatment of completely resected stage II and stage III thymomas has typically included adjuvant radiation rather than adjuvant chemotherapy.

E. **Summary of stage-specific therapy**

Stage I patients are effectively treated with complete resection alone and have excellent expectation for 95% to 100% long-term disease-free survival without the addition of any adjuvant therapy. Stage II resected patients are more controversial. Although the survival curves of stage I and stage II patients are not statistically different in most large series, conclusions are confounded because none of the stage I patients have received adjuvant therapy, whereas many or most of the stage II patients will have received adjuvant radiotherapy. Furthermore, many tumors formerly classified as stage I on the basis of gross absence of invasion are now classified as stage IIa on the basis of microscopic capsular invasion. This further confounds the ability to analyze many previous series with respect to the difference in prognosis between stage I and stage II thymoma. There has been some enthusiasm for neoadjuvant therapy for certain stage III and IV tumors. Venuta et al. stratified patients into three groups according to prognosis. The three groups roughly correspond to the classifications described as “best,” “intermediate,” and “worst” in the Pescarmona classification scheme summarized in Table 23.3. The authors offered neoadjuvant chemotherapy in the form of cisplatin, epirubicin, and etoposide every 3 weeks for three cycles before radical surgical resection and 2 to 3 times postoperatively depending on each patient's hematologic status. Patients with invasive tumors (Masaoka II or higher) were given postoperative radiation therapy to 30 Gy for complete resections or 50 Gy for incomplete resections. Applying this strategy led to improvements in survival over those seen in historical controls at the same institution who were not offered neoadjuvant therapy.

F. **Prognosis**

The clinical stages at the time of operation vary between centers, but in general, 50% will be Masaoka stage I, 25% will be stage II, 20% will be stage III, and 4% will be stage IV. No reliable difference in the distribution of clinical stages has been detected between patients with myasthenia gravis and those without.

Perioperative survival is generally excellent with more than 95% of patients surviving to hospital discharge. The appropriate perioperative management of myasthenia gravis has essentially eliminated the problem of postoperative respiratory failure in these patients. The 10-year actuarial survival for all patients with thymoma will be 60% to 70%. Typically, half the deaths will be recorded in patients in whom the disease has recurred, and half in patients in whom it has not recurred, so the disease-free survival is often 85% for long-term follow-up. Stage-specific survival will be as follows: Masaoka stage I and stage II patients can expect a 90% to 95% 5-year survival and 75% to 80% 10-year survival. Stage III predicts a survival less than 50% for 10 years, and stage IV predicts a poor outcome, with 5-year survival less than 10%.

G. **Other thymic tumors**

Thymic carcinoids are rare neuroendocrine tumors in the anterior mediastinum. There is little to distinguish these tumors from thymomas clinically, and the diagnosis will often be made on a fully resected tumor that was thought to be a thymoma at the time of resection. These tumors have a wide range of malignancy that corresponds well to the histologic grade determined by atypia, necrosis, and mitotic rate. All thymic carcinoids appear to have malignant potential, prompting some authors to advocate renaming these tumors “neuroendocrine carcinoma of the thymus.” Thymic carcinoid tumors found in patients with multiple endocrine neoplasia type 1 (MEN1) account for 25% of reported cases.

H. **Conclusions**

Thymomas are unusual neoplasms with generally indolent courses even for patients with advanced disease. Principles of the surgical approach remain basic: complete median sternotomy, opening of both pleural sacs, total thymectomy including all normal thymus, extended resection in stage III patients, and excision of all pleural implants in Masaoka stage IVa patients. There should be no attempt made to identify or separate benign from malignant forms of thymoma based on histologic features, because in all likelihood, these tumors may all have malignant potential from inception. The different degrees of malignancy will correlate with histologic grading and clinical staging of the lesions. Tumors thought to be encapsulated without invasion on CT scan can be primarily excised. Tumors thought to be invasive, and very large tumors, should be first treated with chemotherapy and then resected. Postoperative radiotherapy should be applied according to the operative findings and the histopathology of the tumor.

V. **Mesothelioma**

A. **Presentation**

1. **Subjective.** Patients with malignant pleural mesothelioma often report a history of slowly progressive shortness of breath associated with chest pain. These two symptoms occur in more than 90% of all patients with malignant mesothelioma. Weight loss also is identified in approximately one third of the patients. Because of the nonspecific nature of the patient's symptoms, the interval from the onset of dyspnea to the diagnosis of mesothelioma is often longer than 3 months.
2. **Objective.** On physical examination, the patients have decreased breath sounds in the posterior aspect of the affected hemithorax. Occasionally patients with advanced disease may have palpable supraclavicular lymph nodes or a palpable chest wall mass. The remainder of the physical examination is often unremarkable.

B. **Workup and staging**

Radiographic evaluation begins with a posteroanterior (PA) and lateral chest radiograph. This study often demonstrates a unilateral pleural effusion. CT imaging confirms this effusion and frequently demonstrates diffuse pleural thickening with discrete pleura-based masses. CT imaging allows evaluation of the mediastinum for lymphadenopathy, as well as the liver and contralateral lung, which are the most frequent sites of metastases. MRI of the thorax does not appear to add any significant information not provided by CT imaging and therefore is used infrequently.

Direct pleural biopsy is the most accurate method for making the diagnosis of malignant mesothelioma. Although pleural fluid cytologic analysis is positive for malignancy in approximately 30% of patients, it is often difficult for the cytopathologist to differentiate poorly differentiated adenocarcinoma from mesothelioma. Video-assisted thoracoscopic surgical (VATS) drainage of the effusion with pleural biopsies provides the pathologist with adequate tissue for the diagnosis and characterization of this tumor. In addition, the surgeon can visually inspect the thorax for evidence of advanced disease that would preclude resection and allows pleurodesis to be performed to prevent a recurrent pleural effusion. In advanced disease, the pleural space is completely obliterated with tumor. In these cases, open pleural biopsy is performed by using a small posterolateral incision with resection of the underlying rib. The parietal pleura is then excised and sent to pathology for examination

C. **Staging**

One of the difficulties associated with identifying prognostic risk factors in patients with diffuse malignant pleural mesothelioma (DMPM) is the lack of an accurate, universally accepted staging system. The staging system initially used is the one proposed by Butchart. In this system, stage I disease defines tumor involving only ipsilateral pleura, lung, pericardium, and diaphragm. Stage II disease defines tumor invading chest wall or adjacent mediastinal structures and also includes patients with positive lymph nodes within the chest. Stage III disease defines tumor penetrating the diaphragm to involve the peritoneum, and also includes patients whose disease involves the contralateral chest or lymph nodes outside of the chest. Stage IV disease includes those patients with distant metastases. The staging system of Butchart was subsequently modified by Sugarbaker et al. in the following manner. Stage I represents patients with resectable disease and negative lymph nodes. Stage II represents patients with resectable disease with microscopically positive resection margins and intrapleural adenopathy. Stage III represents patients with extension of disease into peritoneum, chest wall, aorta, heart, or esophagus, and patients with extrapleural lymph node metastases (Butchart stages II and III). Stage IV continues to define patients with distant metastatic disease.

Recently the International Mesothelioma Interest Group (IMIG) proposed a new international staging system for DMPM (Table 23.5). This tumor (T), lymph node (N), and metastases (M) staging system includes T descriptors that are much more detailed than those in previous systems. In addition, the descriptors for nodal involvement are the same as those used in the staging of non–small cell lung cancer. With this new system, patients with DMPM were accurately staged according to prognosis. Median survival by stage was 35 months, 16 months, 11.5 months, and 5.9 months for stages I through IV, respectively. The difference in survival by tumor stage remained statistically significant when assessed with multivariate analysis. Based on these data, adoption of the IMIG staging system would allow more accurate comparison of results between groups treating patients with DMPM.

TABLE 23.5. STAGING SYSTEM PROPOSED BY THE INTERNATIONAL MESOTHELIOMA INTEREST GROUP (IMIG)

D. **Treatment**

The optimal management of patients with mesothelioma is influenced by the extent of tumor and the patient's underlying physiologic reserve. Therapeutic options include surgery, radiation therapy, and chemotherapy. The majority of patients receive multimodality therapy. Patients with adequate physiologic

reserve and early-stage disease (stage I or II) may be candidates for extrapleural pneumonectomy or pleurectomy and decortication. Extrapleural pneumonectomy describes the *en bloc* resection of the parietal pleura, lung, diaphragmatic pleura, and involved pericardium. The procedure begins with an extended posterolateral thoracotomy and resection of the sixth rib. The extrapleural plane between the parietal pleura and the endothoracic fascia is bluntly dissected under direct vision to the apex of the chest and inferiorly to the diaphragm. Careful dissection of the parietal pleura away from the esophagus and the aorta is required. Resection of the diaphragmatic pleura is then performed, mobilizing the pleura and lung centrally to the mediastinum. Involved pericardium is excised *en bloc* with the specimen. Finally, division of the main pulmonary artery, superior and inferior pulmonary veins, and the main-stem bronchus are performed to complete the pneumonectomy. The subcarinal and paratracheal lymph nodes are removed and sent to pathology for staging purposes. The diaphragmatic and pericardial defects are then reconstructed by using a Gore-Tex patch.

Pleurectomy and decortication involve the removal of all gross tumor from the parietal and visceral pleura surfaces with preservation of the lung. Resection of the parietal pleura is performed in a similar manner to that described for extrapleural pneumonectomy including the diaphragmatic pleura and the pericardium. The parietal pleura are opened, and the visceral pleural tumor is excised, often leaving a large raw surface of the lung parenchyma exposed. Specific attention is addressed to the pleural surfaces in the oblique and horizontal fissures. Reconstruction of the diaphragmatic and pericardial defects are performed by using a Gore-Tex patch.

The morbidity and mortality associated with extrapleural pneumonectomy are significant. The morbidity in most series approaches is 50%. The operative mortality ranges from 4% to 6% at institutions that frequently perform this procedure. Pleurectomy and decortication are associated with lower morbidity and mortality. Early recurrence of mesothelioma with surgery alone has led to the use of adjuvant therapy. Most patients have received adjuvant irradiation to the affected hemithorax, to a total dose ranging from 45 to 54 Gy. Other investigators have used trimodality therapy incorporating surgery, radiation therapy, and adjuvant chemotherapy with cisplatin, doxorubicin, and cyclophosphamide. Median survival for patients treated with aggressive multimodality therapy ranges from 15 to 19 months.

Patients with advanced disease who are not candidates for extrapleural pneumonectomy or pleurectomy and decortication are treated with chemotherapy. In addition to using cisplatin, doxorubicin, and cyclophosphamide, recent studies have suggested encouraging response rates with the antimetabolite agent gemcitabine. A phase II study from Australia reported a response rate of 48% in patients with malignant mesothelioma treated with a combination of cisplatin and gemcitabine (*J Clin Onco*l 1999;17:25–30). Single-agent vinorelbine has been reported to have a response rate of 24% in malignant mesothelioma (*J Clin Oncol* 2000;18:3912–3917). Early clinical trials involving the multitargeted antifolate pemetrexed (Alimta) have shown very encouraging results in patients with malignant mesothelioma. A multinational phase III study comparing Alimta and cisplatin with cisplatin alone in patients with malignant mesothelioma has recently been completed. In view of the high levels of expression of epidermal growth factor receptors (EGFRs) in malignant mesothelioma, a phase II study of ZD 1839, a compound that inhibits EGFR tyrosine kinase activity, is under way in the United States.

E. Epidemiology

Approximately 2,000 to 3,000 new cases of DMPM are diagnosed each year in the United States. Exposure to asbestos remains the greatest risk factor for the development of this disease. However, additional factors are likely to contribute to the development of this malignancy because approximately 20% of patients in whom DMPM develops have no history of asbestos exposure.

F. Prognosis

Regardless of its cause, the natural history of DMPM is one of locoregional progression of disease with the ultimate development of distant metastases. Despite aggressive multimodality therapy, the median survival of patients diagnosed with this disease ranges from 9 to 20 months. Apart from staging, other factors have been described to assess prognosis in these patients. These factors can be broadly grouped as clinical factors and pathologic factors (Table 23.6). Clinical factors associated with a favorable prognosis include (a) good performance status, (b) absence of chest pain, (c) long duration of symptoms, (d) age younger than 65 years, and (e) a normal platelet count. Surgical–pathologic factors include (a) epithelial histology, (b) early surgical–pathologic stage, and (c) complete resection. Although some of the clinical factors identified by univariate analysis lose their statistical significance when evaluated by multivariate analysis, they remain important because they often serve to identify patients with advanced disease who are unlikely to benefit from aggressive multimodality therapy.

Clinical Factors	Pathologic Factors
Good performance status	Epithelial histology
Absence of chest pain	Early surgical–pathologic stage
Long duration of symptoms	Complete resection
Age younger than 65 yr	
A normal platelet count	

TABLE 23.6. FAVORABLE CLINICAL AND PATHOLOGIC PROGNOSTIC FACTORS

G. Clinical factors

Many prognostic factors in mesothelioma have been identified by using retrospective analyses of large groups of patients with this disease including age, chest pain, duration of symptoms, gender, performance status, platelet count, presence of a pleural effusion, and weight loss. However, good performance status, absence of chest pain, long duration of symptoms, age younger than 65 years, and normal platelet count are the variables that have been associated with a favorable prognosis in multiple studies.

1. **Performance status.** Many studies have observed that patients with a performance status of less than or equal to 1, with the Eastern Cooperative Oncology Group (ECOG) scale (Table 23.7) at the time of initial presentation, have longer median survival times compared with patients with a score of greater than 1. Other investigators observed a median survival time of 16 months for patients with ECOG performance values of 0, and 10 months for patients with ECOG performance values of 1, compared with a median survival time of only 5 months for patients with ECOG performance values of 2. Similarly, a retrospective review of 337 patients with mesothelioma treated on investigational protocols sponsored by the Cancer and Leukemia Group B (CALGB) found that ECOG performance score at the time of diagnosis was an independent predictor of outcome in both univariate and multivariate analyses. In this study, patients with an ECOG performance score equal to 0 had a median survival time and 2-year survival of 13.9 months and 38%, respectively. In patients with a performance score of 1, the median survival time and 2-year survival decreased to 9.5 months and 21%, respectively.

Performance	Score
Fully active	0
Ambulatory	1
In bed <50% of the day	2
In bed >50% of the day	3
Fully bedridden	4

TABLE 23.7. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

2. **Chest pain.** The presence of chest pain in patients with pleural mesothelioma often suggests progression of disease through the parietal pleura and into the endothoracic fascia. In both univariate and multivariate analysis, Antman et al. found that patients with chest pain at the time of presentation had a shorter median survival than did those patients that presented without chest pain (10 vs. 17 months). This finding also was noted in the review of patients treated on protocols sponsored by the CALGB.
3. **Duration of symptoms.** In contrast to those many other malignancies, a long time interval (longer than 6 months) from the onset of symptoms to the time of diagnosis of pleural mesothelioma has been associated with a longer median survival in patients with this disease. This most likely reflects a less aggressive biology of the individual patient's tumor. Symptoms of longer than 6 months' duration were associated with a median survival of 12 months versus 8.7 months in patients with a duration of symptoms less than 6 months. This difference was significant in both univariate and multivariate analysis. Antman et al. also found in their multivariate analysis that a time interval of longer than 6 months was associated with a longer median survival compared with that of patients who presented within 6 months of the onset of symptoms. However, this is not a universal finding. In a retrospective review of 332 patients with diffuse malignant pleural mesothelioma, Ruffie et al. found no statistical difference in median survival between patients with symptoms of longer than 6 months' duration compared with symptoms of less than 6 months' duration (10.4 months vs. 8.4 months).
4. **Age.** Multiple studies have demonstrated that patients aged 65 years or younger with diffuse malignant pleural mesothelioma are noted to have a longer median survival compared with that of patients who are older than 65 years. Ruffie et al. found that patients aged 65 years or younger had a median survival of 10 months compared with 6 months in patients older than 65 years. This difference was significant in both univariate and multivariate analyses. In a separate review of 167 patients with diffuse malignant pleural mesothelioma, the authors noted a similar finding with median survivals of 12.0 months versus 8.1 months, respectively. Importantly, this latter study found a significantly worse prognosis in patients older than 74 years (median survival, 4.0 months), a finding also noted by other investigators. Two smaller series also suggested a better prognosis in younger patients. One study found a median survival of 15.0 months in 46 patients younger than 65 years compared with 10 months in 11 patients aged 65 years or older. In a separate review of 80 patients with diffuse malignant pleural mesothelioma, the authors noted a median survival of 19 months in patients younger than 65 years versus 11 months for patients aged 65 years or older. However, this trend did not achieve statistical significance in the multivariate analysis.
5. **Platelet count.** The importance of thrombocytosis (platelet count greater than 400,000/µL) as a prognostic variable in patients with diffuse malignant pleural mesothelioma has been demonstrated in multiple series. Patients with a platelet count greater than 400,000/µL had a significantly shorter median survival compared with patients whose platelet count was less than 400,000/µL. These differences were highly statistically significant by both univariate and multivariate analysis. The median survival of patients after surgical treatment for mesothelioma correlated with the preoperative platelet count. Patients with platelet counts greater than 462,000 had a significantly shorter median survival compared with patients whose platelet counts were less than 462,000. Patients with normal platelet counts (179,000 to 295,000) had the longest median survival. The Lung Cancer Study Group Trial, examining the role of extrapleural pneumonectomy in the treatment of diffuse malignant pleural mesothelioma, identified a platelet count greater than 400,000/µL as a significant prognostic factor in the univariate analysis; however, thrombocytosis did not retain statistical significance in the multivariate analysis.

H. **Pathologic factors**

1. **Histology.** According to the 1982 World Health Organization (WHO) typing of lung tumors, pleural mesotheliomas are classified into three categories: (a) epithelial, (b) sarcomatoid, and (c) mixed (biphasic). Several investigators have found that patients with epithelial tumors have a more favorable prognosis compared with patients whose tumors are classified as sarcomatoid or mixed, although this is not a universal finding. The exact reasons for the poor prognosis of sarcomatoid mesothelioma are not well understood; however, the presence of sarcomatoid malignant cells in the pleural biopsies of mixed tumors is associated with a significantly decreased median survival.

   A number of additional cellular markers have been examined in malignant mesothelioma. These markers include the oncogene Wilms tumor 1 (WT1), the tumor suppressor gene p53, the cell-proliferation markers proliferating cell nuclear antigen (PCNA) and Ki-67, and markers for angiogenesis such as thrombospondin-1 (TSP-1). Although these markers may give insight into the cellular processes associated with the development of malignant pleural mesothelioma, they do not serve as independent prognostic indicators in this disease.

2. **Surgical stage.** The importance of surgical stage as a prognostic variable in patients with malignant pleural mesothelioma has been confirmed in two large surgical series. Rusch and Venkatraman used the IMIG staging system in a series of 131 patients with diffuse pleural mesothelioma who were surgically explored. The majority of patients had stage III (44%) and stage IV (29%) disease. Analysis of the data demonstrated that the median survival of patients with stage I (35 months) and stage II (16 months) disease was significantly better when compared with that of patients with stage III (11.5 months) and stage IV (5.9 months) disease. In this series, 50% of patients undergoing mediastinal lymph node dissection were found to have N2 disease.

   The second series verifying the importance of surgical stage in the prognosis of patients with DMPM was reported by Sugarbaker et al. With the modified Butchart staging system, survival was significantly stratified by stage. Median survival intervals for patients with stage I, stage II, and stage III disease were 25, 20, and 16 months, respectively. Importantly, no patients with stage III disease survived longer than 30 months in this series.

3. **Completeness of resection.** Because of the diffuse infiltrative behavior of malignant pleural mesothelioma, complete resection of tumor with pathologically negative margins can be difficult to achieve. Contraindications to curative resection either by pleurectomy/decortication or by extrapleural pneumonectomy include (a) extension of tumor into the chest wall, (b) transdiaphragmatic extension of tumor into the peritoneum, (c) direct extension of tumor into one or more mediastinal organs or into the spine, and (d) extension of tumor through the pericardium with or without involvement of the myocardium. Identification of these contraindications to surgical resection often can be determined preoperatively by using CT and MRI of the thorax and upper abdomen.

   In many series, complete resection is defined as no gross residual tumor at the completion of the operation. However, Sugarbaker et al. performed a standardized pathologic analysis of each extrapleural pneumonectomy specimen to determine whether positive microscopic margins remained along the chest wall. In addition, the bronchus, pericardium, and diaphragm were examined for microscopic margins. In this series, univariate analysis demonstrated that patients with negative resection margins were noted to have prolonged 2-year and 5-year survivals (44%, 25%) compared with patients who had positive resection margins (33%, 9%). The importance of negative surgical margins as a prognostic variable remained statistically significant in the multivariate analysis.

I. **Conclusion**

The management of patients with diffuse pleural mesothelioma remains a challenge. Most patients are first seen with advanced disease and subsequently have a limited survival regardless of the treatment that they receive. However, certain subsets of patients have been shown to benefit from an aggressive multimodality treatment protocol combining extrapleural pneumonectomy, adjuvant radiotherapy, and adjuvant chemotherapy.

Based on this information, a thorough preoperative evaluation should be performed to stage the extent of disease carefully (Table 23.8). Histologic confirmation of the diagnosis of should be performed through open pleural biopsy, pleuroscopy, or VATS, being careful to position biopsy or port sites in the eventual posterolateral thoracotomy incision. Although the value of mediastinoscopy in this disease has not been independently demonstrated, the presence of mediastinal lymph node metastases is associated with poor survival. Therefore, pathologically staging these nodes before the initiation of extrapleural pneumonectomy would help to identify those patients most likely to benefit from this aggressive therapy. Combined-modality therapy including extrapleural pneumonectomy should most likely be reserved for patients with epithelial tumors, negative mediastinal lymph nodes, and disease that can be completely resected with extrapleural pneumonectomy. Patients with sarcomatous or mixed tumors or patients with metastatic mesothelioma in the mediastinal lymph nodes should be offered extrapleural pneumonectomy very selectively, if at all.

1. Epithelial histology
2. Absence of mediastinal lymph node metastases
3. Complete resection

TABLE 23.8. PROGNOSTIC FACTORS ASSOCIATED WITH PROLONGED SURVIVAL IN PATIENTS TREATED WITH COMBINED MULTIMODALITY THERAPY FOR DIFFUSE MALIGNANT PLEURAL MESOTHELIOMA

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CHAPTER 24. PAIN MANAGEMENT AND PALLIATIVE CARE

Gary Ratkin and Robert Swarm

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I. **Background.** The care of the cancer patient has traditionally focused on objective responses, survival, and ultimately cures as the most important outcomes. A change has occurred in the palliative-care model from symptom care primarily at the end of life or in hospice programs to a continuum of care throughout the course of the illness. The emphasis on symptom control and palliation throughout all stages of cancer is the new model of palliative care. Subjective symptoms and emotional distress should be managed while recognizing physical impairments and psychosocial influences in this new paradigm.

II. **Delivering bad news** can be one of the most difficult parts of caring for the cancer patient. Communicating with the patient the prognosis of the disease can be a difficult process. A useful approach is the use of the SPIKES protocol (Buckman R et al. *How to break bad news: a practical protocol for healthcare professionals.* Baltimore: Johns Hopkins University Press, 1993), which may be summarized as follows.

Setting: get the setting right for best communication. This should allow privacy. Participants may be seated. Allow comfortable body language and eye contact.

Perception: question the patient about what he or she perceives about the disease and the seriousness of his situation. Listen for clues from the patient of comprehension and vocabulary appropriate to patient's understanding. Note denial.

Invitation: find out what the patient wants to know. Some will desire a greater level of detail. Listen especially to the patient's request; family members may complicate preferences.

Knowledge: provide information starting at the patient's level of comprehension, using vocabulary that the patient can easily understand. Give information in small chunks, using simple language. Stop regularly to ask the patient if he or she understands.

Emotions: explore emotions and empathize with the patient: acknowledge all reactions and feelings.

Strategy and summary: summarize major areas discussed, asking if there are other important issues to discuss. Specify a clear contract for the next contact with the patient.

III. **The palliative care model.** In 1990 the World Health Organization stressed the need for a continuum of palliative with curative oncology management approaches. By integrating regular assessment and proactive care of symptoms into the management of all oncology patients, caregivers can improve the patient's quality of life, as well as responses to therapy and survival.

A. **Symptom history.** In taking a patient history and developing a palliative plan, consider a wide range of symptoms that may need treatment at various stages in the course of a cancer. Pain, fatigue, and anorexia are the most common symptoms due to cancer or its treatment. Other symptoms such as constipation, nausea, or insomnia may be due to the effects of cancer or to drugs used to treat pain or other symptoms.

B. **Multiple, simultaneous symptoms** experienced by the cancer patient require creative management. In a survey of 1,000 patients at a palliative care center, a median of 11 symptoms per patient was reported.

C. **General principles of palliative care management**

1. Assess and reassess the symptom: this allows **stepwise dose adjustment** or changes in medications
2. Discern the cause of a symptom to define the best approach to palliation.
3. Use **scheduled doses** of medications rather than as needed (prn) dosing.
4. **Use adjuncts** to analgesics to maximize pain relief.
5. Anticipate treating multiple symptoms per patient.
6. Treat concomitant **depression** and anxiety along with other symptoms.
7. Anticipate side effects of pain for other palliative therapies.
8. **Consult allied health professionals:** nurses, occupational and physical therapists, social workers, mental health workers, other physician specialists (e.g., anesthesiology, gastroenterology, pulmonary, radiation oncology) where appropriate to develop the palliative care plan.

D. **Develop a palliative care plan** to provide patients with comprehensive symptom care from the time of diagnosis to the end of life.

1. **Take a proactive approach** to pain management by taking a careful history of pain symptoms.
2. **Make creative choices** of drug therapy to cover multiple symptoms with fewer medications to minimize side effects of these therapies.
3. **Develop an integrated approach to outpatient or home care** for inpatients starting from the day of hospital admission.
4. **Understand patient wishes** in setting goals for palliative treatment. Patients may wish to involve their family and friends in their palliative plan, so good communication and a clear direction of care are needed.
5. **Written palliative care plans** can be helpful by highlighting a specific approach to one or more symptoms. An example of a palliative care worksheet is shown in Fig. 24.1.

FIG. 24.1. Symptom control or palliative care plan.

IV. **A comprehensive approach to pain management requires a thorough assessment of the pain history,** including pain intensity, duration, provoking and alleviating factors, radiation, etc. Analgesics should be chosen in a stepwise fashion, reassessing the patient for relief and side effects of therapy. Use of adjuvant therapies may provide better relief while minimizing the need for opioid analgesics (Table 24.1).

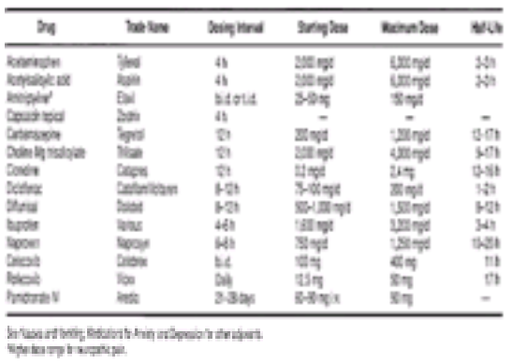

TABLE 24.1. ANALGESIC ADJUNCTS TO NARCOTIC THERAPY

A. **The pain history** should include a detailed description of the character of the pain. Is it sharp, burning, or dull, intermittent or constant? Describing the distribution of pain may help in differentiating neuropathic pain, such as that seen with dermatomal herpes zoster from plexopathies. The location of pain may help in determining a bony origin or symptoms due to hepatomegaly. Palliative treatment of each of these circumstances will differ accordingly.
   1. Patients should be queried about a previous history of pain and what drugs were effective or ineffective in his or her management.
   2. **Comorbid conditions** may influence the type of drug or dose of analgesic, especially in elderly patients. Patients with gastrointestinal disease may be prone to constipation, whereas patients with respiratory insufficiency may worsen their lung function with narcotic analgesics or sedatives.

B. **A pain-assessment scale,** with visual clues to help patients, family members, or health care staff is valuable. A card with a numeric scale (0 to 10) and happy to sad faces can be shown to the patient to allow quantitative measurement of a subjective symptom of pain.
   1. **Charting pain as a vital sign** facilitates reassessment and allows the best adjustment of pain therapy. Patients, family members, nursing staff, and physicians should be trained to score pain as routinely as pulse, blood pressure, temperature, and respiration rate. Documentation of pain as the fifth vital sign is becoming standard hospital practice.
   2. **Teaching outpatients** and their families to assess pain by using a numeric score facilitates communications with nurses and physicians to assist outpatient management. Regular documentation of pain scores and pain therapy is critical for outpatients as well as inpatients.

C. **Documentation of all narcotic (opioid) prescriptions** is required by regulatory agencies including federal and state drug-enforcement agencies. A written log in every patient's chart, such as the example, fulfills these requirements and aids in the adjustment of pain therapy.

D. **Pain therapy:** the World Health Organization analgesic ladder is a stepwise approach to pain therapy based on an assessment of the intensity of the patient's pain. In this schema, patients with less severe pain are managed with nonsteroidal antiinflammatory drugs (NSAIDs). Moderately severe *pain* may be managed with the addition of weak opioids, whereas more severe or uncontrolled pain is managed with the addition of strong opioid drugs. Adjuvant drugs may be added at any step as appropriate.

E. **Use of systemic analgesics**
   1. Opioids are most effective when given *around-the-clock* rather than prn.
   2. **Meperidine** has limited usefulness because it is poorly absorbed from the gastrointestinal tract, and even moderate doses can result in elevated levels of a toxic metabolite, normeperidine, and the risk of seizure. Severe reactions, after even a single dose, may occur in patients being treated with **monoamine oxidase (MAO) inhibitors,** including excitation, delirium, hyperpyrexia, convulsions, and death.
   3. **Consider the use of adjuncts** such as NSAIDs, antidepressants, or anxiolytic drugs.
   4. **Long-acting analgesics** (morphine sulfate, sustained release, 30 to 60 mg orally q8 to 12 hours, or oxycodone, sustained release, 10 to 20 mg orally twice daily) improve compliance.
      a. These agents should not be crushed. Patients unable to swallow pills may use morphine sulfate sustained release tablets (MS Contin) as a rectal suppository.
      b. Although short-acting, immediate-release preparations (morphine sulfate, immediate release, 15 to 30 mg q2 to 4 hours, oxycodone, 5 to 10 mg q4 to 6 hours) are used concomitantly for **breakthrough pain.** Choosing the same agent in long-acting and immediate-release forms may be helpful in adjusting doses to gauge total dose required in an average day.
   5. **Intractable pain** may require inpatient admission for parenteral opioids, with daily assessment of analgesic requirement. Morphine sulfate is started as a bolus dose (e.g., 1 to 2 mg i.v., q10 minutes), usually administered by a patient-controlled anesthesia (PCA) pump. The dose may then be titrated to achieve pain control and to determine the dose required to establish a basal infusion rate.
   6. **Naloxone,** two ampules i.v. (0.4 mg/ampule), should be available at the bedside when using a morphine drip in case of respiratory depression. However, narcotic reversal with naloxone may cause patients to experience extreme pain, and use should be carefully considered.
   7. **Laxatives** (senna tablets, one to two orally twice daily, or lactulose syrup, 15 to 30 mL orally q12 hours) should be begun together with opioid medications because of the incidence of constipation. Table 24.2 lists additional laxatives that may be useful in the management of constipation.

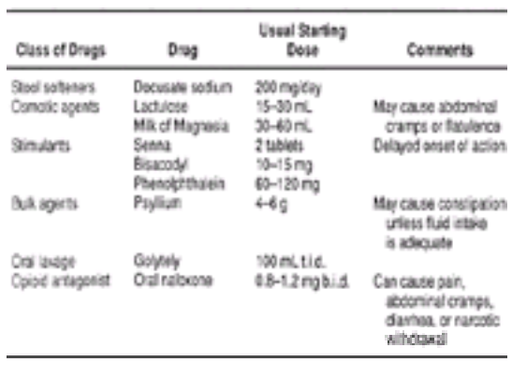

TABLE 24.2. LAXATIVES AND STOOL SOFTENERS

8. **Equipotent analgesic doses** of various narcotic analgesics available are listed in Table 24.3 for comparison.

Drug	Trade Name	i.m./i.v. Dose	p.o. Dose	Duration (h)	Half-Life (h)
Codeine	Various	130 mg	200 mg	3–4	3
Hydrocodone	Various	—	30 mg	3–4	4
Hydromorphone	Dilaudid	1.5 mg	7.5 mg	4–5	2–3
Levorphanol	Levo-Dromoran	2 mg	4 mg	4–6	12–16
Methadone	Various	10 mg	20 mg	4–6	15–30
Morphine	Various	10 mg	30 mg	4–6	2–3.5
Oxycodone	Various	—	30 mg	3–4	3
Oxymorphone	Numorphan	1 mg	—	4–6	2–3

Transdermal fentanyl (Duragesic 72-h patch) 100 μg/h ≈ morphine 2–4 mg/h i.v.
This table is intended to show comparative doses of narcotic analgesics (i.e., morphine, 10 mg i.v. is considered equipotent to morphine, 30 mg p.o., or codeine, 200 mg p.o.

TABLE 24.3. EQUIPOTENT ANALGESIC DRUG DOSES

9. **Combination analgesics** listed in Table 24.4 include opioids with an NSAID or acetaminophen. Although these are widely used, keep in mind that toxic doses of acetaminophen can be inadvertently given if six to eight tablets a day are administered. **Oxycodone** is available in a short-acting form with aspirin or acetaminophen or as a single agent in both immediate-release and sustained-release forms, increasing the usefulness of this agent in patients with more severe pain.

Trade Name	Narcotic	Nonnarcotic
Tylenol #3	Codeine, 30 mg	Acetaminophen, 300 mg
Tylenol #4	Codeine, 60 mg	Acetaminophen, 300 mg
Tylox, Roxilox, Roxicet	Oxycodone, 5 mg	Acetaminophen, 500 mg
Percocet 5/325	Oxycodone, 5 mg	Acetaminophen, 325 mg
Percodan	Oxycodone, 5 mg	Aspirin, 325 mg
Lortab 2.5/500	Hydrocodone, 2.5 mg	Acetaminophen, 500 mg
Lortab 5/500	Hydrocodone, 5 mg	Acetaminophen, 500 mg
Lortab ASA	Hydrocodone, 5 mg	Aspirin, 500 mg
Vicodin	Hydrocodone, 5 mg	Acetaminophen, 500 mg
Vicoprofen	Hydrocodone, 7.5 mg	Ibuprofen, 200 mg
Wygesic	Propoxyphene, 65 mg	Acetaminophen, 650 mg
Darvocet-N 100	Propoxyphene, 100 mg	Acetaminophen, 650 mg

TABLE 24.4. CONTENT OF COMBINATION ANALGESIC TABLETS

10. **Fentanyl** transdermal patches may provide an attractive option for patients unable to swallow pills. Initial dose is a 25- to 50-μg/hour patch applied to the skin every 72 hours. The dose may be increased slowly to titrate to optimal pain control.
    a. Some patients will note better pain control during the first 48 hours, and the patches may need to be replaced more frequently in these patients.
    b. Patients who are cachectic or are experiencing night sweats may have poor absorption of the medication.
    c. A form of fentanyl lollipop (Actiq), absorbed through the oral mucosa, may be used for breakthrough pain.
11. **Sedation** is common with opioid analgesic use. If sedation persists for more than a day or two, other central nervous system depressants may need to be discontinued. If pain control is adequate, doses may need to be reduced approximately 25%.
    a. If dose reduction is not possible, consider adding a psychostimulant such as methylphenidate (Ritalin; 5 to 10 mg, 2 to 3 times a day), or pemoline (Cylert R; 18.75 mg daily).
    b. Adding a nonnarcotic adjuvant drug may allow dose reduction of the opioid to reduce sedation.
    c. Administration of opioids through an **intraspinal** route or other anesthetic techniques may allow adequate pain control without sedation.
    d. **Anticonvulsants** such as carbamazepine (Tegretol; 100 mg twice daily) or gabapentin (Neurontin; 300 mg thrice daily) may be used for neurogenic pain such as the syndrome due to brachial plexopathy.
12. **Antidepressants** such as amitriptyline, 50 to 100 mg (Elavil) daily may be helpful in postherpetic neuralgia and other neurogenic pain.
13. **NSAIDs** may prove particularly useful in patients with bone pain, alone or in combination with opioids.
    a. Gastrointestinal side effects may be less with selective cyclooxygenase 2 (COX-2) inhibitors, celecoxib (Celebrex; 100 mg twice daily) or rofecoxib (Vioxx; 12.5 mg daily).
    b. Renal insufficiency can be a problem with all NSAIDs, whereas qualitative platelet dysfunction may be a potential problem with nonselective COX inhibitors.
14. **Bisphosphonates:** pamidronate (90 mg i.v. over 90 minutes every 4 weeks) has demonstrated improvement in bone pain in multiple myeloma and metastatic breast cancer patients.

F. **Special techniques for management of resistant cancer pain**

Systemic opioid analgesics have efficacy in a wide variety of clinical pain problems, whereas anesthetic techniques for cancer pain management are useful pain-management therapies with specific indications. The etiology of pain must be known so that the appropriate technique can be selected; therefore radiographic or other diagnostic evaluations may be necessary. When these techniques are needed, it may be best to consult pain-management specialists or others with specific expertise in the clinical use of these procedures. In general, therapies dependent on neuraxial or regional injection techniques are contraindicated in the setting of sepsis, localized infection at the injection site, and/or abnormalities in coagulation or platelet function.

1. **Spinal administration of analgesics** delivers medication more potently to the spinal cord to enhance analgesic efficacy and minimize systemic (brain) adverse effects. Spinal analgesics may be indicated when (a) systemic analgesics fail to control pain adequately or (b) are associated with unacceptable side effects (especially sedation). Spinal analgesics (opioids, local anesthetics, and/or clonidine) are used singly or in combination for either subarachnoid or epidural administration (*Neural blockade in clinical anesthesia and management of pain.* 3rd ed. Philadelphia: Lippincott-Raven, 1998:915–983).
    a. **Spinal opioids** (especially morphine, hydromorphone) have significantly increased potency; 100 mg per day i.v. morphine is roughly equivalent to 10 mg per day epidural morphine, which is roughly equivalent to 1 mg per day subarachnoid morphine; however, actual doses must be titrated to effect. Fentanyl, because of its high lipid solubility, has rapid systemic absorption after spinal administration; therefore spinal administration of fentanyl may have little advantage over systemic administration. Adverse effects of spinal opioids may include sedation, respiratory depression (onset may be delayed for several hours), constipation, nausea, pruritus, peripheral edema, and urinary retention. Exceptionally high doses of spinal opioids may result in myoclonic jerks or even diffuse muscle rigidity (*J Pain Symptom Manage* 2000;20:12).
    b. **Spinal administration of local anesthetics** (bupivacaine, lidocaine) may markedly decrease pain without sedation or many other of the potential adverse effects associated with opioid analgesics. After epidural administration of low doses of local anesthetic, but less consistently with subarachnoid administration, pain relief may be obtained without significant motor blockade or extremity weakness. Hypotension (especially orthostatic hypotension), extremity weakness, and urinary retention are the most common side effects of spinal local anesthetic administration for pain control.
    c. **Clonidine** has analgesic efficacy after epidural or subarachnoid administration, through action at spinal α_2-adrenergic receptors. The epidural administration of combined opioid, local anesthetic, and clonidine is an especially potent analgesic therapy. Adverse effects of spinal clonidine administration may include hypotension (especially orthostatic hypotension), bradycardia (with worsening of preexisting congestive heart failure), and sedation.
    d. Factors contributing to the **selection of subarachnoid versus epidural routes of administration** include (*Reg Anesth Pain Med* 1999;24:74) the following.
        1. **Anticipated duration of analgesic therapy.** For short-term analgesic use (several days to a month or two), epidural systems may be preferred because of lower initial device cost. With longer-term use, the risk of infection of epidural catheter systems is 10% to 20% or higher, whereas the risk of infection with totally implanted subarachnoid infusion pumps is less than 1%.
        2. **Anticipated need for local anesthetic.** Sharp, severe, somatic pain and/or episodic pain (e.g., pathologic fracture) may require the use of spinal local anesthetic. The therapeutic goal of pain relief without extremity motor blockade may be more readily achieved with epidural than with subarachnoid administration.

3. **Logistic support for analgesic therapy.** Initiation of spinal analgesic therapy is indicated only if sufficient follow-up support is available. Epidural systems will require an external infusion pump and will likely need ongoing home health/nursing support. Implanted, computer-controlled spinal infusion pumps require percutaneous refill only every 30 to 90 days, but refills and dose adjustments require the use of a dedicated programming device (*Reg Anesth Pain Med* 2000;25:117).

2. **Vertebroplasty** is the percutaneous injection of bone cement (methylmethacrylate) into vertebral bodies affected by compression fractures due to metastatic tumor, destructive vertebral hemangiomas, or osteoporosis. Vertebroplasty can be highly effective in control of pain from vertebral compression fractures, resulting in good control of pain in 80% to 90% of patients with pain from osteoporotic compression fractures and in 50% to 60% of patients with pain from compression fractures of metastatic origin. Thorough radiographic evaluation [including computed tomography (CT) or magnetic resonance imaging (MRI) of involved spinal segments] is essential before vertebroplasty to determine the integrity of the remaining portions of the vertebral body, spinal stability, and the degree of spinal canal stenosis or other neuraxial compromise. Potential adverse effects of vertebroplasty include spread of unhardened cement beyond the vertebral body, most often via venous embolization to epidural veins or the vena cava. Spread of cement (which hardens within minutes) to the spinal canal can cause significant neural injury. Vertebroplasty need not delay treatment of spinal metastases with radiation therapy, but may provide rapid onset of pain relief, which may facilitate the use of appropriate antitumor therapies (*Radiol Clin North Am* 1998;36:533).
3. **Neurolytic neural blockade** should be considered for patients with terminal disease in whom pain that is poorly responsive to less-invasive therapies is localized to a particular region of the body. In appropriately selected patients, 60% to 80% can have good to excellent control of pain with some neurolytic techniques (*Oxford textbook of palliative medicine.* 2nd ed. Oxford: Oxford University Press, 1998:390–414).
   a. **Subarachnoid neurolysis** may be considered in terminal illness when pain is limited to a few spinal dermatomes. The goal of this intervention is to interrupt the neural transmission of pain to the spinal cord by localized chemical rhizotomy. Careful attention to injection technique and patient positioning serves to limit the spread of neurolytic solution to intended spinal segments. Subarachnoid neurolytic blocks are best used for (a) perineal ("saddle area") pain, in patients with colostomy/ileostomy and urinary drainage (due to risk of bowel and/or bladder incontinence after "saddle block"), or (b) unilateral somatic pain of the chest wall or trunk (e.g., locally invasive chest wall tumors such as mesothelioma). From 50% to 60% of appropriately selected patients with otherwise poorly controlled pain can achieve good pain control with these techniques. Generally, unintended neural destruction can be avoided so that normal functioning of the extremities is preserved. The risk of significant complication (1% to 14%) may be acceptable in the context of intractable pain in terminal illness, but generally precludes the use of subarachnoid neurolysis in other clinical settings.
   b. **Neurolytic celiac plexus block,** the most commonly performed neurolytic technique for management of cancer-related pain, is indicated for the management of upper abdominal visceral pain from pancreatic or other upper abdominal malignancy. Celiac plexus block is a reasonable consideration in any person with significant visceral pain of malignant origin, especially if pain is not adequately controlled with systemic analgesics, or if use of such analgesics is associated with adverse effect (e.g., sedation, constipation, and/or nausea). Up to 85% of appropriately selected patients report good to excellent pain relief after neurolytic celiac plexus block. The side effects of orthostatic hypertension and increased frequency of bowel movements (diarrhea) transiently affect the majority of persons after neurolytic celiac plexus block, but only 1% to 2% require long-term medical management of these symptoms. Significant neural damage or paralysis is a rare but devastating complication of celiac plexus block that generally precludes the use of this technique in nonterminal illness. The risk of paralysis may cause some patients to decide against celiac plexus block, but to others, the potential for good-to-excellent pain relief (75% to 85%) that may be associated with improvements in constipation, nausea, and general sense of well-being outweighs the risk of paralysis (0.1%).
   c. Hypogastric plexus block may be an effective technique for management of visceral pain from pelvic malignancy. Its use is not significantly associated with extremity weakness, but ejaculatory failure/ anorgasmia is a potential adverse effect. Neurolytic hypogastric plexus block is not likely to provide good pain control if there is tumor invasion of somatic or neural structures.
4. **The management of intractable pain** not responsive to prior intervention must begin with thorough patient evaluation (history, physical examination) to identify additional, treatable causes of pain. Especially if systemic analgesics fail to control pain, it is necessary to identify the etiology of pain (if possible) so that clear decisions can be made as to its management.
   a. **Neurosurgical techniques** for pain control are rarely used, but are potentially powerful tools in the management of resistant pain. Spinal cord procedures (e.g., cordotomy) and even brain surgeries (e.g., cingulotomy) may be of real benefit in management of intractable pain. Especially for unilateral lower body or lower extremity pain, in the setting of terminal illness, percutaneous cordotomy (done with CT or fluoroscopic imaging) may provide remarkable control of previously intractable pain. Neurosurgical techniques for pain control are not commonly used; however, where such techniques are available, they have an important role in pain management (*Oxford textbook of palliative medicine.* 2nd ed. Oxford: Oxford University Press, 1998:414–421).
   b. **Management of refractory pain and/or other symptoms of terminal illness.** In the last hours to days of life, in some people who are dying, severe symptoms such as intractable pain, dyspnea, delirium, and/or emesis develop (e.g., fecal emesis due to distal bowel obstruction beyond surgical intervention). These symptoms may persist despite best efforts at management. If such symptoms are truly intolerable to the patient, but would be refractory to further acceptable efforts at palliative intervention, consideration should be given to alleviation of distress through administration of sedatives. When needed, sedatives should be offered to the patient (and discussed with family members, as possible) as part of ongoing supportive care. Such terminal palliative sedation is appropriate only for people who are dying, and should be considered only for those who have requested not to be resuscitated ("no code") in the event of cardiac/respiratory arrest (*J Palliat Care* 1994;10:31). Benzodiazepines (diazepam, 5 to 10 mg p.o., 2 mg i.v. q2 hours, prn), barbiturates (thiopental infusion, 0.5 mg/kg i.v. loading dose, followed by 0.25 to 0.5 mg/kg/hour i.v. infusion), or neuroleptic sedatives (haloperidol, 1 to 4 mg i.v./p.o. q1 hour, prn) may be titrated to good effect to ease suffering from otherwise intractable symptoms (*N Engl J Med* 1992;327:1678). These drugs generally have long elimination half-lives and will accumulate to steady-state level over a few days. The use of palliative terminal sedation to provide a dying person relief from intractable, intolerable suffering is firmly within the realm of good, supportive palliative care and should not be confused with euthanasia (*South Med J* 1991;84:332).

V. **Respiratory symptoms**
   A. **Dyspnea** is present in 50% of cancer patients and can be one of the most frightening symptoms experienced. Lung cancer, pulmonary metastases, and pleural or pericardial effusions are causes of dyspnea directly attributable to cancer. Anemia, congestive heart failure, and renal insufficiency due to the effects or cancer, chemotherapy, or radiation can produce similar symptoms.
      1. Prednisone, 60 mg orally daily and bronchodilators may give transient relief of dyspnea due to pulmonary infiltration with cancer.
      2. **Thoracentesis** may relieve symptoms of dyspnea due to pleural effusion. These results may be temporary if fluid repeatedly accumulates. Measures to sclerose the pleural space to prevent reaccumulation of fluid produce more durable results.
      3. **Malignant pericardial effusion** may result in tamponade and symptoms of dyspnea. Pericardiocentesis and sclerosis or surgical placement of a pericardial window may relieve symptoms.
   B. **Intractable cough** is not only annoying but also can contribute to a patient's weakness and inability to eat. It may be associated with hoarseness in patients with mediastinal involvement impinging on the recurrent laryngeal nerve.
      1. **Cough suppressants** often include narcotics. There is no advantage to codeine over other narcotics that may be used for pain relief. Long-acting formulations of morphine or oxycodone may be better for relieving cough.
      2. **Benzonatate** (Tessalon Perles, 100 to 200 mg orally q8 hours) is a nonnarcotic antitussive related to anesthetic agents. It is swallowed whole to anesthetize stretch receptors in the airways, reducing the cough reflex without suppressing the respiratory center in the brain.
      3. **Dextromethorphan** (available in many preparations combined with mucolytic agents) is the *d* isomer of the codeine analogue levorphanol and acts centrally to elevate the threshold for coughing without analgesic or addictive properties.
      4. Excessive mucus production can worsen cough and dyspnea. Expectorants such as guaifenesin (contained in many prescription and over-the-counter cough preparations) can be useful in treatment of cough.
      5. Corticosteroid therapy may also help control cough.

VI. **Gastrointestinal symptoms**
   A. **Nausea and vomiting** may be a symptom of many cancers or metastases. Gastrointestinal symptoms can occur as a result of chemotherapy or radiation and are some of the most feared side effects of treatment. Recent progress in the pathophysiology of nausea and emesis has promoted the development of new drugs to prevent or treat nausea. Table 24.5 lists clinical approaches and antiemetic agents that are useful in countering nausea and vomiting.

TABLE 24.5. CLINICAL APPROACHES AND ANTIEMETIC AGENTS THAT ARE USEFUL IN COUNTERING NAUSEA AND VOMITING

1. Use antiemetics on a scheduled basis for nausea or vomiting due to cancer.
2. Treat pain or anxiety with specific therapy; nausea control may follow.
3. Use intramuscular antiemetics only if no i.v. access is available.

B. **Nutritional support.** Anorexia and resultant cachexia are recognized as a common problem in cancer management. Providing adequate nutrition to a patient under treatment can be one of the most difficult supportive tasks in allowing a patient to maintain an adequate quality of life during chemotherapy or radiation. This complex of symptoms is as limiting to a patient's quality of life as are pain and other symptoms. Table 24.6 lists the goals of nutritional management and specific techniques that might be useful in patients undergoing cancer therapy or palliative support. Although enteral feedings using a percutaneous endoscopic gastrostomy (PEG) or Dobhoff nasogastric tube can be valuable in supporting a patient who cannot swallow enough nutritional material to sustain, parenteral nutrition is beyond the scope of this manual because of ethical and financial considerations. A progestational hormone, megestrol acetate (Megace; 160 to 800 mg/day) is often useful in stimulating an appetite. Another approach is to use a cannabis extract, dronabinol (Marinol; 2.5 mg b.i.d. with lunch and supper) to counter anorexia or nausea associated with cancer or chemotherapy.

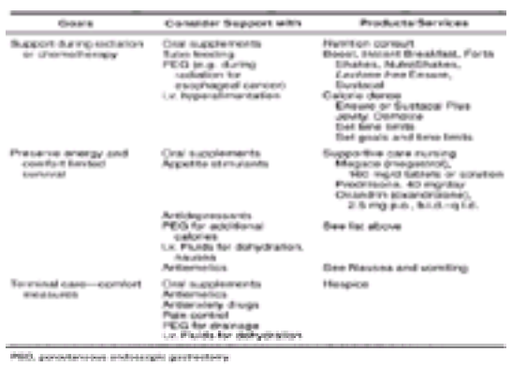

TABLE 24.6. NUTRITIONAL MANAGEMENT OF THE CANCER PATIENT

VII. Fatigue

Fatigue, the decreased capacity to maintain performance, is being recognized as one of the most common symptoms in patient surveys. Lassitude or fatigue can be a systemic symptom of the cancer, paraneoplastic complications, chemotherapy, or radiation therapy. It is important to consider the possible etiology of fatigue in developing a treatment strategy, as listed in Table 24.7.

TABLE 24.7. MANAGEMENT OF FATIGUE

A. **Erythropoietin** (Procrit) injections can be valuable in correcting the anemia that occurs with cancer treatments or in selected hematologic conditions, with improvement in fatigue as well.
B. **Planning daily activities** and scheduled physical exercise such as walking or weight training can be helpful in managing fatigue without pharmacologic intervention.

VIII. Psychologic distress and end-of-life care

Psychological distress may occur in many cancer patients. The symptoms of sleep disturbance, anxiety, and depression may require pharmacologic measures to allow a patient to cope and to return to a near-normal level of function and improve quality of life, as listed in Table 24.8. Behavioral modification or psychiatric consultation may be helpful in managing patients requiring combinations of psychoactive drugs.

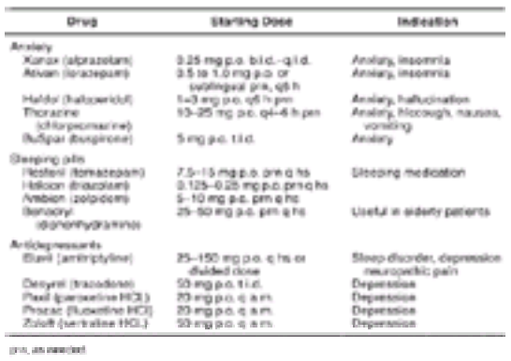

TABLE 24.8. MEDICATIONS TO TREAT ANXIETY OR DEPRESSION

End-of-life care has been the proving ground for palliative medicine. As we communicate with patients and their families about their cancer and palliation, basic decisions about the direction of care are important to discuss and document. The following legal documents or negotiations may need to be discussed with the patient and/or family. The laws of each state determine the exact form and power of each of these documents. It is important to understand the legal standing of any of these decisions in the state in which the patient is receiving the health care.

A. **The living will** is a form of a health care directive that allows an individual to place limits on extraordinary measures of life support in advance.
B. **Viatical settlements** allow prepayment of a percentage of the face value of a patient's life insurance policy when a physician deems the patient “terminal.”
C. **Health care directives** are legal documents in which a patient can list specific treatments, including life-support measures, he or she prefers not to receive, such as mechanical ventilation or tube feedings.
D. **Durable power of attorney for health care** is a legal document that specifies who should make end-of-life or palliative cares decisions in the event the patient is incapacitated.
E. **Hospice services** are available today in all communities and are provided by hospital-based or community programs. Nurses and other health care workers in hospice programs are usually expert in outpatient palliative care. Regular communication with these hospice professionals can be valuable resource to assess symptoms and facilitate changes in symptom management. Patients who enter hospice programs typically do not receive cancer treatments because the emphasis is on the control of pain and other symptoms. To qualify for most hospice programs, the patient must be terminally ill and have a life expectancy of less than 6 months.

SUGGESTED READINGS

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CHAPTER 25. COAGULATION DISORDERS IN CANCER

Morey A. Blinder and Rajesh Behl

Introduction
Venous thromboembolism in cancer
Venous thromboembolism as a sign of occult malignancy
Hypercoagulability in patients with cancer
Clinical and laboratory diagnosis of venous thromboembolism
Prophylaxis against venous thromboembolism
Treatment of venous thromboembolism
Syndromes of intravascular coagulation
Disseminated intravascular coagulation
Nonbacterial endocarditis and arterial thromboembolism
Thrombotic microangiopathy associated with cancer
Clinical findings and pathogenesis
Treatment of thrombotic microangiopathy
Hemorrhagic complications associated with malignancy
Thrombocytopenia
Coagulation factor deficiency

I. Introduction

The association between hemostatic abnormalities and cancer has been known since Trousseau observed migratory thrombophlebitis in patients with cancer in the nineteenth century. Thromboembolic disease, disseminated intravascular coagulation (DIC), thrombotic microangiopathy (TMA), and hemorrhage may occur in cancer patients, complicating the clinical course and occasionally hampering additional cancer treatment. The incidence of venous thromboembolism (VTE) in patients with cancer is substantial. For example, it is estimated that approximately 10% of stage 2 breast cancer patients, 10% to 20% of patients with visceral malignancy, and an even higher percentage of patients undergoing surgery or with an indwelling venous-access device will develop VTE in the absence of prophylactic anticoagulants. Therapeutic approaches have evolved substantially because of an increased awareness of thrombotic risk, early diagnosis of thromboembolic events, and the coincident development of new anticoagulants. DIC is a common syndrome of complex pathogenesis that occurs in a variety of settings. It is estimated to complicate the course in 10% to15% of patients with mucin-producing adenocarcinoma. Thrombotic microangiopathy also has received much attention recently as a disease state and may be the result of endothelial damage from cancer, a pharmacologic agent, or marrow transplantation. In allogeneic bone marrow or stem cell transplantation, TMA is estimated to occur in up to 5% of patients. Bleeding disorders primarily due to thrombocytopenia remains a common feature from the use of cytotoxic chemotherapeutic agents and at times may exceed blood bank resources in providing adequate transfusion support. Other bleeding disorders such as an acquired factor deficiency are uncommon but potentially serious complications of malignancy that may be difficult to identify and treat. We discuss the diagnostic and therapeutic implications of each of these coagulation disorders in patients with cancer

II. Venous thromboembolism in cancer

A. Venous thromboembolism as a sign of occult malignancy

A symptomatic deep venous thrombosis (DVT) or pulmonary embolism is the presenting finding in 5% to 10% of patients diagnosed with a malignancy, discovered by routine investigation at the same time. By comparison, in patients with a prior VTE, a recurrent thrombotic event is not likely to be associated with a concomitant cancer. In patients with an idiopathic VTE, in which the diagnosis of cancer is not overt, the risk of diagnosing a malignancy over the next few years remains substantial. Estimates predict that from 4% to 14% of patients with VTE will develop a cancer over the next 2 years. Visceral adenocarcinomas of the pancreas, lung, breast, ovary, and prostate seem to be most prevalent in these circumstances. Cancer diagnosed within a year of a VTE generally has a poor prognosis with a high risk of metastasis at the time of diagnosis. Defining the appropriate cancer screening in patients with idiopathic VTE has been difficult, but the general recommendations include a medical history, physical examination including digital rectal examination for occult blood, screening laboratory studies (complete blood count, liver and kidney function tests, and urinalysis), and a chest radiograph. Age- and gender-appropriate testing including mammography, Papanicolaou (Pap) smear, testicular examination, prostate-specific antigen (PSA) and carcinoembryonic antigen (CEA) determination, computed tomography (CT) scanning, and colonoscopy also should be considered. A small number of patients may benefit from curative or palliative surgery, although there is no proven impact on life expectancy (*Thromb Res* 2001;102:187–194).

B. Hypercoagulability in patients with cancer

A number of biochemical alterations that occur in malignant cells are thought to lead to an increased risk of thrombosis. Tissue factor and other direct activators of the coagulation cascade are expressed on the surface of tumor cells, which may directly lead to a fibrin clot. In addition, tumor cell interaction with other host cells such as monocytes, platelets, and endothelium also increase procoagulant activities by a variety of mechanisms. Pharmacologic agents and radiation therapy also may play a role in the development of a hypercoagulable state by the release of procoagulants and cytokines from damaged cancer cells, endothelial cell toxicity, or a decrease of physiologic anticoagulants. A number of biochemical assays detecting activation of the hemostatic system in cancer, including markers of activation of the coagulation cascade, endothelial injury, and platelet aggregation, have been described but at present are generally not used in the clinical setting (*Haemostasis* 1998;28:50–60). In contrast, the role of inherited molecular defects known to be thrombotic risk factors in the general population such as the factor V Leiden mutation are not likely to play a significant role in assessing risk for a hypercoagulable state in cancer patients. Under most circumstances, testing for these risk factors is unlikely to alter the therapeutic approach.

C. Clinical and laboratory diagnosis of venous thromboembolism

The clinical signs and symptoms of VTE are nonspecific and particularly unreliable when other complications of cancer occur, so that laboratory testing is typically needed to confirm the diagnosis. Duplex ultrasonography is noninvasive and accurate, with a sensitivity and specificity of 95% or more for the diagnosis of a lower-extremity DVT. This has replaced contrast venography under most circumstances. Ultrasound also is effective in evaluating the venous circulation in the upper extremity and jugular system but is not useful for the diagnosis of a thrombosis of the intrathoracic vessels. The diagnosis of pulmonary embolism has typically been made by ventilation/perfusion lung scanning, but the predictive value of this test is not ideal. Spiral CT scan has proven reliable for diagnosing emboli in central pulmonary arteries but less so in detecting thrombosis in smaller subsegmental vessel. However, a spiral CT also may be of benefit in detecting other lung abnormalities such as metastatic disease. Pulmonary angiography remains the definitive approach for the diagnosis of pulmonary emboli and should be considered if the diagnosis is in doubt (*Oncology* 2000;14:409–421). A marker of fibrin polymerization, D-dimer, has been helpful in excluding the diagnosis of venous thromboembolism in patients without cancer in whom this test is negative. However, in patients with a malignancy, a negative result has not proven as reliable to exclude the diagnosis of DVT, so that about 20% of patients with a negative result have a thrombosis diagnosed by other means. This suggests that other mechanisms leading to thrombosis such as platelet aggregation are likely to have occurred (*Ann Intern Med* 1999;131:417–422).

D. Prophylaxis against venous thromboembolism

1. **Perioperative setting.** The postoperative risk of DVT in the absence of prophylactic anticoagulation is exceedingly high. For example, 20% to 50% of cancer patients undergoing general surgery develop symptomatic DVT without anticoagulant prophylaxis. Several pharmacologic and mechanical approaches to the prevention of a DVT have proven effective. Intermittent pneumatic calf compression decreases the incidence of DVT in patients undergoing surgery and is without significant bleeding risk. Unfractionated heparin, 5,000 IU s.q., given 2 hours before surgery and repeated every 8 to 12 hours for 7 to 10 days, is effective in reducing the risk of a proximal DVT to about 5%. The risk of major bleeding is estimated to be 5% to 10%, and a significant portion of this is due to wound hematomas. Recently low-molecular-weight heparin (LMWH; dalteparin, 2,500 to 5,000 U s.q. qd, or enoxaparin, 40 mg s.q. qd) have also proven effective, and the risk of major bleeding appears to be low. Comparisons between heparin and LMWH suggest a modest increased benefit in VTE prevention by using LMWH with no increased bleeding risk (*Haemostasis* 1998;28:61–65).
2. **Associated with hormonal therapy or chemotherapy.** The risk of thromboembolism in patients receiving hormonal agents or chemotherapy is high,

particularly in patients being treated for breast cancer. Low-dose warfarin with a target international normalized ratio (INR) of 1.3 to 1.9 has proven effective in reducing the incidence of a DVT in breast cancer patients receiving chemotherapy as either adjuvant or metastatic treatment compared with placebo (*Lancet* 1994;343:886–889). Although not so well defined, LMWH (dalteparin, 5,000 U s.q. qd, or enoxaparin, 40 mg s.q., qd) is likely to be effective in this situation as well. Treatment with L-asparaginase, in particular, also is associated with a high risk of venous thrombosis, particularly in the intracerebral circulation. This appears to be accentuated by a decrease in antithrombin III (ATIII) activity, but the prophylactic administration of ATIII concentrate has not been proven to affect clinical outcome.

3. **Indwelling venous-access device.** Establishing long-term venous access in patients with malignancy to facilitate additional cancer treatment has become widespread and is clearly associated with an increased risk of a localized upper-extremity venous thrombosis. The role of factor V Leiden in predicting patients at increased thrombotic risk in this situation is not clear, but this does not seem to be a potent risk factor. Warfarin, 1 mg p.o. daily, is safe and effective in preventing thrombosis in patients with an indwelling central venous catheter device, with the thrombotic risk decreased by about 75% compared with placebo (*Haemostasis* 1998;28:61–65). Similarly, LMWH (e.g., dalteparin, 2,500 U s.q. qd) significantly decreases catheter-related thrombosis compared with that in an untreated group, so that either method of anticoagulation is considered effective.

E. **Treatment of venous thromboembolism**

1. **Initial anticoagulant therapy.** Most patients with venous thromboembolism should be treated with either unfractionated heparin or LMWH. Unfractionated heparin has been the mainstay of therapy for decades. At present, unfractionated heparin is usually dosed based on the patient's weight and a dosing nomogram. A frequently used initial dose of 80 U/kg body weight i.v. bolus followed by 18 U/kg/hour continuous i.v. infusion typically results in patients reaching a therapeutic threshold within 24 hours. Although other approaches to monitoring have been advocated, the heparin infusion rate is usually adjusted to maintain the activated partial thromboplastin time (aPTT) at 1.5 to 2.5 times the upper limit of the laboratory control. Several LMWHs also are available for the initial treatment of VTE. Therapeutic doses of LMWH are higher than the doses used for thrombosis prevention. Dalteparin, 200 U/kg s.q. qd, and tinzaparin, 175 U/kg s.q., are usually dosed once daily. Enoxaparin is typically administered at 1.5 mg/kg s.q. qd; however, some data suggest that dosing enoxaparin at 1 mg s.q., b.i.d., is more effective than once-a-day dosing in the cancer patient. Numerous studies in patients with VTE with and without malignancy show similar results between unfractionated heparin and LMWH; however, the convenience of LMWH make this an attractive alternative for patients who are otherwise able to be treated as outpatients. The risk of bleeding with either unfractionated heparin or LMWH appears to be similar (*Semin Thromb Hemost* 1999;25:245–249). Typically oral anticoagulation with warfarin, 5 mg p.o. daily, is started at the time of heparin or LMWH therapy and is adjusted based on the INR. Loading doses of warfarin are no longer considered effective in shortening the time until therapeutic levels occur and are not recommended. Unfractionated heparin or LMWH is recommended for a minimum of 5 days and should be continued until a therapeutic INR of 2.0 to 3.0 is obtained.
2. **Long-term anticoagulant treatment.** Warfarin remains the most commonly used anticoagulant for long-term treatment of VTE. For most indications, including cancer-associated VTE, the target INR is 2.0 to 3.0. The recommended treatment duration of warfarin for patients with VTE and cancer is for 12 months if the cancer has resolved. Otherwise, if the cancer remains, lifelong therapy is generally recommended. In patients with a transient risk factor for thrombosis (e.g., postoperative DVT), treatment of 3- to 6-months' duration may be adequate. Increasingly, LMWH given for the duration of treatment also is considered an option because of its relative ease of administration, favorable safety profile, and absence of a need for monitoring. Individual characteristics such as age, patient preference, or comorbidity may affect the choice and duration of therapy. At present, it is unclear whether there is an advantage to warfarin or LMWH therapy for long-term treatment. Warfarin dosing may be affected by diet, medications, and hepatic function and requires careful monitoring. In contrast, body weight and renal function affect LMWH dosing. The risk of major bleeding with any long-term anticoagulant is substantial and is estimated to be about 5% over a 12-month period. Whether this is significantly higher in cancer patients is uncertain but should be considered (*Thromb Haemost* 2000;840: 805–810).
3. **Vena caval filters for the treatment of deep vein thrombosis.** The placement of a filter in the inferior vena cava should be considered in patients with recurrent thromboembolic disease despite adequate anticoagulation, high bleeding risk or hemorrhage with anticoagulants, or in patients with advanced malignancy in whom chronic anticoagulation would be a burden. Vena caval filters significantly decrease the incidence of pulmonary emboli in the short term, but the clinical benefit is not sustained. In addition, anticoagulation is generally recommended whenever feasible (*Blood* 2000;95:3669–3677).
4. **Special considerations in treating cancer patients with thrombosis.**
   a. **Catheter-related thrombosis.** Indwelling venous catheters pose a risk for *in situ* thrombosis

      There is a lack of general consensus as to the treatment of this complication. Thrombolytic therapy [e.g., tissue plasminogen activator (t-PA), 2 mg in 2 mL normal saline] should be considered when the thrombosis is limited to the catheter tip. However, if the thrombus extends beyond the catheter tip, anticoagulation with heparin or LMWH followed by warfarin (see preceding paragraphs) for about 3 months is typically recommended. Catheters may be left in place despite thrombosis if they remain functional, but if catheter function is not restored after several days of fibrinolytic or anticoagulation therapy, removal should be considered.

   b. **Anticoagulation in the setting of central nervous system malignancy.** Venous thrombosis is a common complication in patients with primary or metastatic central nervous system (CNS) disease. Anticoagulation of patients with brain metastasis poses the risk of an intracranial hemorrhage. However, for most malignancies, this seems to be a modest risk, and standard anticoagulation should be used. Brain metastases from melanoma and renal cell carcinoma are of particularly high risk of causing intracranial bleeding, so that in these tumors, anticoagulation should be avoided.
   c. **Portal and hepatic vein thrombosis.** Thrombosis of the portal or hepatic vein usually appears with abdominal pain and occurs in patients with myeloproliferative disorders or in those individuals with vascular obstruction due to an intraabdominal malignancy. Catheter-directed treatment with thrombolytic therapy (e.g., t-PA over a 24-hour period) should be considered, particularly with patients with an underlying myeloproliferative disorder. Otherwise, unfractionated heparin or LMWH followed by warfarin is recommended.
   d. **Treatment of recurrence despite anticoagulation.** Despite therapeutic warfarin anticoagulation, recurrent thromboembolic disease rates are high, with estimates of approximately 33% of patients with adenocarcinoma and about 20% of all cancer patients with a subsequent thrombotic event. Under these circumstances, therapeutic doses of LMWH similar to those used for the initial therapy should be considered. In this setting, insertion of a vena caval filter may be of benefit.
5. **Anticoagulation and cancer mortality.** The role of anticoagulation in survival of patients with malignancy that is unrelated to thromboembolic events was suggested a number of years ago and remains of ongoing interest. To date, there is no convincing evidence that unfractionated heparin has an effect on response rates or survival in patients with malignancy. Several randomized studies comparing unfractionated heparin with LMWH for the initial treatment of DVT treatment had suggested a reduced mortality over 3 to 6 months in patients with cancer receiving LMWH. Recent data have not confirmed this finding, and it is difficult to generalize this in patients without thrombosis. The role of warfarin in improved survival in patients with lung cancer also has been suggested but remains in doubt. Currently, there is no proven role for anticoagulants in the treatment of malignancy in the absence of a thromboembolic indication (*Thromb Haemost* 1999;92:1600–1604).

III. **Syndromes of intravascular coagulation**

A. **Disseminated intravascular coagulation**

DIC occurs when systemic activation of coagulation leads to intravascular formation and deposition of fibrin, leading to thrombosis of small and midsize blood vessels. Consumption of platelets and coagulation factors also may result in diffuse bleeding. Although no single laboratory test establishes the diagnosis, a platelet count less than 100,000/µL (or the decline from a previously high level) frequently occurs. The prothrombin time (PT) and aPTT may be prolonged, and the presence of fibrin(ogen) degradation products (FDPs) or D-dimer also is common. A decreased fibrinogen may not be detected because this is an acute-phase reactant and tends to be low only in patients with severe disease. DIC increases the risk of organ failure due to vascular ischemia.

Treatment with low doses of unfractionated heparin (300 to 500 U/hour continuous infusion) is generally recommended, particularly in patients with evidence of associated thromboembolism or organ ischemia. In the absence of bleeding, plasma products and platelet transfusion are not usually recommended (*N Engl J Med* 1999;341:586–592).

A unique association between DIC and acute promyelocytic leukemia has been described in which activation of the coagulation system and increased fibrinolysis frequently results in bleeding. In the past, up to 15% of patients developed fatal hemorrhage during induction chemotherapy. All- *trans*-retinoic acid (ATRA), given alone or in combination with chemotherapy, seems to have a dramatic effect on the coagulopathy, with a demonstrated effect of increased complete response rates and ease of management during chemotherapy (*Blood* 1998;91:3093–3102).

B. **Nonbacterial endocarditis and arterial thromboembolism**

An association between cardiac valvular disease and peripheral embolization occurs in patients with cancer. Although not so common as VTE, this may result in end-organ damage such as a stroke. This may be seen with any malignancy but is most common in patients with mucin-producing adenocarcinomas of the lung and pancreas. Therefore any ischemic event in a patient with cancer should lead to evaluation for endocarditis. The diagnosis is usually

established by echocardiogram, and ventricular wall-motion abnormalities are frequently present, suggesting concurrent silent emboli to the coronary arteries. Treatment with low-dose unfractionated heparin similar to that for DIC is generally recommended.

IV. **Thrombotic microangiopathy associated with cancer**

A. **Clinical findings and pathogenesis**

The clinical findings of unexplained neurologic deficits or renal insufficiency along with the laboratory findings of thrombocytopenia, hemolytic anemia with schistocytes, elevated lactate dehydrogenase (LDH), and decreased haptoglobin are concerning for the diagnosis of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). In patients with significant renal insufficiency, the diagnosis is generally termed HUS, but the distinction is not well defined, so that “thrombotic microangiopathy” has increasingly been used to describe the syndrome. At times this diagnosis may be difficult, because other comorbid illnesses or DIC leads to similar findings. The likely cause of the microangiopathy in some cancer patients is damaged vascular endothelium, although the underlying etiology is not clear in most cases. Recently patients with either a deficiency or an inhibitor of von Willebrand factor–cleaving protease have been described in a number of patients with TTP, but these are not usually found in patients with cancer or drug-associated TTP/HUS. A small number of chemotherapeutic agents including mitomycin C, daunorubicin, bleomycin, and cisplatin have been associated with TMA. Other agents including the immunosuppressants cyclosporine and FK-506, along with the antiplatelet agents ticlopidine and clopidogrel, appear responsible for some cases (*Semin Hematol* 1997;34: 140–147).

B. **Treatment of thrombotic microangiopathy**

Treatment of TMA is particularly difficult in the cancer patient and is associated with significant morbidity and mortality. Discontinuation of any offending agent is necessary and may be sufficient to reverse the process, particularly in cyclosporine-induced TMA. Nevertheless, treatment with plasma exchange by pheresis is the usually initial therapy, particularly because the syndromes are indistinguishable. Complete remission rates are difficult to achieve in drug-associated TMA. Concurrent use of aspirin and glucocorticoids has been advocated in cases of sporadic TTP, but the role in cancer-associated TMA is uncertain and unlikely to be significant. In patients who do not respond to immunosuppressive therapy (e.g., prednisone, 1 to 2 mg/kg/day) or splenectomy is recommended.

V. **Hemorrhagic complications associated with malignancy**

A. **Thrombocytopenia**

1. **Chemotherapy-induced thrombocytopenia.** Chemotherapy is a frequent cause of thrombocytopenia, which may lead to significant bleeding, particularly when the platelet count is less than 10,000/μL. Prophylactic platelet transfusions are generally recommended under these circumstances, but at higher platelet counts are generally not advocated in the absence of bleeding. A platelet infusion from six pooled donors or a single donor of pheresed platelets should result in an increment in the platelet count 1 hour after infusion by 30 to 60,000/μL. Recombinant interleukin-11 (Neumega; 50 μg/kg s.q. qd) appears to shorten the period of chemotherapy-induced thrombocytopenia and may result in decreased bleeding, but appears to be ineffective in the treatment of other causes of thrombocytopenia. Adjunctive treatment with antifibrinolytic agents such as e-aminocaproic acid (Amicar), 2 g i.v. or p.o. every 4 to 6 hours, may be helpful in the treatment of bleeding.
2. **Immune thrombocytopenia.** Immune platelet destruction may occur in patients with lymphoproliferative disorders such as chronic lymphocytic leukemia. Treatment of the underlying disease generally improves the thrombocytopenia. An approach similar to that for idiopathic immune thrombocytopenic purpura is usually of benefit. Treatment with intravenous immunoglobulin (IVIG; 1 g/kg/day for 2 days) or prednisone (1 mg/kg/day for 2 weeks followed by a taper) usually results in an increased platelet count.

B. **Coagulation factor deficiency**

1. **Vitamin K deficiency.** Vitamin K deficiency typically occurs in patient with poor oral intake and the concomitant use of antibiotics. The diagnosis should be suspected in patients with bruising or unexplained bleeding and a prolonged PT. Under these circumstances, empiric therapy with vitamin K, 10 mg p.o., s.q., or i.v. daily for 3 to 5 days is recommended.
2. **Acquired factor X deficiency.** In 10% to 20% of patients with amyloidosis, a deficiency in factor X is identified. This appears to be due to enhanced clearance of factor X from the plasma. Treatment of the amyloidosis may result in improved factor X levels. Splenectomy also has been reported to improve the factor X deficiency, presumably because of removal of high levels of amyloid deposits in the spleen.
3. **Inhibitors of coagulation.** Acquired inhibitors of coagulation are uncommon abnormalities but may result in serious bleeding and are often difficult to treat. A factor VIII inhibitor may occur in any setting and should be suspected in a bleeding patient with a prolonged aPTT that does not correct with a 1:1 mix of normal plasma. The diagnosis is confirmed by the detection of a low factor VIII level. Successful treatment of a bleeding episode may be achieved with high doses of purified or recombinant factor VIII (100 U/kg i.v., q8 to 12 hours) but often requires another agent that bypasses the factor VIII–dependent reaction. Recombinant human factor VIIa (Novoseven; 90 μg/kg i.v., q2 to 4 hours) has recently been used with good success. Acquired von Willebrand syndrome is most often seen in patients with a monoclonal gammopathy of undetermined significance (MGUS) or other lymphoproliferative disorder and should be suspected in patients with mucosal bleeding and bruising and a low von Willebrand factor. Treatment with IVIG, 1 g/kg, for 1 to 2 days and repeated every 3 to 4 weeks has proven effective in many cases (*Blood* 1998;92:2707–2711).

CHAPTER 26. INFECTIONS IN CANCER PATIENTS

Thomas Bailey and Russell Little

Febrile Neutropenia
Risk factors
Published guidelines
The empiric use of antibiotics
If the patient becomes afebrile
When an etiologic agent is identified
For patients whose fever persists
Duration of therapy
Colony-stimulating factors [granulocyte–colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF)
Epidemiology of infection
Gram-positive cocci
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Issues in antibiotic choice
Vancomycin for initial empiric therapy
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Opportunistic Viral Infections
Herpes simplex virus (HSV)
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Effective therapeutic agents
Prevention of varicella and zoster
Cytomegalovirus
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Influenza and respiratory syncytial virus infections
Influenza treatment
Respiratory syncytial virus disease
Respiratory syncytial virus treatment
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Empiric antifungal therapy
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Treatment options and recommendations
For severe pulmonary or central nervous system infection
Communicating hydrocephalus
Aspergillosis
Presentation
Positive cultures
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Aspergillus fumigatus
Aspergillus spp. are commonly isolated from environmental sources
Treatment
Pseudallescheria, Fusarium, Muco and dematiaceous fungi
Pseudallescheria boydii
Zygomycosis
Fusarium spp
Phaeohyphomycoses
Opportunistic Mycobacterial Infections
Populations at risk
Wound infections
Catheter infections
M. kansasii
M. chelonae
Nocardia and Pneumocystis Infections
Nocardia spp
Presentation
Treatment
Pneumocystis carini pneumonia
Therapy for PCP
Prophylaxis
Suggested Readings

FEBRILE NEUTROPENIA

I. In general, improving survival of patients with malignancies is attributable to earlier detection and improved methods of treatment. However, these improvements include more intensive tumor ablative therapy, which tends to prolong the duration and intensity of treatment-related myelosuppression. Lengthened periods of neutropenia have made opportunistic infection a common complication. **Neutropenia** is defined as an absolute neutrophil count (ANC) fewer than 500 cells/mm ^{3}. Both mature neutrophils and band forms are included in the calculation of ANC. Fever in a neutropenic patient is defined as a single observation of greater than 38.3°C (101°F) or a sustained temperature of 38.0°C or greater (100.4°F) for at least 1 hour. Early studies suggested that the majority of patients with febrile neutropenia had occult bacterial infections (*Arch Intern Med* 1985;145:1621–1629). Even in the absence of fever, patients with neutropenia who exhibit a body temperature of 36°C or less and clinical deterioration [pulse (P) greater than 90, or respiratory rate (RR) greater than 20, or blood pressure (BP) less than 90] should be assumed to be infected.
   A. **Risk factors.** An increased understanding of febrile neutropenia has led to an enhanced ability to distinguish between high- and low-risk subsets of patients. The most accepted and readily identifiable risk factor for severe infection is the depth and duration of the neutropenia but the rate of ANC decline confers an independent risk. Susceptibility to infection is increased for patients with an ANC less than 1,000 cells/mm ^{3}, but it is successively higher when the ANC is less than 500 or less than 100. Morbidity and mortality are also increased in patients with ANC less than 100 cells/mm ^{3}. Patients with more than 7 to 10 days of neutropenia also incur a higher rate of significant infections. The type of malignancy also is related to infection risk. Patients with leukemia and those with bacteremia or significant focal infections have a higher risk of infection-related morbidity and mortality. Other factors conferring a higher risk at the time of presentation include significant comorbid medical conditions and/or having a cancer that is progressive. Clinical trials have in general supported the use of some or all of these criteria to help identify neutropenic patients at **lower** risk who may be managed at home and possibly even on oral antimicrobials.
   B. **Published guidelines.** The 1997 Infectious Diseases Society of America (IDSA) practice guidelines for treatment of febrile neutropenia are evidence-based recommendations by experts in adult and pediatric infectious diseases and oncology (*Clin Infect Dis* 1997;25:551–573). They also are provided on the web at the IDSA home page (http://www.idsociety.org/).

1. **The initial evaluation** of patients with febrile neutropenia should include cultures of blood (samples from a peripheral site and from a central venous catheter, if present), any skin or mucous membrane lesions and any diarrheal stools obtained before the administration of antibiotics.
2. **Blood cultures** should be obtained routinely from patients with febrile neutropenia. Blood samples should be at least 20 mL each. If initial blood cultures are negative, and the patient does not respond satisfactorily to empiric antibiotic therapy, it is often desirable to obtain separate fungal and mycobacterial "isolator cultures" of peripheral blood. Isolator System cultures are sterile samples of blood collected in saponin, which lyses leukocytes and erythrocytes, releasing intracellular organisms that are then concentrated by centrifugation during sample preparation. The concentrated sediment is transferred to enriched media, depending on which organism(s) are suspected (e.g., fungi, mycobacteria, *Francisella* sp.). These lysis/centrifugation cultures are preferred for detection of intracellular organisms such as typical or atypical mycobacteria, *Histoplasma capsulatum,* or other systemic fungi, and because of the centrifugal concentration step, they may offer more sensitive detection of some extracellular species such as *Candida* sp.
3. **Other tests** that should be obtained routinely include a chest radiograph, complete blood count, and blood tests for alkaline phosphatase, transaminases, electrolyte concentrations, creatinine, and blood urea nitrogen (BUN).

II. **The empiric use of antibiotics** (before the results of cultures are known) has been shown to reduce the mortality of patients with fever and neutropenia, and it has become the standard of care. Three initial empiric antibiotic treatment regimens derived from the IDSA guidelines are (a) vancomycin plus cefepime, and because vancomycin often is not needed, (b) monotherapy with cefepime, imipenem, or meropenem; or (c) an aminoglycoside such as gentamicin or amikacin and an antipseudomonal b-lactam (e.g., cefepime). Recent experience has led to a preference for cefepime over ceftazidime because it preserves antipseudomonal activity but has greater resistance than ceftazidime to class 1 b-lactamases (often present in *Enterobacter, Serratia,* and *Citrobacter* spp.). Cefepime also has significantly greater activity than ceftazidime against many gram-positive cocci. The preference for cefepime has reduced the need for initial empiric use of vancomycin unless there is a perceived need to provide coverage for methicillin/oxacillin-resistant *Staphylococcus aureus* (MRSA/ORSA) or coagulase-negative staphylococci (e.g., *S. epidermidis*).

A. **If the patient becomes afebrile** during the first 3 days of treatment and no etiology is identified, low-risk patients (see Section I.A. Risk factors; mild, brief neutropenia and absent comorbidity or progressive neoplasm) may be changed to an oral antibiotic (e.g. cefixime) or an extended-spectrum fluoroquinolone (levofloxacin, gatifloxacin, or moxifloxacin). For relatively low-risk patients, especially pediatric patients, there is a proposed basis for an early switch from parenteral to oral antibiotics if the blood cultures are sterile at 48 hours. One randomized controlled trial found equivalent failure rates for children with cancer switched to oral cefixime (28% failed) compared with a control group continued on intravenous (i.v.) antibiotics (27% failures) (*Clin Infect Dis* 2001;32:36–43). High-risk patients who become afebrile during the first 3 days should in general have their empiric i.v. antibiotics continued.

B. **When an etiologic agent is identified,** treatment should be adjusted to the most appropriate antibiotic for the isolated pathogen with as narrow an antimicrobial spectrum as possible.

C. **For patients whose fever persists** during the first 3 days of empiric antibiotic treatment, reassess on day 4 or 5, and consider obtaining isolator blood cultures for intracellular pathogens. If no clinical change is found, continue antibiotics but consider stopping vancomycin if cultures are negative.

1. **Empiric antifungal therapy.** If signs of infection are progressive, change antibiotics. If the patient is still febrile on days 5 to 7, add itraconazole or fluconazole (400 to 600 mg daily) or amphotericin B-deoxycholate (Fungizone, AmB; 0.5 to 0.7 mg/kg i.v., daily), amphotericin B lipid complex (Abelcet; 3 to 5 mg/kg daily), or liposomal amphotericin B (AmBisome; 3 to 5 mg/kg i.v., daily) with or without a change in antibacterial therapy. A recent trial showed similar efficacy for patients receiving AmB or fluconazole (*Eur J Cancer* 1996;32A:814–820). However, fluconazole is less likely to be effective for patients who have received previous therapeutic courses or prophylaxis with fluconazole, and it should not be used if *Aspergillus* infection is suspected.
   a. **Nephrotoxicity** from AmB can be reduced if the patient receives hydration (preferably 500 mL i.v. saline) before and after the AmB infusion and if the AmB infusion is administered slowly (4 hours or longer). When fungicidal therapy is needed, AmB is the drug of choice for patients with normal renal function, and ABLC or liposomal AmB are indicated for patients with renal insufficiency. Periodic monitoring of serum K^+ and Mg^{2+} concentrations should be part of routine care for patients receiving any amphotericin preparation.
2. **Failure of response** to routinely used antibacterial agents in neutropenic patients with severe pneumonia also should lead to consideration of atypical infectious agents such as *Chlamydia, Mycoplasma,* and *Legionella* sp. A recent report of severe *C. pneumoniae* infection in patients with neutropenia highlights the need for further study of this pathogen–host combination (*Clin Infect Dis* 2000;31:181–184).
3. **Antiviral therapy.** The routine empiric use of antiviral agents during episodes of febrile neutropenia is not recommended. However, herpes simplex and varicella zoster prophylaxis with oral acyclovir (or valacyclovir or famciclovir) is widely used in bone marrow or stem cell transplant recipients (see Chapter 5, Section VIII.E). Antiviral prophylaxis with i.v. ganciclovir (or oral valganciclovir) also is used in bone marrow or stem cell transplant patients at risk for development of active cytomegalovirus (CMV) infection.

III. **Duration of therapy.** The IDSA guidelines for the duration of antibiotic therapy have three categories (Fig. 26.1).

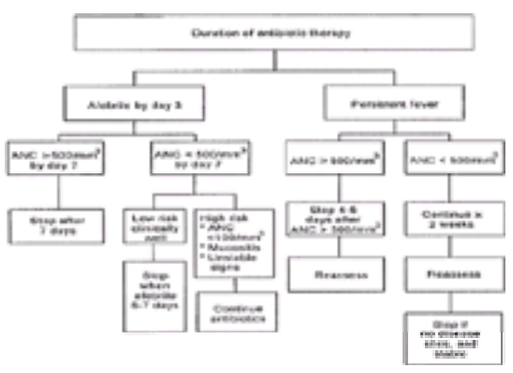

FIG. 26.1. Duration of antibiotic therapy. ANC, absolute neutrophil count. (From Hughes WT, Armstrong D, Bodey GP, et al. 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. *itshape Clin Infect Dis* 1997;25:551–573, with permission.)

1. If the patient is afebrile by day 3 with ANC 500/mm^3 or greater by day 7, stop antibiotics after 7 days.
2. If ANC is less than 500 on day 7, continue antibiotics.
3. If the patient receiving empiric antibiotic therapy has persistent fever and an ANC of 500/mm^3 or greater, stop antibiotics after 4 to 5 days, and reassess. If ANC is less than 500/mm^3 after 4 to 5 days of therapy, continue antibiotic coverage for 2 weeks, but then stop, and reassess, if no disease sites are apparent.

IV. **Colony-stimulating factors [granulocyte–colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF)** in the prevention and treatment of ongoing neutropenic fever. Administration of these bone marrow stimuli should be considered in cases with a worsening course or in those with prolonged and intense neutropenia after previous courses of chemotherapy, although studies show no discernible effect on overall mortality. Guidelines for the use of CSFs have been formulated by the American Society of Clinical Oncology (*J Clin Oncol* 1996;14:1957–1960). Cost-containment issues are discussed in the IDSA guidelines.

V. **Epidemiology of infection.** A major epidemiologic shift has occurred in many countries, including the United States, in which gram-positive cocci now represent the predominant causes (60% to 70%) of monomicrobial bacteremia in patients with malignancy.

A. **Gram-positive cocci** isolated most frequently are *S. aureus* and the coagulase-negative staphylococci. The latter group embodies more than 20 different staphylococcal species, of which *S. epidermidis* is the most commonly isolated pathogen. Medical center clinical microbiology laboratories will often compile a regularly updated report of their experience with susceptible and resistant strains, including *S. aureus,* coagulase-negative staphylococci, pneumococci, and enterococci. If these are not available, then as a rough guide, about one third to one half of *S. aureus* isolates and about two thirds of the coagulase-negative staphylococci will be methicillin/oxacillin resistant.

1. **Altered penicillin-binding proteins** provide the common mechanism for resistance, and therefore the use of an agent containing a b-lactamase inhibitor [e.g., piperacillin and tazobactam (Zosyn), ampicillin and sulbactam (Unasyn), ticarcillin and elavulanic acid (Timentin), or amoxicillin and elavulanic acid (Augmentin)] is *inappropriate* for the treatment of MRSA/ORSA.
2. ***In vitro* susceptibility testing** is generally reliable with *S. aureus* strains, but sometimes it may be necessary to assess the presence of the *mecA* gene, which provides a strong predictor of clinical failure with b-lactam antibiotics. The presence of *mecA* indicates resistance to all b-lactams. The high frequency of resistance to b-lactams and the incompletely reliable susceptibility tests with coagulase-negative staphylococci have led to the common empiricism that initial therapy for these organisms should be with vancomycin.
3. Food and Drug Administration (FDA) approval of dalfopristin/quinupristin (Synercid) and linezolid (Zyvox) has afforded two possible alternatives to vancomycin for the treatment of MRSA/ORSA and for coagulase-negative staphylococcal strains that are *mecA* positive. However, until there is more experience than is now available to assess the relative efficacy of vancomycin (which is bactericidal) and linezolid or Synercid (both are generally bacteristatic), it is prudent to prefer vancomycin in neutropenic and other immunocompromised hosts.

B. **Enterococci** continue to be a major cause of nosocomial bloodstream infections and have now ascended to third place on the list of all causes.

1. **Vancomycin-resistant enterococci** (VRE) are increasingly common in hospitalized patients, occurring predominantly among *Enterococcus faecium* rather than *E. faecalis* strains of enterococci. Enteric VRE colonization (usually defined by a stool or rectal-swab culture yielding VRE) is common in debilitated patients including those with malignancies. In one report, 10 of 11 VRE-infected patients were neutropenic, and the mortality rate was 73% (*Clin Infect Dis* 1995;20:1126–1133). However, others have found that resistance to vancomycin does not independently increase the risk of mortality associated with VRE bacteremia (*Clin Infect Dis* 2000;30:466–472.).
2. Useful agents for the treatment of VRE urinary tract infection include ampicillin (which achieves high and therefor effective concentrations in the urine even when routine susceptibility tests suggest ampicillin resistance), chloramphenicol, linezolid, Synercid, or nitrofurantoin. Notably, Synercid is not clinically active against vancomycin-sensitive or -resistant strains of *E. faecalis*

C. **Viridans group streptococci** are common pathogens for patients with neutropenic fevers, often related to mucosal damage resulting from chemotherapy. Increasing rates of antimicrobial resistance among the viridans streptococci have been noted in results from large collections of blood culture isolates. The SENTRY Antimicrobial Surveillance Program has provided data from the United States, Canada, Latin America, and Europe. Analysis of more than 9,000 bloodstream isolates reported on the changing rates of antimicrobial resistance (*Clin Infect Dis* 2001;32:81–167).
1. Penicillin resistance among the viridans streptococci isolated in the United States was present in 48.5% of bacteremia isolates. *Streptococcus mitis* strains were the most resistant and *S. milleri* were the most susceptible. The penicillin-resistant viridans streptococcal strains also tended to be resistant to other b-lactams such as cephalexin, oxacillin, and ceftazidime.
2. The b-lactams with greatest *in vitro* activity against viridans streptococci were imipenem, cefepime, cefotaxime, and ceftriaxone. However, there is evidence of geographic variation in these results, probably reflecting local antibiotic-use patterns. The most useful guide to antibiotic selection is derived from the data provided by the individual local hospital clinical microbiology laboratories, and the laboratory director should be consulted for compiled results and changing local trends in antimicrobial resistance.

VI. **Issues in antibiotic choice**

A. **Vancomycin for initial empiric therapy.** A large retrospective review from the National Cancer Institute suggested that vancomycin use is probably not necessary as part of the initial empiric therapy for patients with febrile neutropenia (*Ann Intern Med* 1988;108:30–35).
1. Vancomycin adds to both cost and toxicity of the empiric regimen, and it also may contribute to the prevalence of VRE. Recently published studies concluded that vancomycin should not be used as empiric treatment, citing equal mortality rates and greater toxicity in vancomycin recipients (*Clin Infect Dis* 1999;29:503–507). In 1994 the Hospital Infection Control Practices Advisory Committee (HICPAC *MMWR* 1994;44:1–13), responding to the emergence of VRE as a new and increasing problem in nosocomial infections, published a set of recommended guidelines for vancomycin use. These guidelines stipulated six appropriate uses of vancomycin:
    1. Serious infections due to b-lactam–resistant gram-positive bacteria.
    2. Infections due to gram-positive bacteria in patients with severe b-lactam allergy.
    3. Metronidazole-refractory and potentially life-threatening *C. difficile* colitis.
    4. Surgical prophylaxis involving implantation of prosthetic material in institutions with high rates of MRSA/ORSA or coagulase-negative staphylococci.
    5. Endocarditis prophylaxis in b-lactam–allergic patients.
    6. Initial empiric use for serious infections that may possibly be due to resistant gram-positive bacteria.
2. HICPAC specifically identified empiric vancomycin use in febrile neutropenic patients as **unjustified** unless the patient was thought to have a gram-positive infection or in particular hospitals with a high incidence of MRSA/ORSA. The availability of linezolid (Zyvox) and dalfopristin/quinupristin (Synercid) with activity against MRSA/ORSA and other resistant gram-positive organisms may reduce the need to use vancomycin in the empiric treatment of febrile neutropenia. For patients receiving vancomycin, periodic trough blood levels (every 4 to 7 days) are recommended, and these should be between 5 and 15 mg/L. Peak vancomycin levels are rarely useful and should not be obtained routinely.

B. **Empiric monotherapy versus combination therapy.** Selections of empiric treatment regimens for patients with febrile neutropenia are generally in a state of flux. By the time a set of recommendations is printed, it may already have been superseded by new FDA approvals or publication of randomized trials contradicting published recommendations. There also is the problem of regional differences in the pathogen mix or in the prevalence of antibiotic-resistant strains. The following represents a selection of i.v. antibiotics for empiric monotherapy in the order of the authors' preference, and a similar selection was previously published (*Clin Infect Dis* 1999;29:495–502).
1. Monotherapy: (a) cefepime (2 g i.v. q8h); (b) imipenem/cilastatin (1 g i.v. q6 to 8h) or meropenem (1 g i.v. q8h); (c) piperacillin/tazobactam (Zosyn; 3.375 g i.v. q6h); (d) levofloxacin (500 mg i.v. qd) or gatifloxacin (400 mg i.v. qd).
2. Combination therapy: (a) cefepime or piperacillin/tazobactam or imipenem; PLUS amikacin (7.5 to 8.0 mg/kg i.v. b.i.d.), gentamicin, or tobramycin (1.7 to 2.0 mg/kg i.v. q8h, for each). Generally aminoglycoside blood levels are most useful when the trough is measured immediately before the third dose and the peak is measured 1 hour after the start of the third infusion. Target blood levels for gentamicin and tobramycin are peaks of 6 to 10 mg/L and troughs of less than 2 mg/L (Table 26.1). In contrast to traditional dosing, once-daily dosing of aminoglycosides has become widely accepted and has potential advantages over traditional dosing, including a straightforward dosing regimen, fewer interventions through i.v. lines, convenience, and a higher percentage of peak serum concentrations in the therapeutic range (*Clin Infect Dis* 1997;24:786–795). Patient exclusions from once-daily dosing are anasarca, hemodialysis, endocarditis, infants, pregnancy, and CrCl less than 20 mL.

CrCl (mL/min)	$t_{1/2}$ h	q8h	q12h	q24h
>90	3.1	84%	100%	—
80	3.4	80%	91%	—
70	3.9	76%	86%	—
60	4.5	—	84%	—
50	5.3	—	79%	—
40	6.5	—	—	92%
30	8.4	—	—	85%
25	9.9	—	—	81%
20	11.9	—	—	75%

The **loading dose** is based on ideal body weight and severity of illness: UTI, 1.5 mg/kg; systemic illness, 2 mg/kg; sepsis/shock, 2.5–3 mg/kg.
The **maintenance dose** (MD) is shown as a percentage of the selected loading dose (LD).
Example: 70-kg patient with sepsis, CrCl, 60 mL/min; LD, 175 mg; MD, 147 mg q12h (rounding down to 145 mg q12h).
For CrCl <20 mL/min, give loading dose, then follow levels and redose when level drops below 2 mg/L.

TABLE 26.1. TRADITIONAL MAINTENANCE DOSE ADJUSTMENTS FOR GENTAMICIN AND TOBRAMYCIN IN PATIENTS WITH VARYING LEVELS OF CREATININE CLEARANCE

C. **Prophylactic antimicrobial therapy.** The great majority of chemotherapy-related infections are caused by the patient's endogenous microbial flora. It is therefore very tempting to think that continuous suppression of the growth of normal flora by administration of prophylactic antibiotics would inhibit and perhaps even prevent the occurrence of infection. This rationale has been tested in randomized clinical trials and in meta-analyses without any convincing evidence for reduced infection or mortality rates associated with administration of prophylactic antibiotics. The oral fluoroquinolone studies showed lower rates of gram-negative bacteremia in antibiotic recipients but no reduction in the infection-related mortality rates. As fungal pathogens emerged in a significant fraction of patients with neutropenia, trials were performed with fluconazole, itraconazole, and even AmB. In general, no differences were found in the incidence of invasive aspergillosis or in infection-related mortality or overall mortality in antibiotic recipients. Consequently there is wide agreement that antibiotic prophylaxis should **not** be offered to patients who are expected to have neutropenia (*Curr Clin Top Infect Dis* 2000; 19:160–180).

OPPORTUNISTIC VIRAL INFECTIONS

I. **Herpes simplex virus (HSV)** stomatitis or even generalized HSV infection occurs commonly in patients receiving antineoplastic therapy for lymphoma or leukemia. Painful moist or crusted lip lesions with or without extensive mucosal ulcers should lead to viral culture for HSV, especially in those patients with a history of occasional or recurrent “cold sores” earlier in life. It is somewhat surprising that even in the presence of extensive mucosal ulceration, HSV encephalitis is uncommon. Because asymptomatic salivary shedding of HSV has been noted in 2% to 9% of adults, a positive viral culture without supporting evidence may be misleading. Because the presence of extensive mucosal ulcers includes other entities such as bacterial mucositis, Stevens–Johnson syndrome, and *Mycoplasma pneumoniae* infections, a mucosal biopsy for routine histology and immunospecific staining for cells containing HSV antigens should be considered during the diagnostic workup. Optimal antiviral therapy for severely affected individuals often requires i.v. administration of acyclovir or foscarnet for 14 to 21 days.

   A favorable response to acyclovir therapy is typical unless the patient has received prolonged suppressive antiviral therapy in the past (e.g., oral acyclovir, or one of its derivatives, for recurrent HSV-2 genitalis). The antiviral activity of acyclovir and its congeners is dependent on viruses that specify a thymidine kinase (TK) capable of recognizing acyclovir as a substrate for phosphorylation. Prolonged suppressive therapy with any member of this drug class may result in the selection of drug-resistant viral mutants (often these are TK mutants). Therapeutic failure with acyclovir therefore requires consideration of alternative, more

toxic agents, such as foscarnet (40 mg/kg i.v., q8 to 12h, for 2 to 3 weeks), cidofovir (induction with 5 mg/kg i.v. weekly and maintenance infusions, 5 mg/kg, every other week). Serious adverse reactions to foscarnet include pancreatitis, renal failure, bone marrow suppression, and electrolyte abnormalities (Table 26.2). Serious reactions to cidofovir include nephrotoxicity, nausea, fever, alopecia, iritis, bone marrow suppression, and metabolic acidosis. Some patients with labial or mucosal HSV may be sufficiently mildly affected to justify the use of oral antiviral preparations such as famciclovir (500 mg b.i.d. for 7 days), valacyclovir (500 mg b.i.d. for 5 days), or oral acyclovir (400 mg t.i.d. for 5 to 7 days).

Creatinine Clearance	Acyclovir Dosage	Foscarnet Dosage
60 mL/min	5 mg/kg q8h	40 mg/kg q8h
25–60 mL/min	5–10 mg/kg q12h	40 mg/kg q12h
10–25 mL/min	5–10 mg/kg q24h	10 mg/kg qd
0–10 mL/min	2.5–5.0 mg/kg q24h (and after dialysis)	Not recommended

TABLE 26.2. ACYCLOVIR AND FOSCARNET DOSING ADJUSTMENTS FOR RENAL FUNCTION

II. **Varicella-zoster virus (VZV).** Reactivation of VZV is more common and more severe in patients with depressed cell-mediated immunity. Most epidemiologic studies show an increased frequency of VZV recurrence in patients with lymphoproliferative malignancies, especially Hodgkin disease and chronic lymphocytic leukemia. In both varicella and zoster, the skin lesions are initially maculopapular, evolving to fluid-filled vesicles and then pustules that drain, crust, and heal. The skin lesions spread centrifugally (face/trunk first, extremities later) and are typically present simultaneously at all stages of their development. The frequency of VZV for patients with other malignancies, including acute leukemia and solid tumors, approaches that of the general population. Laboratory confirmation of the diagnosis may be unnecessary because the appearance or dermatomal distribution of the rash can be diagnostic. The virus is labile, and only 30% to 60% of cultures are positive. Detection of VZV in skin scrapings or vesicular fluid by immunofluorescence microscopy is more rapid and sensitive than are culture techniques. Amplification of VZV-DNA by polymerase chain reaction (PCR) is diagnostic, especially in skin biopsies and samples of cerebrospinal fluid (CSF) and vitreous fluid (e.g., acute retinal necrosis).
   A. **Effective therapeutic agents** for primary or reactivation VZV infection are acyclovir, valacyclovir, famciclovir, and foscarnet. All four drugs inhibit viral DNA polymerase. Controlled trials demonstrated that acyclovir shortens virus shedding and new lesion formation and speeds lesion healing in immunocompromised as well as healthy patients (*J Pediatr* 1992;120:627–633). Intravenous acyclovir (10 mg/kg q8h for 7 to 10 days) or foscarnet (40 mg/kg q8h for 14 days or until healing) is required for serious VZV infections. It is clear that in normal hosts, most virus replication has ceased by 72 hours after onset of the rash. However, in immunocompromised patients, the duration of virus replication and shedding is extended, so even late treatment may be justified. Intravenous acyclovir has been shown to prevent VZV progression in patients at high risk for dissemination (*N Engl J Med* 1986;314: 208–212).
   B. **Prevention of varicella and zoster** is now feasible for certain patient groups. For immunocompromised hosts exposed to a known case of varicella, only one product is licensed for postexposure prophylaxis: varicella-zoster immune globulin (VZIG), which is now very difficult or impossible to obtain. Two alternative strategies exist for VZV-nonimmune immunocompromised hosts exposed to a case of varicella. The first is administration of a short course of high-dose oral acyclovir (800 mg 5 times daily for 5 to 7 days) started as soon as possible after exposure. Active immunization against VZV is now possible by using the Oka strain attenuated varicella vaccine (Varivax, Varicella Virus Vaccine Live, Oka; Merck). The vaccine also may be considered as a preventive strategy for immunocompromised individuals exposed to an active case of varicella. However, it is generally contraindicated for patients during the week before or the week after high-dose chemotherapy administration **or** for patients receiving high-dose prednisone. Regarding the risks of disseminated infection with the vaccine strain, it is reassuring that the Oka strain is susceptible to acyclovir.

III. **Cytomegalovirus.** Among cancer patients other than BMT patients, CMV infection is an unusual cause of symptoms. Latent infection with CMV is common. Worldwide seroprevalence studies indicate that 35% to 100% of adults have evidence of previous infection. Vertical transmission of CMV infection by breast milk or childhood infections acquired from other children is thought to be common forms of inapparent primary infection. CMV, like other herpesviruses, becomes latent in the host after primary infection but may be reactivated in the context of serious illness. However, CMV is unlike HSV and VZV, because it is a true opportunist that nearly always produces severe infections only after reactivation from latency in immunocompromised hosts. Patients treated intensively with chemotherapy, and particularly those with BMT, are at risk for CMV reactivation. This may occur as pulmonary, gastrointestinal, central nervous system or disseminated infection.
   A. **The diagnosis of CMV** infection is complicated by the occurrence of CMV shedding without tissue invasion. This happens commonly in the lung; sputum or bronchoalveolar lavage samples from immunocompromised patients may yield positive CMV cultures during active *Pneumocystis,* bacterial, or other pulmonary infections. Generally the presence of positive CMV cultures from host tissue or detection of CMV antigen in multiple host cells of biopsies provides strong evidence for significant CMV disease. PCR testing for CMV DNA in blood (or other body fluids) indicates viremia and possibly disseminated infection.
   B. **In bone marrow allograft transplantation** (allo-BMT), CMV is an important opportunistic infection. Stem cell and auto-BMT recipients are much less likely to experience CMV reactivation. Both total body irradiation and graft-versus-host (GVH) reactions are potent stimuli for reactivation of latent virus present in either host or donor lymphoid cells. Without antiviral therapy, in about 50% of all allogeneic transplant recipients, active CMV infection develops, and in 20% to 25%, symptomatic CMV disease develops (*J Infect Dis* 1990;162:373–380). Preemptive antiviral therapy (not the same as prophylactic therapy), with full therapeutic doses of ganciclovir or foscarnet administered parenterally, can significantly reduce the rate of CMV reactivation in CMV-seropositive bone marrow recipients. CMV pneumonitis is a particularly virulent form of infection, which is often treated with ganciclovir (5 mg/kg i.v., q12h for 7 to 14 days) and either CMV hyperimmune globulin or pooled intravenous immune globulin (IVIG), although controlled clinical trials to support the efficacy of antibody therapy are lacking. Maintenance therapy with i.v. ganciclovir (5 mg/kg i.v. daily for at least several weeks) is recommended for BMT patients (*Principles and practice of infectious diseases.* 5th ed. New York: Churchill Livingstone, 2000:3141).

IV. **Influenza and respiratory syncytial virus infections**

Immunocompromised patients are at risk for infection with the same respiratory viruses that affect the general community during the same periods. Typically, outbreaks of influenza and respiratory syncytial virus (RSV) occur in the winter. Influenza immunization campaigns are generally widely publicized, and patients undergoing treatment for malignancies should receive influenza vaccine despite a possibly suboptimal immune response. Attempts to make an etiologic diagnosis of respiratory virus infection should include appropriate nasopharyngeal sample collection by sterile saline nasal wash or nasopharyngeal swab (preferably Dacron or cotton swab rather than calcium alginate). To sample the lower respiratory tract secretions, endotracheal aspirates or bronchoalveolar lavage (BAL) samples are particularly useful. Tissue biopsy samples offer advantages when BAL samples are inconclusive. Transport of samples to the laboratory should be expedited because RSV is quite labile. Specimens should not be frozen. Viral replication in culture is the gold standard for etiologic diagnosis, but antigen-detection methods are widely used for identification of RSV, influenza, and parainfluenza viruses in clinical samples. The sensitivity and specificity of antigen-detection methods for RSV and influenza in children are in the range of 70% to 90%, but in immunocompromised adults, the sensitivity is somewhat less (about 50%), although specificity remains quite high. RSV culture provides higher sensitivity, but 7 to 12 days of incubation is required. Antigen-detection assays for influenza A and B viruses also are sensitive (approximately 75%) and approach 100% specificity.

A. **Influenza treatment.** Four antiviral agents are available for the treatment of influenza. Amantadine (Symmetrel) and rimantadine (Flumadine) are approved for treating influenza A, whereas the neuraminidase inhibitor drugs, zanamivir (Relenza, inhaled) and oseltamivir (Tamiflu, oral) are approved to treat both influenza A and B. Amantadine and rimantadine also are approved for **prophylaxis** against influenza A, and oseltamivir has recently been approved for prophylaxis against influenza A and B. Prophylactic efficacy is about 75% to 90%. There may be an improved benefit/risk ratio with rimantadine (100 mg p.o. daily) compared with amantadine. Special caution is recommended in prescribing zanamivir in patients with underlying asthma or chronic obstructive lung disease because it is a self-administered inhaled particulate, and it may cause bronchospasm and/or a decline in pulmonary function.
B. **Respiratory syncytial virus disease.** The two major strains (A and B) of RSV circulate concurrently in the United States during the winter-through-spring (November through May) season of maximal respiratory virus outbreaks, and they produce illness of roughly equal severity. In the lung, RSV produces bronchiolitis and pneumonia, and infants are the most vulnerable. Most children will become infected during the first year of life. In immunocompetent adults, RSV infections usually produce self-limited upper respiratory tract illnesses or tracheobronchitis. In immunocompromised patients, RSV has often been associated with fatal viral pneumonia. Chest roentgenograms reveal focal or diffuse interstitial infiltrates to lobar consolidation. The highest morbidity and mortality (more than 75%) have been among BMT recipients and patients with acute leukemia. Because RSV is highly contagious and spread by airborne droplets, there must be enforcement of strict infection-control policies on BMT units (*Am J Med* 1997;102:48–52). Diagnosis is usually made with

immunofluorescence assays for detection of RSV antigens in respiratory secretions. These assays are not so sensitive in immunocompromised adults as they are in children.

C. **Respiratory syncytial virus treatment.** The only currently licensed antiviral agent for RSV infection is ribavirin, which is usually administered by aerosolization for 3 to 7 days via ventilator, in an O_2 tent, or by face mask. Its efficacy remains controversial despite its use in the United States since FDA approval in 1986. The recommended concentration for aerosol production is 6 g/300 mL for 12- to 16-hour continuous administration daily. The drug tends to crystallize in some ventilators, and use of a negative-pressure room with frequent air exchanges is necessary to minimize health care worker exposure (potentially carcinogenic and teratogenic). Passive immunoprophylaxis with parenterally administered neutralizing antibodies to RSV has been demonstrated to be of benefit in high-risk infants and young children. Several small trials of combined therapy with ribavirin and a commercial IVIG preparation (RespiGam) in adult leukemia and BMT patients showed reduced mortality compared with that in an untreated group (*Curr Clin Topics Infect Dis* 2000;20:233–255). These trials emphasize the importance of the early initiation of therapy before respiratory failure has occurred. A humanized RSV-specific monoclonal antibody (palivizumab) has been studied in a multicenter randomized comparative trial in high-risk infants (1,502 children; *Pediatrics* 1998;102:531–537). Efficacy was shown by a 55% reduction in the incidence of RSV hospitalizations in the palivizumab group compared with placebo. No trials in adults or in BMT or leukemia patients of any age have been reported.

SYSTEMIC FUNGAL INFECTIONS

OL type=I>

- **Empiric antifungal therapy** in febrile, neutropenic hosts not responding to broad-spectrum antibacterial agents is widely accepted. The antifungal agents currently available for the treatment of systemic fungal infections are in four classes.

1. Amphotericin B-deoxycholate (AmB) is the traditional agent, but newer less toxic lipid preparations of amphotericin are available.
2. The azoles (fluconazole, itraconazole, and voriconazole) interfere with fungal cell membrane formation.
3. Flucytosine inhibits fungal protein and nucleic acid synthesis.
4. Caspofungin, an echinocandin derivative, inhibits fungal glucan and cell wall synthesis. Caspofungin is FDA approved only for the treatment of refractory *Aspergillus* infection.

In this section we review the use of theses agents and the management of specific opportunistic fungal infections.

- ***Candida* spp.** IDSA practice guidelines for the treatment of *Candida* infections have been published recently (*Clin Infect Dis* 2000;30:662–678). *Candida* spp. are the most common fungal infections seen in immunocompromised patients. Invasive candidiasis with candidemia occurs often in neutropenic hosts, although the IDSA guidelines are derived mainly from experience in immunocompetent hosts. Both AmB and the azoles are important in treatment. The choice of therapy for candidiasis, although initially empiric, has come to rely more heavily on *in vitro* susceptibility testing than is the case with other fungal infections. Susceptibility testing is most helpful in the management of the nonalbicans species of *Candida.* Data-driven interpretive break points are available for testing the susceptibility of *Candida* spp. to fluconazole, itraconazole, and flucytosine (*Clin Infect Di*s 1997;24:235–247). Unfortunately, reliable break-point concentrations for AmB are not yet available; however, a substantial body of information suggests that most isolates of *C. lusitaniae* and a significant proportion of isolates of *C. glabrata* and *C. kruzei* may display some resistance to AmB. Alternatively, AmB resistance appears to be uncommon among *C. albicans, C. tropicalis,* and *C. parapsilosis.* Parenteral amphotericin products are often the drugs of choice **for critically ill hosts** with *Candida* fungemia before species identification or after the identification of *C. glabrata, C. parapsilosis,* or *C. tropicalis,* which frequently display significant azole resistance.

A. ***Candida* bloodstream infections** are frequently associated with clinical evidence of sepsis syndrome and have a high mortality rate. Several studies have demonstrated that fluconazole (400 mg/day) or AmB (0.5 to 0.7 mg/kg i.v. daily) are similarly effective. Lipid preparations of AmB are indicated for patients intolerant to AmB-deoxycholate therapy. Without adequate therapy, endophthalmitis, endocarditis, and other severe complications of fungemia may occur. If feasible, initial management of disseminated candidiasis should include removal of any intravascular devices. However, the strength of evidence for this recommendation is less vigorous in neutropenic hosts, in which the role of the gut as a possible source of disseminated candidiasis is evident from autopsy studies. An exception to this generalization occurs with *C. parapsilosis* fungemia, frequently a nosocomial infection associated with intravenous catheters. In stable patients who have not recently received azole therapy and whose isolate is **not** *C. glabrata* or *C. kruzei,* fluconazole (400 mg i.v. daily) is recommended. In clinically unstable patients infected with an isolate of unknown species, AmB (0.7 mg/kg i.v. daily) is preferred, at least for initial therapy, mainly because of its broader spectrum. Antifungal therapy should be continued for at least 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection. After a favorable clinical response to 2 weeks of treatment, AmB may be switched to fluconazole (i.v. or p.o.) for completion of therapy. The most appropriate therapy, if any, for neutropenic hosts with multiple sites of *Candida* colonization is unknown.

B. **Hepatosplenic candidiasis** (HSC) is a special category of disseminated *Candida* infection with a generally more chronic course and a high mortality rate. Patients with acute leukemia and those treated with cytosine arabinoside are at particularly high risk. The onset is usually subacute with fever, vague upper abdominal symptoms, and/or hepatomegaly, and it often occurs during the neutropenic period after chemotherapy. Routine laboratory tests may reveal elevated transaminase values but especially elevated alkaline phosphatase and g-glutamyl transferase levels. Classically microabscesses are present in the liver and/or spleen, but they may elude radiologic detection until recovery from neutropenia. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound imaging have been used successfully for detecting the typical, multiple abscesses in the liver more often than in the spleen. Surprisingly, blood cultures may be sterile in about half of the cases. This syndrome is not acutely life threatening, but requires prolonged therapy to achieve a cure. Consequently, it is important to select a nontoxic long-term regimen. Fluconazole (600 mg i.v. or p.o. daily) is generally preferred in stable patients. AmB (0.7 mg/kg i.v. daily) may be used in acutely ill or refractory patients. Treatment should be continued until radiographic (CT scan) resolution of the lesions. However, it may require treatment throughout the course of antineoplastic chemotherapy.

C. **Urinary candidiasis** includes an ill-defined group of syndromes occurring in patients with urinary tract instrumentation (including Foley catheterization), recent antibiotic therapy, and advanced age. Nonneutropenic asymptomatic patients often do not require therapy. In neutropenic patients, especially those with fever, funguria may be a clue to disseminated infection (fungemia), and treatment with i.v. fluconazole or AmB for 7 to 14 days is justified. AmB bladder irrigation is appropriate only for patients with fungal infection limited to the bladder, and whose bladder catheter cannot be removed.

- **Cryptococcal infection** in immunocompromised patients usually occurs as meningitis or less commonly as focal brain or lung lesions with or without meningitis. The lung is the principal route of entry for *Cryptococcus neoformans,* and a wide spectrum of infections may occur, from asymptomatic nodular lung disease to acute respiratory distress syndrome (ARDS). A positive cryptococcal antigen titer in blood implies tissue invasion and a high probability of disseminated infection.

A. **Treatment options and recommendations** for human immunodeficiency virus (HIV)-negative as well as HIV-positive individuals are provided in guidelines by an expert panel of IDSA members and published recently (*Clin Infect Dis* 2000;30:710–718).

B. **For severe pulmonary or central nervous system infection,** combination therapy is recommended with AmB (0.7 to 1.0 mg/kg i.v. daily) plus flucytosine (5-FC; 50 to 150 mg/kg p.o. daily, usually in four divided doses). The potential bone marrow–suppressive effects or other toxicity of 5-FC [rash, gastrointestinal (GI) symptoms, including bleeding, cardiorespiratory symptoms] may constitute intolerable risks. Flucytosine-containing regimens have an advantage in that they often permit AmB administration in shorter courses or lower doses with a correspondingly reduced risk of AmB-induced nephrotoxicity.

1. **Monitoring 5-FC blood levels** (optimal levels are 30 to 80 µg/mL in venous blood obtained 2 hours after an 5-FC dose) can reduce the risks of its administration.
2. To gauge the efficacy of treatment, a follow-up lumbar puncture is recommended at 2 weeks of therapy. Combined therapy with AmB and 5-FC will often sterilize the CSF within 2 weeks of treatment, permitting a change to fluconazole (400 mg i.v. or p.o. daily) if a corresponding clinical improvement has occurred. If the 2-week sample of CSF yields cryptococcal growth, combined AmB–flucytosine therapy should be continued for at least 6 weeks.
3. In many immunocompromised patients, the “induction phase” of therapy with AmB and 5-FC is followed by a “consolidation phase” of therapy with fluconazole, 400 mg p.o. daily for 8 to 10 weeks.

C. **Communicating hydrocephalus.** Many patients with cryptococcal meningitis will have elevated opening CSF pressure measured at the initial diagnostic lumbar puncture, and such a measurement should always be obtained. Elevated pressure is defined as more than 20 cm H_2O with the patient in the lateral decubitus position. Elevated CSF pressure is an important contributor to morbidity and mortality of cryptococcal meningitis. Among HIV-positive individuals, an elevated opening pressure has been associated with uncontrolled fungal growth and a poorer clinical response to therapy. Such data are not available for HIV-negative patients, but repeated lumbar punctures (daily if necessary) or placement of a CSF lumbar drain are recommended as long as opening-pressure measurements remain elevated. Large volumes of CSF should be removed to reduce the opening pressure by 50%. Treatment with corticosteroids to reduce CSF pressure has yielded mixed results in both HIV-positive and HIV-negative patients, but the use of acetazolamide and mannitol have not been shown to provide benefit and are not recommended.

- **Aspergillosis.** *Aspergillus* spp. are etiologically related to four major clinical syndromes: invasive aspergillosis, chronic necrotizing pulmonary aspergillosis,

aspergilloma, and allergic bronchopulmonary aspergillosis. Of these, only invasive aspergillosis constitutes a major diagnostic and therapeutic challenge in the immunocompromised host. Those who are most at risk are BMT patients who have had prolonged neutropenia and/or treatment with corticosteroids or cytotoxic agents.

A. **Presentation.** The earliest symptoms of invasive aspergillosis may be pleuritic chest pain and hemoptysis; both reflect the proclivity of *Aspergillus* to invade blood vessels and cause distal hemorrhagic infarction. Pulmonary infiltrates are often large and wedge shaped, and cavitation is common. Chest CT scans may show multiple nodules not visible on the chest roentgenogram. The lungs are the most common sites of primary invasive aspergillosis, and dissemination to brain, skin, and other organs is frequent. Invasive aspergillosis has a very high mortality rate, and treatment must often be initiated even when definitive proof of diagnosis is lacking.
B. **Positive cultures,** particularly those from respiratory tract secretions, may only reflect colonization of the airway, which is especially common in patients with chronic sinusitis. However, BAL samples from a neutropenic host, yielding *Aspergillus* sp., generally require initiation of antifungal therapy. A positive culture from a biopsy sample is the gold standard.
C. **Histopathologic evidence** should be sought in the form of acute angle branching, septated nonpigmented hyphae in biopsy specimens from involved organs. These are best detected in Gomori methenamine silver (GMS)-stained specimens examined by an experienced mycologist or pathologist.
D. ***Aspergillus fumigatus*** is the most frequently pathogenic species. *A. flavus, A. niger,* and other *Aspergillus* spp. cause invasive disease less commonly. *A. terreus* tends to show poorer responses to antifungal therapy and, once disseminated, has a mortality rate approaching 100%.
E. ***Aspergillus* spp. are commonly isolated from environmental sources** such as moist wallboard in hospital rooms or on vegetation such as potted plants, fresh fruit or vegetables, or bouquets, which should be prohibited in immunocompromised patient rooms. Patient clusters or outbreaks of aspergillosis occur on BMT units near areas of active construction or renovation creating dust, which often contains *Aspergillus* conidia.
F. **Treatment.** The clinical diagnosis of disseminated aspergillosis should justify prompt empiric therapy if typical radiographic findings are present, even in the absence of a positive culture or biopsy sample. The following recommendations are derived mainly from the recently published practice guidelines for the management of aspergillosis by a panel of experts from the Infectious Diseases Society of America (*Clin Infect Dis* 2000;30:696–709).
    1. **Four antifungal agents** are available for treatment of invasive aspergillosis: AmB-deoxycholate, the lipid preparations of amphotericin, itraconazole, and caspofungin (a member of a new class of antifungal agents, the echinocandins, and FDA approved for the treatment of invasive aspergillosis **in patients refractory to or intolerant of other antifungal therapies**), and the investigational drug, voriconazole (available in i.v. and p.o. formulations from Pfizer, Inc., for compassionate use in patients for whom amphotericin therapy fails). The i.v. preparations of itraconazole and voriconazole contain a solubilizing agent, cyclodextrin, which should not be administered i.v. to patients with renal functional impairment. Caspofungin (Merck Pharmaceuticals) inhibits cell-wall synthesis and disrupts the structural integrity and cell-wall osmotic stability of many fungi. Recommended dosing is 70 mg i.v. loading dose followed by 50 mg i.v. daily, but dosage adjustment is recommended for moderate hepatic insufficiency. Early clinical trials as well as extensive testing in animal models of disseminated fungal infections have been encouraging. However, it has not yet been studied as **initial** therapy for invasive aspergillosis.
    2. **Initial treatment of aspergillosis** is usually with AmB (1.0 to 1.5 mg/kg i.v. daily) for patients with normal renal function. Patients who have renal insufficiency or develop it with therapy should probably receive one of the lipid-based preparations such as liposomal AmB (AmBisome; 5 mg/kg i.v. daily) or ABLC (Abelcet; 5 mg/kg i.v. daily), which are less nephrotoxic but much more expensive than AmB. Lipid-based AmB preparations may be preferred as initial therapy for patients with poor renal function or for those receiving other nephrotoxic drugs (e.g., aminoglycosides).
    3. **Response and duration of treatment.** In well-characterized patients with invasive aspergillosis, the response rate to AmB therapy has been about 37% (*Clin Infect Dis* 1996;23:608–615). The optimal duration of therapy with AmB or other antifungal agents is unknown and probably depends on the extent of fungal disease, response to antifungal therapy, and the patient's underlying malignancy and/or immune status. A reasonable sequence would be to use i.v. therapy first (AmB-deoxycholate), at least until disease progression is arrested, and then follow with oral itraconazole (400 to 600 mg daily) for a prolonged period.
    4. **Surgical excision** as an adjunctive modality has been successful for some cases of invasive pulmonary aspergillosis, especially for bulky lesions near the mediastinum, because they pose a risk of catastrophic pulmonary hemorrhage. Other adjuvant modalities such as colony-stimulating factors, granulocyte transfusions, or the interferons are not recommended for routine therapeutic use. The reader is referred to the IDSA Guidelines cited earlier for further discussion of the management of sinonasal, ocular, brain, and other forms of invasive *Aspergillus* infection.

- ***Pseudallescheria, Fusarium,* Mucor and dematiaceous fungi.** Several other filamentous fungi besides *Aspergillus* spp. may cause infections in neutropenic hosts. This group of fungi is generally ubiquitous, and they behave like classic opportunists (e.g., *Candida, Aspergillus*), rarely causing disease in normal hosts unless there is massive exposure.

A. ***Pseudallescheria boydii***, also called *Scedosporium apiospermum,* is found in soil, swamps, and polluted water. It may cause infection by inoculation or inhalation. Localized disease in soft tissues (e.g., the eye or thyroid gland), as well as bone, joint, or brain abscesses, is well described. Disseminated infection or pulmonary disease in neutropenic hosts has a high mortality and has been resistant to AmB. Surgical debridement has value in localized infection, and itraconazole or miconazole have been associated with clinical responses. Painful cutaneous nodules provide opportunities for biopsy and an etiologic diagnosis. *Pseudallescheria* is rarely cultured from blood. Pulmonary disease mimics aspergillosis with fever, cough, pleuritic pain, and hemoptysis.
B. **Zygomycosis** refers to infections caused by the order Mucorales. These agents are ubiquitous in nature. *Rhizopus* is the commonest clinical species, and it is associated with focal infections in patients with uncontrolled diabetes mellitus, corticosteroid therapy, or neutropenia. Treatment with desferrioxamine also is a risk factor for infection. Rhinocerebral and pulmonary infections occur most commonly. High-dose, prolonged AmB (1.0 to 2.0 mg/kg i.v. daily) plus surgical debridement is the treatment of choice, but the mortality rate remains high.
C. ***Fusarium* spp.** produce disseminated infections called fusariosis in patients with acquired immunodeficiency syndrome (AIDS) or hematologic malignancies, especially acute leukemia and BMTs. This fungus is found in soil and organic debris. It can produce inoculation infections in the eye (e.g., fungal keratitis) or skin. Disseminated infections usually result in positive blood cultures, and many patients will have painful skin papules or nodules with hyphae present in skin biopsies. High-dose AmB is the treatment of choice, but the mortality remains very high (50% to 80%) unless neutropenia subsides, graft-versus-host reaction is absent, and malignancy is in remission.
D. **Phaeohyphomycoses** are melanin-pigmented, septated hyphal forms also called “black molds” or dematiaceous fungi. They tend to produce focal infections including brain abscess. AmB-deoxycholate (1.0 to 1.5 mg/kg i.v. daily) is recommended for therapy, but its efficacy is questionable. Focal excision of infected tissue should be considered, if possible.

OPPORTUNISTIC MYCOBACTERIAL INFECTIONS

I. **Populations at risk.** Two groups of patients with acquired immune defects have been noted to be particularly susceptible to infections caused by the nontuberculous mycobacteria (NTM). These are (a) the HIV/AIDS population, for whom the ubiquitous *Mycobacterium avium/intracellulare* complex (MAC) organisms commonly cause disseminated infections; and (b) patients with hairy cell leukemia, who seem predisposed to infections with *M. kansasii* and occasionally other NTM. With the advent of vigorous chemotherapy and BMT, other ubiquitous mycobacteria have been recognized as causes of opportunistic infections. Three fairly common mycobacterial pathogens belong to the group of rapidly growing mycobacteria (RGM). These include *M. fortuitum, M. chelonae,* and *M. abscesses,* all displaying growth in culture in less than 7 days.

A. **Wound infections.** The best-known clinical syndrome caused by RGM is a localized wound infection after accidental trauma, but it also may occur in surgical wounds. Usually about 3 to 6 weeks after the trauma, local redness, swelling, and spontaneous drainage occur. Systemic symptoms such as fever, chills, and malaise are usually absent. The most common cause is *M. fortuitum,* which is susceptible to many antibiotics including ciprofloxacin, imipenem, and trimethoprim/sulfamethoxazole (TMP/SMX). Most isolates also are susceptible to clarithromycin, cefoxitin, and doxycycline (*Am J Respir Crit Care Med* 1997; 156:1–25).
B. **Catheter infections.** *M. fortuitum* also causes nosocomial infections, the most common of which is catheter-associated bacteremia. This may be discovered as a result of surveillance blood cultures, or it may occur as granulomatous hepatitis, septic lung infiltrates, or tunnel or catheter-exit-site infections. Recommended regimens are 2 to 4 weeks of i.v. treatment (usually TMP/SMX, 10 mg/kg/day of the TMP component) followed by oral antibiotic therapy (TMP/SMX, 1 DS t.i.d.) for 6 months. Catheter removal is crucial to the successful management of catheter-related infections caused by *M. fortuitum.* In general, susceptibility testing is not necessary, but if the clinical response is poor, alternative drug-susceptibility testing can be performed by Dr. Richard J. Wallace, University of Texas Health Center at Tyler, Tyler, Texas.
C. ***M. kansasii*** is much less prevalent in environmental samples is than is MAC, and it is seen less frequently as a cause of disease. Contamination of laboratory specimens and colonization of the airways may occur infrequently. Cutaneous as well as pulmonary infections are most frequent in older white men. Disseminated infections occur in immunosuppressed patients. Pulmonary infections with *M. kansasii* are associated with thin-walled cavities with relatively little surrounding infiltrate. Treatment administered for 18 to 24 months is generally with rifampin, ethambutol, and isoniazid (INH) despite the common occurrence of resistance to INH *in vitro.*
D. ***M. chelonae*** and ***M. abscessus*** are two other RGM commonly isolated from patients who have received prolonged corticosteroid therapy, cancer chemotherapy, or BMT. Most often these patients have fever, malaise, and disseminated papular skin lesions. Blood cultures or skin-biopsy cultures may be positive for mycobacteria, and the origin of infection may be an indwelling central venous catheter or port.

1. ***M. chelonae*** isolates are typically susceptible to clarithromycin, amikacin, tobramycin, imipenem, and occasionally (fewer than 20% of isolates) to doxycycline, TMP/SMX, and ciprofloxacin.
2. ***M. abscessus*** tends to produce disseminated infections in patients with rapidly fatal disorders such as poorly controlled leukemia or lymphoma. Cultures of blood and bone marrow are often positive, and a portal of entry may not be apparent, although it may be a central catheter. *M. abscessus* offers fewer possibilities for effective antimicrobial therapy, but most isolates are susceptible to amikacin, clarithromycin, cefoxitin, and imipenem. Susceptibility to cefoxitin also serves as a criterion of differentiation from *M. chelonae,* which are cefoxitin resistant. In the approach to treatment of *M. abscessus* infection, it is desirable to initiate therapy with a prolonged course of intensive multidrug therapy [cefoxitin or imipenem and amikacin at maximal dosage parenterally, with oral clarithromycin (500 mg twice daily)]. This should be followed by prolonged, perhaps indefinite suppressive therapy (clarithromycin, 500 mg p.o. twice daily, along with a second oral agent if it is supported by *in vitro* susceptibility testing).

NOCARDIA AND PNEUMOCYSTIS INFECTIONS

I. ***Nocardia* spp.** are aerobic, weakly gram-positive bacteria distinguished by filamentous growth and true branching with fragmentation into pleomorphic cocci and rods. A helpful identifying characteristic is partial acid-fast staining. *Nocardia* spp. retain fuchsin less tenaciously than *Mycobacterium* spp., and the "modified acid-fast staining" procedure is used for their identification. This involves the use of 1% sulfuric acid for decolorization rather than acid alcohol. Some pathogenic *Nocardia* strains fail to exhibit this staining characteristic.
   A. **Presentation.** The common routes of infection are the respiratory tract and direct inoculation into the skin, but it may occur clinically with hematogenous dissemination including central nervous system involvement. The overall mortality of *Nocardia* infections is 35% (*Clin Microbiol Rev* 1994;7:213–264). Bone marrow allograft recipients are at high risk. Other populations at risk include those receiving high-dose steroids, azathioprine-containing immunosuppressive regimens, and neutropenia (*Infect Dis Clin Pract* 1999;8:27–32). *N. asteroides* is the most prevalent species, and the lung is the most common site of infection (from which dissemination is common).
   B. **Treatment** The greatest clinical experience in the treatment of nocardiosis is with sulfonamides, and these remain the drugs of choice. TMP/SMX (5 to 15 mg/kg/day i.v. or p.o., of the TMP component) has been effective in the treatment of most isolates of *Nocardia* spp. If there is a prompt clinical response, the dosage may be reduced after the first 6 to 8 weeks of therapy. Sulfa levels in the blood should be monitored, with target peak serum concentrations of 80 to 160 µg/mL. If sulfa drugs cannot be used because of allergy, intolerance, or toxicity, susceptibility testing may be used to choose an alternative. Nonsulfa drugs found to be effective are amikacin (7.5 mg/kg i.v. q12h), minocycline (200 mg p.o. b.i.d.), imipenem-cilastatin (500 mg i.v. q6h), ceftriaxone (1 to 2 g i.v. q12h), and cefotaxime (2 g i.v. q8h). Treatment is generally for 6 months or longer in immunocompromised individuals. The efficacy of secondary prophylaxis with TMP/SMX is unclear.

II. ***Pneumocystis carinii* pneumonia**

Although it is less common than in AIDS patients, *Pneumocystis carinii pneumonia* (PCP) is an acknowledged opportunistic infection in patients with hematologic malignancy, solid organ tumors, or allograft transplantation, including BMT (*Arch Intern Med* 1995;155:2436–2441). Other risk factors for development of PCP include treatment with fludarabine or long-term therapy with adrenal steroids. PCP is especially associated with cellular immunodeficiency, and it is potentially preventable, because prophylaxis with oral TMP/SMX is highly effective. However, the precise degree of immunodeficiency at which PCP occurs is not clear, and so it remains uncertain which patients would benefit from prophylaxis. The overall mortality rate in the 78 patients described in the earlier reference was 35%. Another important observation from that study was the large variation in the duration and cumulative dosage of immunosuppressive agents. This implies that the predisposition to PCP cannot be predicted by the total amount of previous immunosuppression alone.

Another recent report described 116 patients with PCP without AIDS (*Mayo Clin Proc* 1996;71:5–13) and found a similar distribution of underlying disorders (i.e., hematologic malignancies, organ transplants, inflammatory disorders, and solid tumors). Respiratory failure was present in 43%, and the in-hospital mortality was 34%. Of the patients, 23% had other infections (bacteria, CMV, fungi) occurring concurrently with PCP. Similar to that with the AIDS patient, the diagnosis of PCP should be pursued with microscopic examination of stained sputum or BAL samples.

A. **Therapy for PCP** is the same for patients with or without AIDS. TMP/SMX [5 mg/kg of TMP component i.v. q8h, plus prednisone, 40 mg b.i.d. for 5 days, followed by prednisone taper for patients with significant hypoxemia (i.e., P_{O_2} less than 70 mm Hg)] is the regimen of choice. Several clinical provisos in the evaluation of patients with PCP are worthy of note (*Antimicrob Agents Chemother* 1998;42:1309–1314).
   1. The clinical response to appropriate therapy may be slow.
   2. Radiologic appearance lags behind clinical improvement or deterioration.
   3. Empiric therapy is generally avoided in immunocompromised patients without AIDS.
B. **Prophylaxis.** Selection of immunocompromised patients without AIDS who should receive TMP/SMX prophylaxis remains somewhat arbitrary. Many centers have routinely administered prophylaxis to BMT recipients and children with lymphoblastic leukemia (*Arch Intern Med* 1995;155:1125–1128). Some also recommended prophylaxis for those who are immunosuppressed **and** receive a course of corticosteroid therapy for longer than 4 weeks at a level equivalent to 20 mg of prednisone daily.

SUGGESTED READINGS

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CHAPTER 27. ONCOLOGIC EMERGENCIES

William Read and Alex Denes

Cardiac tamponade
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Objective
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I. Cardiac tamponade

A. Subjective

Dyspnea is the most common presentation and often the only symptom of pericardial tamponade. Other symptoms include cough, chest pain, orthopnea, and generalized weakness. Impaired right-heart filling may lead to symptoms of right-heart failure, such as peripheral edema, hypotension, and elevated jugular venous pressure (JVP). Severe hypotension and pulseless electrical activity are the final consequences of untreated tamponade.

B. Objective

Patients with tamponade are often found to have tachycardia and hypotension. Pulsus paradoxus (a decrease in systolic blood pressure of 10 mm Hg or more on inspiration) is classically associated with tamponade and should be looked for in patients suspected of having pericardial effusion. Examination of the neck veins may reveal distended nonpulsatile jugular veins.

C. Workup

Chest radiograph may reveal an enlarged cardiac silhouette (water-bottle heart). The characteristic findings on electrocardiogram (ECG) in patients with pericardial effusion include low voltage and possibly electrical alternans as the heart swings within the distended pericardium. Two-dimensional echocardiography is the most frequently obtained study and can demonstrate both the effusion and collapse of the right atrium and ventricle. Collapse occurs because extrinsic compression by the effusion overcomes venous pressure and prevents right heart filling. Impaired right heart filling also can be demonstrated with right heart catheterization. Cardiac tamponade is a clinical diagnosis, and the absence of one or more findings or symptoms should not prevent a trial of pericardiocentesis in symptomatic patients in whom tamponade is suspected. Examination of pericardial fluid is essential in establishing the diagnosis, even in patients known to have malignancy. In malignant involvement of the pericardium, cytology will be positive in only 65% to 85% of cases; therefore pericardial biopsy remains the gold standard for establishing malignant involvement. Other etiologies of pericardial effusion include inflammatory disorders, drug side effects, infections, radiation, uremia, and hypothyroidism, any of which may exist in cancer patients. Hemopericardium should be suspected in patients with known coagulopathy. Computed tomography (CT) or magnetic resonance imaging (MRI) images of the heart may reveal the presence of a pericardial effusion but cannot determine hemodynamic significance.

D. Therapy

Increased use of echocardiography and sensitive imaging has shown that many cancer patients have asymptomatic pericardial effusions. Asymptomatic patients generally do not require treatment unless the effusion is significant or the etiology unclear. In tamponade, the initial goal of treatment is to drain the fluid. This is usually done by placement of a draining catheter under ultrasound guidance, although bedside needle aspiration may be attempted in urgent situations. After local anesthesia, the needle is inserted to the right of the xiphoid and advanced toward the tip of the left scapula, with constant aspiration during the procedure. A large syringe or a catheter with a stopcock should be available to allow removal of 50 to 60 mL of fluid.

If the underlying malignant process causing pericardial effusion cannot be controlled, repeated accumulation of fluid occurs commonly. In this situation, a surgical pericardial window will usually prevent repeated accumulation and is the treatment of choice, even if the effusion cannot be confirmed to be malignant by cytology. If the patient is not a surgical candidate, pericardial sclerosis can be performed via catheter instillation of sclerosing agents, such as bleomycin, doxycycline, thiotepa, and cisplatin. We do not recommend talc sclerosis, because it may cause considerable pain. A recent series described 36 patients with malignant pericardial effusion who were treated with ^{32}P radioactive colloid (*Br J Cancer* 1955–1957;80:12). Each patient received an intrapericardial instillation of 185 MBq of ^{32}P; 14 (39%) patients required a second dose within 2 weeks because of recurrent effusion. Ninety-four percent of patients had complete resolution of pericardial effusion and died of progressive disease at other sites. Toxicity was minimal, with only one instance of transient tachycardia. This approach may be a reasonable alternative to surgery in patients with malignant tamponade, especially in patients who are poor surgical candidates.

E. Natural history

While 10% to 15% of patients dying of cancer are found to have pericardial involvement at autopsy, only a small proportion develop clinical tamponade in life. Breast cancer, lung cancer. and lymphoid malignancies are the most common causes of malignant pericardial effusion and tamponade. The median survival of patients with tamponade ranges from 80 to 170 days and is greatly influenced by the success of controlling the underlying malignancy.

II. Hypercalcemia

A. Subjective

The symptoms may develop insidiously and be difficult to distinguish from those caused by coexisting conditions; conversely, patients may be first seen in acute crisis. The student mnemonic “stones, bones, abdominal groans, and psychic moans” has long been used to remember the manifestations of hypercalcemia. “Stones” (nephrolithiasis) are more common in hyperparathyroidism than in hypercalcemia of malignancy, but cancer patients with symptomatic hypercalcemia usually have some renal impairment, with dehydration, elevated creatinine, polyuria, and polydipsia. “Bones” refers to the fractures seen in long-standing hypercalcemia as a result of demineralization; bony metastases are often but not invariably present in patients with hypercalcemia of malignancy. “Abdominal groans” refers to constipation, nausea, and anorexia, and “psychic moans” refers to mental-status changes such as confusion and obtundation. Some of these symptoms can erroneously be ascribed to drugs, especially opiate analgesics. In the absence of prompt recognition and treatment, hypercalcemia can progress to renal failure, coma, and death.

B. **Objective**

Physical examination may reveal altered mental status, distended abdomen from ileus, and signs of dehydration.

C. **Workup**

The normal range for total serum calcium is 8.6 to 10.3 mg/dL (2.15 to 2.57 m*M*). About half of the circulating calcium is bound by albumin, and the remaining unbound ionized calcium (normal range, 4. 5 to 5. 1 mg/dL) is responsible for biologic effects. In patients with hypoalbuminemia, the ionized calcium may be higher, and the effective total calcium should be calculated with the formula

Corrected Ca (mg/dL) = measured Ca (mg/dL) – albumin (g/dL) + 4

High levels of paraprotein also can alter calcium binding, and in these cases, the ionized calcium should be measured directly. Symptoms generally develop at total calcium levels of 11.5 to 12 mg/dL, but like those of other metabolic derangements, symptoms are dependent on the rapidity of increase as well as the absolute level. A serum calcium of 14 mg/dL or higher developing over days may render a patient comatose, whereas the same level developing over months may be relatively asymptomatic.

Malignant hypercalcemia usually develops in patients with extensive skeletal metastases (e.g., breast cancer, lung cancer, prostate cancer, or multiple myeloma), paraneoplastic secretion of parathyroid hormone–related peptide (PTH-rp; squamous cell carcinoma of the lung, cervix, or upper aerodigestive tract), or excessive 1,25-OH vitamin D production (non-Hodgkin lymphoma). All patients with malignant hypercalcemia should have a histologic diagnosis and staging to determine the extent of metastases so that appropriate treatment of the underlying malignancy can be initiated.

In patients with hypercalcemia without a previous history of malignancy, other causes of hypercalcemia should be considered. Chief among these is hyperparathyroidism: because the immunoassay for PTH does not detect PTH-rp, patients with elevated PTH are more likely to have hyperparathyroidism than malignant hypercalcemia. The differential diagnosis of hypercalcemia also includes thyrotoxicosis, adrenal insufficiency, 1,25-OH vitamin D toxicity (through ingestion or granulomatous conversion), and inherited disorders of calcium metabolism.

D. **Treatment**

Hypercalcemia of malignancy is treated uniformly regardless of the underlying process. Patients with symptomatic hypercalcemia are often dehydrated and may have impaired renal function. Such patients should be rehydrated with normal saline (usually 2 to 3 L) and then maintained on intravenous fluid (0.9% saline or 0.45% saline) if oral intake is insufficient. Electrolytes should be carefully monitored and potassium and magnesium repletion achieved as necessary. Hypophosphatemia is common in hypercalcemia but should not be repleted unless symptomatic, because an increase in the calcium × phosphorus product to 70 or more can cause precipitation of calcium salts in the kidney and other soft tissues.

1. **Intravenous bisphosphonates** have become the mainstay of treatment for malignancy-associated hypercalcemia, and can successfully control serum calcium in 80% to 90% of patients. Pamidronate is used for this indication at a dose of 90 mg infused over a 2- to 4-hour period. Zoledronate is a third-generation bisphosphonate, approved for treatment of hypercalcemia in the fall of 2001 and has the advantage of a shorter infusion schedule of 4 mg i.v. over 15 minutes. The main side effect is hypocalcemia, which may not be symptomatic. Serum calcium will generally normalize 3 to 4 days after administration, and the nadir is reached around day 10. Serum calcium levels should be monitored, and patients with recurrent hypercalcemia may require repeated dosing every 3 to 4 weeks. Oral bisphosphonates have not been shown to be as effective and are not recommended.
2. **Calcitonin** given intramuscularly or subcutaneously (i.m. or s.q.) at a dose of 6 to 8 units/kg can decrease serum calcium within 2 to 4 hours of administration. Although less potent than bisphosphonates, calcitonin is safe and fast acting, and may be used to manage severe hypercalcemia in the initial 2 to 3 days before bisphosphonates reach full effect. Unfortunately, tachyphylaxis to the hypocalcemic effects of calcitonin often occurs after a few days, limiting its long-term use. Nasal calcitonin is not recommended for control of hypercalcemia. **Corticosteroids** may be effective in controlling hypercalcemia in patients with hematologic malignancies such as myeloma or lymphoma. A dose of 60 mg prednisone p.o. or its equivalents given intravenously can be used alone or in combination with bisphosphonates in patients with hematologic malignancies before definitive therapy or as a bridge to more definitive treatment of the underlying malignancy. Steroids are not effective in the treatment of hypercalcemia in patients with solid tumors.

   Plicamycin also is effective in reducing serum calcium, but because of its renal and hematologic side effects, it has been supplanted by bisphosphonates and should be reserved for refractory cases of hypercalcemia. Gallium nitrate is effective, but also carries considerable side effects and is no longer widely available.

   Squamous cell carcinoma of the lung and breast cancer are the most common neoplasms associated with hypercalcemia. Other cancers that may commonly be complicated by hypercalcemia include multiple myeloma, squamous cell carcinoma of the head and neck, prostate cancer, and malignant lymphomas, but it has been reported in association with almost all tumor types. Hypercalcemia of malignancy has traditionally been classified as humorally mediated hypercalcemia with elevated levels of PTH-rp or arising from osteolytic metastases; however, in some cases, both of these mechanisms may be responsible for hypercalcemia. Myeloma and hematologic malignancies may cause hypercalcemia, through cytokine secretion and increased 1,25-OH vitamin D production.

   Hypercalcemia is usually a marker of advanced malignancy and is ideally addressed by definitive treatment of the underlying cancer. Unfortunately such treatment is not always available. In one series, patients treated for hypercalcemia without antineoplastic treatment had a median survival of only 29 days.

III. **Spinal cord compression**

A. **Subjective**

Back pain is the most frequent symptom associated with cord compression and usually precedes neurologic impairment. The pain may be localized to the back or may radiate either unilaterally or bilaterally in the distribution of spinal roots. Coughing or movement can often exacerbate the pain resulting from radiculopathy. Some patients complain of sensory paresthesias such as burning, skin sensitivity, or numbness. Compression of the long sensory tracts in the cervical cord may cause paresthesias to appear in various lower dermatomes. Motor symptoms usually develop last. Common complaints include weakness or heaviness of the affected limbs, flaccid paralysis, and loss of bladder and bowel control. The symptoms of cord compression may occur abruptly or progress gradually.

B. **Objective**

The most important aspect of the examination is suspicion of the presence of cord compression by the examining physician. New onset of back pain in a patient at risk mandates a careful neurologic examination. In cases of gradual cord compression, patients may be unaware of sensory deficits that may be detectable by neurologic examination. Regions distal to the cord compression may be weak and hyperreflexic with up-going (extensor plantar) reflexes in the toe, whereas reflexes at the level of a lesion are decreased. Urinary retention should be determined by obtaining a postvoid bladder residual. Anal sphincter function is usually preserved until late in cord compression; early deficits in sphincter tone or sensation may be due to involvement of the cauda equina. Acute, severe cord compression can cause spinal shock, with hyporeflexia and flaccid paralysis of all regions below the lesion.

C. **Workup**

The clinical neurologic examination may prompt further evaluation of the spine but is not precise enough to be used to plan treatment. All patients with suspected cord compression should undergo imaging of the spine. MRI is more sensitive than myelography and is the modality of choice when available. Contrast CT is recommended if MRI cannot be performed. It is important to image the entire spine, as some patients may have more than one region of compression. Plain films and bone scans have a limited role because they may miss soft tissue components of tumors. If the nature of the compressing mass is uncertain, surgical or image-guided biopsy for tissue diagnosis is essential. When cord compression is the initial presentation of cancer, further evaluation may reveal a lesion such as a lymph node, on which it may be easier to perform a biopsy.

D. **Management**

Spinal cord compression requires prompt recognition because delay in treatment usually results in reduced recovery of function and poor outcome. Corticosteroids should be started as soon as spinal cord compression is suspected and may be started in the absence of a tissue diagnosis. Steroids decrease edema associated with spinal cord compression and improve symptoms transiently. We recommend dexamethasone be used at the dose of 10-mg loading dose i.v. or p.o. followed by 4 mg every 6 hours. Patients treated with these doses of corticosteroids should receive prophylactic acid suppression (with an H_2 or proton-pump blocker) to prevent the development of gastric stress ulcers. Dexamethasone should be tapered off over the subsequent 2 to 3 weeks regardless of symptom improvement.

External-beam radiation is the treatment of choice and should begin as soon as the diagnosis is confirmed. Standard radiation doses range from 2,500 to 4,000 cGy delivered in 10 to 20 fractions. Traditional indications for surgical intervention include the need for a tissue diagnosis, resection of “radioresistant” tumors and tumors primarily treated by surgery (such as sarcomas), and cord compression in a previously irradiated spine. A very rapid onset of symptoms suggests the possibility of vertebral burst fracture causing bony impingement on the cord. This is an indication for urgent surgical intervention to remove bone fragments from the spinal canal. Patients with extensive bony destruction by tumor and vertebral instability may be at risk for further compression fracture and symptom recurrence after completing x-ray therapy (XRT): these patients should be considered for vertebral stabilization. Surgical patients usually require 7 to 10 days for wound healing before beginning radiation.

Systemic therapy using hormonal and/or chemotherapeutic agents as well as pamidronate should be included when appropriate (for example, in patients with lymphoma). Prostate cancer is a common cause of cord compression, and the treatment of choice is androgen blockade in patients who are not hormone resistant. High-dose ketoconazole (400 mg p.o. every 8 hours) rapidly reduces testosterone levels into the castrate range and should be considered in patients with cord compression known or suspected to be caused by prostate cancer. Patients receiving high-dose ketoconazole should be given replacement doses of corticosteroids (prednisone, 5 mg p.o. in the morning and 2.5 mg p.o. at bedtime), as ketoconazole may cause adrenal insufficiency. One strategy is to initiate treatment with ketoconazole and flutamide (a peripheral androgen blocker) on presentation, and then a few days later discontinue ketoconazole and administer a gonadotropin hormone–releasing hormone (GnRH) agonist (e.g., leuprolide). Flutamide must be continued for 3 to 4 weeks when starting a GnRH agonist to prevent tumor flare.

Course of the disease: In an estimated 1% of cancer patients, spinal cord compression develops in the course of their disease, and this number is expected to increase as improvements in systemic therapy allow these patients to live longer. Metastatic breast, lung, and prostate cancers account for the majority of malignant cord compression. Although cord compression is usually not life threatening, patients with neurologic impairment secondary to cord compression have a markedly reduced quality of life and a significantly shortened overall survival. Exophytic metastases to a vertebral body account for 80% to 90% of cases, with the remaining due to epidural metastases and vertebral fractures. Other less common causes of cord compression include metastases to the posterior vertebral elements, benign and malignant tumors primary to the spine, vascular malformations, and infections. It is critical to begin therapy as soon as possible. In a recent series of 153 patients treated with radiation, all ambulatory patients and those nonambulatory patients who retained lower-extremity sensation were able to ambulate after completing treatment. Sixty percent of patients with combined motor and sensory loss regained ambulation. The median survival of ambulatory patients was 7.9 months, and only 1.2 months for patients who could not walk.

IV. Tumor lysis syndrome

A. Subjective

The tumor lysis syndrome (TLS) refers to the metabolic consequences resulting from the sudden release of potassium, phosphates, and purine metabolites from tumor cells undergoing cell death. TLS is classically associated with malignancies such as acute lymphoblastic leukemia or Burkitt lymphoma that are characterized by a high growth fraction, have substantial systemic tumor burden, and respond rapidly to cytotoxic chemotherapy. TLS can occur in any situation in which considerable tissue bulk is rapidly destroyed within the body, including cytotoxic chemotherapy, biologic treatments, corticosteroids, radiation, and chemoembolization. Symptoms are variable and cannot be relied on to monitor the course of TLS. The presenting symptoms may range from arrhythmias, mental status changes, and renal failure to sudden death from hyperkalemic cardiac arrest. Patients with hyperphosphatemia and/or hypocalcemia are often asymptomatic but may present with tetany or stupor. Ideally, the treating physician should anticipate TLS and intervene before the symptoms or serious metabolic complications develop.

B. Objective

TLS has two main metabolic consequences: renal failure and hyperkalemia. Renal failure occurs from precipitation of phosphate and urate salts in the kidney. The resulting renal impairment leads to further accumulation of phosphorus and uric acid, creating a vicious cycle. Patients at risk for TLS often have some degree of renal insufficiency before chemotherapy, usually in part from dehydration. The presence of an elevated uric acid, phosphorus, and lactate dehydrogenase (LDH) on presentation suggests the presence of large tumor bulk, rapid cell turnover, and possible smoldering tumor lysis, which may be exacerbated after treatment. Increasing potassium and worsening renal failure in a patient at risk suggests the onset of TLS. Because the rate of progression may be unpredictable, we recommend that blood chemistries (electrolytes, creatinine, phosphorous, calcium, and LDH) be checked in patients at risk every 8 to 12 hours during the first 2 to 3 days of treatment.

C. Management

The best approach to TLS is prevention. Patients at risk should be identified promptly so that preventive measures can be initiated before and during initial treatment. Patients at high risk include those with high-grade or bulky lymphoid malignancies, such as Burkitt lymphoma and acute lymphoblastic leukemia (ALL), but patients with chronic lymphoblastic leukemia (CLL) and small cell lung cancer also may be at risk. The laboratory abnormalities that signify increased risk for TLS include elevated LDH and uric acid, and preexisting renal failure.

All patients should have volume repletion before beginning chemotherapy, and isotonic fluids should be infused at 200 to 300 mL/hour to achieve a brisk diuresis during the first 2 to 3 days of chemotherapy. The goal of hydration is to preserve renal function and to eliminate cellular breakdown products as they are released. Furosemide may be given to maintain urine output and also may increase excretion of potassium. The urine pH should be greater than 7 to maintain uric acid and phosphorus in their ionized, soluble form and to prevent crystal deposition in the renal tubules. We recommend urine alkalinization with either one amp $NaHCO_3$ in 0.5N saline or two to three amps in D5W. Bicarbonate also may be needed to correct metabolic acidosis accompanying TLS. Acetazolamide may be used as an adjunct to alkalinize the urine. HCO_3 may be removed from intravenous fluids 2 to 3 days after the serum HCO_3 returns to normal.

Allopurinol blocks purine metabolism by preventing the conversion of xanthine to uric acid. Xanthines are more soluble and easily excreted; thus allopurinol decreases the increase in serum uric acid and urate crystal deposition in the kidney. Allopurinol should be given p.o. or i.v. at 600 mg/day, starting 24 to 48 hours before chemotherapy. The dose should be decreased for preexisting renal insufficiency and as tumor bulk decreases.

Hyperkalemia may develop rapidly, and patients at risk should have serum electrolytes checked at least every 12 hours, and more frequently if TLS develops. Mild hyperkalemia (less than 5.5 m*M*) may be treated with sodium polystyrene sulfonate (Kayexelate resin) and hydration as described earlier. More serious hyperkalemia (greater than 5.5 m*M* or with ECG changes) may be treated immediately with 50 mL of 50% glucose solution with 15 units of regular insulin, i.v. piggyback over an hour. Indications for hemodialysis include volume overload, serum uric acid greater than 10 mg/dL, or rapidly increasing phosphorus levels and uncontrolled hyperkalemia. Renal failure caused by TLS is usually reversible, and even patients requiring hemodialysis often regain normal kidney function as the TLS subsides.

V. Superior vena cava syndrome

A. Subjective

Patients with superior vena cava (SVC) syndrome commonly complain of dyspnea, swelling of the face, neck, and upper extremities, and pain (chest pain or headaches). Symptoms may develop rapidly or gradually and may vary in severity by position. Bending forward or lying flat may worsen symptoms as a result of increased venous pressure proximal to the obstruction. Even in the presence of severe symptoms, patients are rarely critically ill as a result of SVC syndrome alone.

B. Objective

Dilated neck veins are usually present, as is edema of the face, arm, neck, and supraclavicular region. Gradual occlusion of the SVC allows the development of collateral veins, which may be easily visible over the upper chest. The chest radiograph may show mediastinal widening but is normal in some patients.

C. Workup

A tissue diagnosis is essential in the management of SVC syndrome, as specific treatment may be influenced by the tumor type. CT imaging of the chest can provide very useful information regarding the patency of SVC and adjacent structures, including presence or absence of compressive mass lesions, and is useful in planning subsequent biopsy or therapeutic intervention. Patients without a tissue diagnosis or in whom the diagnosis is uncertain should undergo surgical or percutaneous biopsy of an accessible site. If unsuccessful, thoracic surgery should be consulted for bronchoscopy and, if necessary, mediastinoscopy, which can provide a tissue diagnosis in the majority of cases.

D. Treatment

Radiotherapy has been essential in the treatment for SVC syndrome, and 87% of patients respond when treated with regimens delivering 2,000 cGy or more, depending on tumor type and location. Patients with chemoresponsive tumors, such as germ cell, small cell, and lymphoma, might more appropriately be treated with chemotherapy first, followed by radiation if necessary. Expandable vena caval stents may be as efficacious as radiation in relieving SVC obstruction. Stenting can be used to provide immediate relief while radiation or chemotherapy takes effect, or in patients whose symptoms recur after radiation. In a subset of patients, SVC syndrome develops from benign causes. Occlusive SVC thrombosis may occur as a complication of central venous catheters. If there is no contraindication, these patients can be effectively treated with thrombolysis. The central catheter should be left in place and used to administer lytics, and patients should be given anticoagulation afterward, as with any deep vein thrombosis (DVT). Central vein catheters also may cause stenosis of the SVC; this is treatable with fluoroscopy-guided balloon dilatation, with or without stenting.

E. Natural history

The SVC syndrome occurs when extrinsic compression or intrinsic obstruction of the SVC impedes venous return from the head and upper body. SVC syndrome is traditionally included among oncologic emergencies, although it is not now thought to be imminently threatening to life or limb. A methodical and timely approach to diagnosis and treatment is appropriate. Malignancy causes the majority of cases of SVC, and lung cancer, especially small cell lung cancer, accounts for 67% to 85% of cases, with lymphoma and metastatic tumors making up the remainder. The prognosis for patients with SVC syndrome is that of their underlying disease.

VI. Leukostasis

A. Subjective

Leukostasis is a syndrome associated with acute myelogenous leukemia (AML) and consists of respiratory distress, abnormal chest radiograph (CXR), confusion, and central nervous system (CNS) bleeding. Patients may be confused or stuporous. Gingival hyperplasia or skin lesions may occur secondary to invasion of blasts in myelomonocytic (M4) and monocytic (M5) types of AML. Leukostasis is a clinical diagnosis: symptoms are nonspecific and may be attributed to infection or heart failure.

B. Objective

Leukostasis is associated with high and rapidly increasing blast counts, usually more than 50K and often more than 100K; in two series between 56% and 59% of patients with blast counts greater than 100K had clinical evidence of leukostasis. Patients in leukostasis are usually hypoxemic, although live blasts in an arterial blood sample obtained for arterial blood gas (ABG) estimation may lower the Po_2 content spuriously if the specimen is not processed in a timely fashion. A nonspecific diffuse infiltrate is often present on CXR. There may be impairment of other end organs, including the eye, kidney, and liver. Lactic acidosis may be a late event. Symptoms may be fulminant, leading to death in a matter of days or even hours. These patients have a propensity for CNS bleeds after chemotherapy is begun, often in the absence of disseminated intravascular coagulation (DIC) or thrombocytopenia.

C. Management

Prompt initiation of leukapheresis can be lifesaving for these patients and should not be delayed while differential diagnoses are ruled out. Leukapheresis can attenuate or reverse the symptoms of leukostasis, and patients who receive leukapheresis have a decreased incidence of CNS bleeds after beginning chemotherapy. The “debulking” effect of removing circulating blasts may decrease the incidence of subsequent TLS as well. There are few ill effects, and leukapheresis should be considered for all those with leukemia with total white cell count greater than 100,000/dL. It should be instituted without delay in patients with leukostasis; the high-flow dialysis catheter used for the procedure can then be used to administer chemotherapy.

Hydroxyurea might be considered as an adjunct to leukapheresis to decrease cell proliferation before definitive treatment. Intravenous hydration is beneficial, although red blood cell transfusion should be delayed if possible, as this could result in increase or worsening of symptoms associated with leukostasis. DIC or thrombocytopenia should be corrected to minimize the risk of CNS bleeding. Patients suspected of having coexistent infection should have blood drawn for culture and be treated empirically with broad-spectrum antibiotics. Therapy for underlying leukemia should begin expeditiously.

D. Natural history

Myelomonocytic (M4) and monocytic (M5) and AML compose the majority of AML cases that manifest with hyperleukocytosis and leukostasis, although it has been described in other forms of myeloid leukemias. Despite the very high blast counts that can occur in lymphoid leukemias, leukostasis is not very common in ALL. The classic pathologic finding in leukostasis is occlusive intravascular aggregates of blasts blocking the circulation in multiple organs, but especially the lungs and brain.

VII. Paraneoplastic syndromes

Paraneoplastic syndromes are a widely varied group of phenomena encompassing clinical manifestations of malignancy not directly caused by tumor invasion and destruction of normal tissue. They may be roughly divided between syndromes caused by hormones or cytokines secreted by the malignant cells, and syndromes occurring in the context of a malignancy-induced immune response. Paraneoplastic phenomena may herald cancer recurrence or may be the presenting feature of a cancer. Successful treatment of underlying malignancy has the potential to reverse symptoms associated with paraneoplastic syndromes (secondary to ectopic hormone production or cytokine release), although subsequent relapse of malignancy may be associated with recurrence of the paraneoplastic syndrome. Syndromes associated with immune responses and autoantibodies often do not improve after the underlying tumor is controlled. Neurologic paraneoplastic syndromes and paraneoplastic pemphigus are examples of this type; immunosuppressive therapies are often tried for these patients, with variable results.

Table 27.1 shows various paraneoplastic syndromes along with the organ system they affect, associated circulating molecules or antibodies, and the tumor type with which they are most often associated. Note that this tumor type is by no means exclusive; a literature search will discover many case reports of atypical tumor/paraneoplastic syndrome pairings.

TABLE 27.1. PARANEOPLASTIC SYNDROMES ASSOCIATED WITH MALIGNANCIES

SUGGESTED READING

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CHAPTER 28. NURSING ISSUES IN THE PATIENT WITH CANCEF

Edie Romvari and Paula Goldberg

Cancer-related fatigue
Fatigue secondary to underlying cancer
Fatigue due to cancer-related treatments
Concomitant factors and etiologies related to fatigue
Psychosocial responses
Fatigue intervention
Evaluation
Pain
Example of implementation of JCAHO standards on pain assessment
Nutrition
Assessment
Intervention
Parenteral nutrition
Altered skin and mucous membrane integrity
Surgical and procedure-related causes
Radiation therapy impact on skin structures
Management of skin reactions
Skin assessment related to indwelling catheters/access devices
Dry skin and rashes
Mucosal changes
Intervention and treatments
Psychosocial distress
Key assessment points include the following
Oncology nurse as an educator
Role of oncology nurse in clinical research
Resources
Ambulatory oncology telephone triage
Suggested Readings

The nurse who cares for patients with cancer requires knowledge of the disease and its treatment, supportive care, survivorship issues, and end-of-life care.

Cancer patients are seen in various settings (i.e., acute, outpatient, home, and extended care). Oncology nurses must be skilled in working in a multidisciplinary setting because the patients' needs are numerous and complex. The nurse must be adept at identifying needs, planning care, and making appropriate referrals to other members of the health care team and community resources. No matter where the patient is in the course of the disease or treatment, the nurse plays a pivotal role in the management of symptoms. This chapter reviews major categories of symptoms caused by cancer and/or its therapy from the nursing perspective.

I. Cancer-related fatigue

Fatigue has long been recognized as the most common side effect of cancer and cancer-related treatments. Patients diagnosed with cancer readily acknowledge that fatigue is one of the major causes negatively affecting the quality of life. Various sources have estimated that more than 75% of all cancer patients will experience some form of fatigue (*Oncologist* 1999;4:1–10). In addition, a multitude of fatigue-related surveys have shown how severely these subjective symptoms disrupt and affect an established daily routine. Two studies conducted by “The Fatigue Coalition,” an action group comprised of multidisciplinary medical personnel and patient advocates, demonstrated that fatigue is the most bothersome, undertreated, and neglected cancer-related symptom. They found that it surpasses pain, nausea/vomiting, and depression (*Oncol Trials* 2001;23:22–25).

Cancer-associated fatigue affects the physical, psychological, social, and spiritual well-being of the cancer patient. Subjective symptoms are: excessive tiredness, weakness, decreased mobility, lethargy, insomnia, lack of motivation, loss of ability to concentrate, lack of interest in self-expression, decreased socialization and group interaction, depression, disinterest in activities of daily living, and declining interest to participate in spiritual and religious activities (Hassey DK, Dunn Bucholtz J, Iwamoto RR, et al. *Nursing care in radiation oncology.* 2nd ed. Philadelphia: WB Saunders, 1997).

Fatigue can have several different origins. It is important to realize this because treatment options must be specific to the underlying cause to be effective. Three underlying causes are suspected of being responsible for the majority of these symptoms: underlying cancer, therapy-related causes, and those resulting from preexisting comorbid diseases.

A. Fatigue secondary to underlying cancer

Symptoms of fatigue can arise from the cancer itself because of a significant tumor burden. Tumor-stimulated cytokines such as asthenin and tumor necrosis factor (TNF-a), interleukins 6 and 8, and C-reactive protein are thought to be responsible for loss of muscle strength, weight loss, and anemia. (*Oncol Trials* 2001;23:22–25).

B. Fatigue due to cancer-related treatments

Chemotherapy and biologic-response modifiers, radiation therapy, and surgical procedures are thought to be physically and emotionally debilitating as well. This is especially noticeable in patients undergoing radiation therapy, although its origin is not clear (Hassey DK, Dunn Bucholtz J, Iwamoto RR, et al. *Nursing care in radiation oncology.* 2nd ed. Philadelphia: WB Saunders, 1997). Combined-modality therapy further reduces the patient's energy level; thus causing increased fatigue symptoms. Surgical procedures, especially when preceded by other treatments, can have a prolonged period of recovery of physical and psychological strength.

C. Concomitant factors and etiologies related to fatigue

Predisposing factors as well as an underlying disease history must be identified whenever fatigue is assessed (*Oncologist* 1999;4:1–10). They include cardiac, pulmonary, peripheral vascular disease, anemia, diabetes, neuromuscular disease and immobility, hepatic and renal impairment, electrolyte imbalance, hormonal and metabolic disorders, pain, pain medication, anxiety, depression, and a variety of prescribed medications. The use of narcotics when the patient is already anemic is probably the most common factor in causing cancer-associated fatigue.

D. Psychosocial responses

The psychosocial response to fatigue can be profound. Because of the decreased energy levels, less interest is afforded to physical and psychological tasks. Social interactions are too draining; thus the patient becomes more isolated. Especially in patients with limited social support, fatigue can elicit maladaptive behavior patterns such as isolation from family and friends, feelings of despair, and hopelessness. This in turn leads to neglect to follow through with treatment schedules at the cost of optimal treatment outcomes (Fig. 28.1).

FIG. 28.1. Piper's integrated fatigue model. (Reprinted from B. F. Piper, D.N.Sc., RN, AOCN, FAAN, The network project: fatigue in cancer and MOS, http://www.networkproject.org/, with permission.)

1. **Assessment parameters.** Fatigue assessment must include objective data such as physical assessment, laboratory data analysis, and medication history. In addition, several fatigue-assessment tools are available for the practitioner today to capture subjective symptom information. They range from the complex multidimensional questionnaires to one-page visual analogue scales (VASs) similar to the pain VAS.

Examples of published assessment tools:

- Brief Fatigue Inventory (BFI); University of Texas M.D. Anderson Cancer Center.
- Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–F); David Cella, Ph.D.
- Cancer-related Fatigue Distress Scale (CRFDS); Saundra K. Holley, Ph.D., ARNP.
- Visual analogue scales (VASs) similar to the pain VAS are helpful in the day-to-day clinic setting when time constraints prohibit lengthy assessments. For those patients with more obvious symptoms, a more in-depth assessment can be performed (*Oncol Trials* 2001;23:22–25).

The often-cited Fatigue Algorithm (*Oncologist* 1999;4:1–10), with its evaluation and management component, provides multidimensional assessment questions and possible fatigue-treatment options (Fig. 28.2).

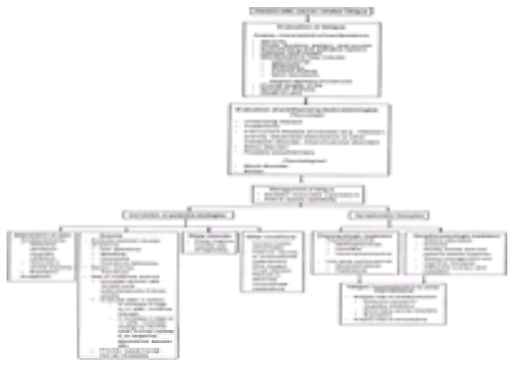

FIG. 28.2. Algorithm for the evaluation and management of cancer-related fatigue. (Reprinted from Portenoy RK, Itri LM. Cancer-related fatigue: guidelines for evaluation and management. *Oncologist* 1999;4:1–10, with permission.)

E. **Fatigue intervention**

Fatigue management is difficult because the underlying cause(s) are not always reversible. Patient must be encouraged to keep daily routines, to be counseled regarding adequate nutrition, hydration, and exercise right at the beginning of the cancer diagnosis, and to continue as treatments start.

Portenoy and Itri's Fatigue Management model serves as a guideline when treating symptoms of fatigue. The authors propose to correct the underlying cause(s) first and whenever possible. Potential etiologies are divided into four categories: depression or pain, anemia, sleep disorder, and other miscellaneous conditions. When fatigue is not responding to these interventions, then symptoms should be addressed by using symptomatic therapies (for example, pharmacologic treatment such as psychostimulants, or nonpharmacologic treatment such as exercise/rest routines, stress management/cognitive therapies). Finally, if none of the interventions is effective, empiric trials of antidepressants or amantadine can be initiated (*Oncologist* 1999;4:1–10). The fatigue-management model by Cella et al. (1998) illustrates three similar strategies. First is treatment of the underlying cause if known; second, conserving energy, devising a sleep/exercise cycle, and considering adding psychotropic medications; and third, managing fatigue consequences, such as setting limitations and realistic expectations.

F. **Evaluation**

Frequent contact with the patient is essential throughout the cancer treatment and the follow-up period. An initial fatigue assessment must be performed at the beginning of treatment and should be updated on a regular basis. This ensures that corrective measures are taken early. A fatigue intervention specific to the patient's needs must be monitored and evaluated for its effectiveness. The use of the same assessment tool is helpful in this situation, because it can give the nurse specific and valuable insight into which fatigue-treatment modifications should be made. Providing the patient and family with fatigue-related educational material stimulates interest in the subject and reinforces the willingness to follow through with suggested behavioral interventions.

It should be mentioned that patients with fatigue also experience a decrease in quality of life.

II. **Pain**

Pain affects the physical, psychological, social, and spiritual well-being of patients and their caregivers (*Hospice J* 1991;7:9–23). It interferes with their comfort and ability to carry out activities of daily living. Patients with pain fear that their pain will not be controlled. The oncology nurse is integral in the effective management of cancer pain. The nurse must understand the anatomic basis for pain, its meaning to the patient, and the tenets of effective pain management.

Pain, as defined by the International Association for the Study of Pain, is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Numerous studies have documented the inadequate treatment of cancer pain. Miaskowski outlines four areas that act as barriers to effective pain management (Table 28.1).

Inadequate knowledge on the part of providers, patients, and family caregivers about pain management
Lack of guidelines to evaluate the quality of pain management within healthcare organizations
Lack of an "ideal" analgesic to control pain
Intolerable side effects associated with analgesic medications

Reprinted from Miaskowski C. Improving pain management: an ongoing journey. *Oncol Nursing Forum* 2000;27:935–942, with permission.

TABLE 28.1. BARRIERS TO IMPROVING PAIN MANAGEMENT

The results of inadequate pain control are numerous, including anxiety, depression, confusion, fatigue, mood disturbances, sleep disruptions, decreased strength, and limited mobility (*J Pain Symptom Manage* 1995;10:1–9). Caregivers of patients in pain report higher levels of psychological distress than do caregivers of patients without pain (*J Pain Symptom Manage* 1997; 13:138–47).

Oncology nurses recognize that they are responsible for accurate assessment of a patient's pain experience. It should be part of every interaction with the patient.

The nurse must advocate for and educate the patient about effective pain control. Patients may be hesitant to initiate a discussion about their pain for various reasons including denial, fear that increasing pain means disease progression, not wanting to bother the physician, and/or the belief that effective treatment does not exist.

The Joint Commission on Accreditation of Health Care Organizations (JCAHO) has revised standards regarding pain assessment and management. This brings pain assessment and management to the forefront of patient care. Guidelines provide for the following:

- Initial assessment and regular re-assessment of pain
- Education of all relevant providers in pain assessment and management
- Education of patients and families, when appropriate, regarding their roles in managing pain as well as the potential limitations and side effects of pain treatment
- After taking into account the personal, cultural, spiritual, and/or ethnic beliefs, communicating to patients and families that pain management is an important part of care.

Assessment of pain begins with the patient's self-report. The nurse guides the assessment by listening to the patient's description of location, intensity, quality, frequency, temporal pattern, aggravating circumstances, and relieving factors. It is considered standard practice to include consistently the patient's report of pain by using some type of pain-rating scale. A score of 3 on the numeric scale indicates the need for intervention.

In addition to physical descriptors of pain, the nurse must assess associated factors such as anxiety, depression, the meaning of pain to the patient, coping strategies, and the effect of pain on activities of daily living, including sleep. The nurse gathers this information in the context of the patient's age, cultural background, and religious beliefs, all of which affect an individual's experience of pain.

A. **Example of implementation of JCAHO standards on pain assessment**
   1. All patients at admission are asked the following screening or general question about the presence of pain: "Do you have pain now? Have you had pain in the last several months?" If the patient responds "yes" to either question, additional assessment data are obtained.
      a. **Pain intensity** (use a pain-intensity rating scale appropriate for the pain population; pain intensity is obtained for pain at present, at worst, and at best or least; if at all possible, the same pain-rating scale is consistently used in the organization and between disciplines).
      b. **Location** (ask the patient to mark on a diagram or point to the site of pain).
      c. **Quality,** patterns of radiation, if any, and character (elicit and record the patient's own words whenever possible).
      d. Onset, duration, variations, and patterns.
      e. Alleviating and aggravating factors.
      f. Present pain-management regimen and effectiveness.
      g. **Pain management history** (including a medication history, presence of common barriers to reporting pain and using analgesics, past interventions and response, manner of expressing pain).
      h. **Effects of pain** (impact on daily life, function, sleep, appetite, relationships with others, emotions, concentration, etc.).
      i. **The patient/client's pain goal** (including pain intensity and goals related to function, activities, quality of life).
      j. Physical examination/observation of the site of pain.
   2. **Patient/clients often have more than one site of pain.** An assessment system or tools with space to record data on each site is provided on the assessment sheet.
   3. A hospital may need to use more than one pain-intensity measure, depending on the patient population. For example, a hospital serving both children and adults selects a scale to be used with each of those patient populations. Assessment of cognitively impaired patients also may require assessment of behavioral factors signaling pain or discomfort.
   4. Staff are educated about pain assessment and treatment including the barriers to reporting pain and using analgesics. Staff encourage the reporting of pain when a patient/client and/or family member demonstrates reluctance to discuss pain, denies pain when pain is likely to be present (for example, postoperative, trauma, burns, cardiac emergencies), or does not follow through with prescribed treatments.
   5. Pain-intensity scales are enlarged and displayed in all areas where assessments are conducted. For organizations using clinical pathways, pain assessment is incorporated in some way into every appropriate clinical pathway (see Chapter 24 on palliative care).

   Pain is best managed through a multidisciplinary approach. These treatments are directed at treating the underlying pathology, changing the perception or sensation of pain, and/or diminishing suffering from the pain. These approaches to pain management are covered in related chapters of this book. Throughout the course of pain management, the nurse's role remains constant. The nurse continually assesses the patient's level of pain, the response to treatment, and side effects. He or she works with all members of the health care team to develop a plan of care that meets the patients' needs.

   One of the mainstays of management of cancer pain is the use of opioid analgesics. This is the most frequently used method of managing moderate to severe cancer pain. When used correctly, opioid analgesics can successfully decrease or eliminate pain. However, the nurse must be aware that many factors influence the successful use of opioids. These include fear of addiction, the desire to save the medication until the pain gets "really bad," inability to afford the cost of the medication, and poor tolerance of side effects, especially confusion, drowsiness, and constipation. The nurse should explore these issues with patients and families and institute a plan of care, which can facilitate pain management.

   In oncologic ambulatory care, it is important to note that successful management of cancer pain depends on the frequent and ongoing nurse–patient dialogue. It is advisable that the patient initially receives detailed verbal and written instructions regarding medication name, dosage, action, timing, and side effects. Immediately thereafter, it is important to reinforce this often new pain-management concept with the patient and family by telephone. At that time, the medication dosage should be titrated until the desired effect and comfort level is achieved.

   Pain-assessment diaries are often helpful in the outpatient setting to help the patient recognize a pattern of pain stimulants and modifiers and what medication dosages work. In addition, the nurse gains a better understanding of the patient's pain level and can adjust the dosage based on a historical data collection. Known opioid-induced side effects such as constipation must be counteracted while the patient receives this type of pain medication. The nurse must reassure the patient that side effects can be managed and that medication schedules should not be altered or discontinued unless instructed.

III. Nutrition

The oncology nurse and patient must make the promotion of the patient's nutritional status a priority from their initial contact. Patients with cancer are at risk for nutritional disturbances from diagnosis throughout the course of the disease. Some people will have significant weight loss on diagnosis, which puts them at a disadvantage to tolerate cancer therapy. The cause of malnutrition in the patient with cancer is multifactorial; however, the basic problem becomes that the patient has an insufficient intake of calories to maintain weight. Psychosocial issues, treatment effects, structural alterations, and financial factors all contribute to a patient's inability to maintain an adequate nutritional status.

A. Assessment

Nursing assessment is the key in identifying which of these factors is affecting the patient's nutritional status. The assessment combines the patient's subjective input with the nurse's observations. The assessment should be consistent and systematic; keeping in mind that symptoms will change throughout the course of the disease. Beginning with the initial contact, the nurse should address the following areas.

- Daily intake: food and fluids by mouth or alternate means (i.e., gastrostomy tube)
- Barriers to intake: nausea, vomiting, early satiety, anorexia, stomatitis, esophagitis, weakness, lack of food or supplements, depression, anxiety
- Output: draining wounds, diarrhea, and fistulas
- Appetite suppressants and supplements: tobacco, medications including narcotic analgesics.
- Complementary therapies: herbal remedies, vitamin supplements
- Activity level: weakness, ability to perform activities of daily living

Physical assessment, which should be collected, includes the following.

- Height/weight: weight gain or loss. Ascites and edema will falsely increase body weight, whereas dehydration will decrease it.
- Muscle loss: temporal muscle loss
- Poor wound healing
- Midarm circumference: index of protein status
- Triceps skinfold measurements: index of subcutaneous body fat
- Condition of skin, nails, and mucous membranes: turgor, pallor, or nail ridges, stomatitis, presence of fungal or viral infections

Laboratory data will assist in confirmation of nutritional status.

- Hemoglobin/hematocrit
- Serum albumin level
- Creatinine clearance
- Total lymphocyte count
- Electrolyte levels
- Blood area nitrogen level
- Blood glucose level

B. Intervention

1. **Consultation with dietitian.** Information from the assessment is used to identify patients at risk for malnutrition. Patients with a recent unintentional weight loss of 10% or more should be referred to a dietitian before initiation of cancer therapies. These patients will be at further nutritional risk once aggressive cancer therapy is started (*Semin Oncol* 1995;22:98–111). It is a good practice to arrange a nutritional consultation for cancer patients who are candidates for chemotherapy and radiation therapy at the beginning of the treatment cycle. The dietitian will be able to develop a nutritional plan to support the patient during therapy. The plan will specify the calorie and protein needs of the patient. The nurse must assist the patient and family with meeting these needs. The method of doing this varies with the cause of nutritional deficit.
2. **Symptom management to improve enteral nutrition**
   a. **Nausea and vomiting**
      - Use antiemetics, antinausea, and tranquilizing medications as prescribed in the palliative-care chapter.
      - Avoid spicy, greasy, acidic, and high-fat foods.
      - Maintain liquid intake with decaffeinated liquids, broth, juice sticks, gelatin, and ice chips.
      - Eat small, frequent meals.
      - Avoid favorite foods around treatment times to prevent food aversions.
      - Report episodes of nausea and vomiting triggered by sight, sounds, or odors similar to those of treatment areas, which forewarns of anticipatory nausea and vomiting.
   b. **Anorexia**
      - Eat small frequent meals.
      - Eat protein-rich foods; add powdered milk to sauces, pudding, and eggs to increase protein content.
      - Use nutritional supplements.
      - Use known appetite stimulants such as megestrol (Megace) suspension.
      - Eat with others, experimenting with new recipes, and eat in restaurants.
      - Maintain activity level.
      - Try foods at room temperature.
      - Avoid high-fat foods.
      - Avoid foods with low nutritional value (i.e., diet sodas).
   c. **Taste changes**
      - Suck on hard candy, mints, or lemon drops.
      - Use plastic cutlery if metal utensils cause a metallic taste.
      - Serve foods at room temperature or chilled.
      - Use additional spices or flavoring if food tastes bland.
      - Substitute fish, poultry, dairy products, red meat, or high-protein liquid nutritional supplements.
   d. **Dyspepsia**
      - Avoid spicy, fatty foods.
      - Avoid caffeinated beverages.
      - Avoid eating immediately before bedtime.
      - Elevate head of bed (for symptoms of reflux).
      - Use antacids, H_2 blockers.
   e. **Xerostomia**
      - Eat foods that are moist or have a liquid base (soups, gravies, puddings).
      - Use liquids with meals to moisten foods.
      - Use artificial saliva.
      - Use lemon drops to elicit saliva production.
      - Pilocarpine (cholinergic agent), 5 mg daily, and titrate up to 3 times a day.
      - Avoid dry, firm-textured foods.
      - Use pureed foods as necessary.
      - Avoid tobacco and alcoholic beverages.
      - Avoid commercial mouthwashes, which are drying to mucous membranes.
   f. **Constipation**
      - Prevent opioid-induced constipation by prescribing natural laxatives such as senna (Senokot) twice daily; titrate until regular bowel routine is established (up to four tablets b.i.d.).
      - Milk of Magnesia, 1 tablespoon, can be added to Senokot if needed.
      - Lactulose (Enulose) syrup, 20 g/30 mL twice daily or every 4 hours to induce rapid laxation.

- Magnesium citrate for relief of more severe constipation; give 150 mL, and repeat in 8 hours if needed.
- Maintain adequate fluid intake.
- Eat a diet high in fiber.
- Maintain physical activity.
- Attempt to maintain previously successful bowel habits (i.e., bowel movements at the same time of day).
- Enemas and suppositories are not recommended, because they can inadvertently cause rectal mucosal injury, which can lead to inflammation and infection in the immunocompromised patient.

g. **Diarrhea**

- Maintain adequate fluid intake.
- Avoid high-fiber, spicy, high-fat, and gas-producing foods.
- Avoid dairy products.
- Eat foods high in potassium.
- Take antidiarrheal medications such as loperamide or diphenoxylate/atropine as prescribed.

C. **Parenteral nutrition**

Parenteral nutrition is reserved for a small number of patients with nonfunctional gastrointestinal tracts who have a good prognosis. Parenteral nutrition can be associated with complications including hyperglycemia, electrolyte disturbance, sepsis, and so on.

IV. Altered skin and mucous membrane integrity

The skin and mucous membranes act primarily as a protective organ for the body. Cancer and its treatments often affect its integrity. Skin cancers alter the affected skin structure. In addition, metastasis to the skin and its substructures can change skin appearance. Treatment-related skin changes and interventions are addressed as follows:

A. **Surgical and procedure-related causes**

Cancer patients undergoing surgical and or invasive procedures also undergo the risk of complicated wound healing. Underlying structures must heal, and the skin must approximate for an uncomplicated healing process to take place. There is a higher risk of wound infection and prolonged healing time in cancer patients, especially when prior chemotherapy or irradiation was given. An altered immune-system response, comorbid diseases, poor nutrition, and fatigue will likewise complicate healing.

B. **Radiation therapy impact on skin structures**

Skin reaction to specific irradiation doses depends on the amount of skin tissue radiated (Perez CA, Brady LW, eds. *Principles and practices of radiation oncology.* 2nd ed. Philadelphia: JB Lippincott, 1992:1–64.). Effects of irradiation on skin tissue can occur during the treatment course, and assessment must therefore be ongoing.

1. **Erythema** is the first sign of dermal tissue distress and is often evident in the first 2 weeks of treatment. *Dry desquamation,* a peeling of the epidermis and erythema, occurs approximately 2 weeks after treatment initiation. Further irradiation will decrease hair growth and alter sweat gland and sebaceous gland function (Hassey DK, Dunn Bucholtz J, Iwamoto, et al. *Nursing care in radiation oncology.* 2nd ed. Philadelphia: WB Saunders, 1997). Pruritus frequently occurs at this point because of the loss of basal cell proliferation (Pruritus PDQ, Cancernet, 2000).
2. **Moist desquamation** is further deterioration of the epidermis and skin substructure, resulting in painful, oozing, denuded areas in the field of continued irradiation.

C. **Management of skin reactions**

- Avoid known skin irritants, strong soaps, astringents, perfumes; avoid direct and prolonged sun exposure.
- Propose gentle skin hygiene with pH-neutral cleansers, soaps.
- Treat early skin reactions with moisture-rich lotions and aloe vera products.
- Cleanse denuded areas gently with sterile normal saline solution or lukewarm running water. Avoid soaps and antiseptic solutions.

Treat moist desquamation with one of the following dressings: **Hydrogel, Vigilon or Nu gel.** These are absorbent, cooling, and soothing. **Sulfadiazine (Silvadene) cream** is another option. **Air-permeable dressings** are occlusive but do not absorb the serous exudate.

Late skin changes manifest 2 to 3 months after irradiation and are usually irreversible. They include hyper- and hypopigmentation, fibromatous changes, skin atrophy, xerosis, and telangiectasia (Hassey DK, Dunn Bucholtz J, Iwamoto, et al. *Nursing care in radiation oncology.* 2nd ed. Philadelphia: WB Saunders, 1997).

At each follow-up appointment, it is important to perform a quick survey of the previously irradiated skin. Careful skin inspection assesses skin integrity and looks for dermal and cutaneous rashes and nodules that could be suggestive of cancer recurrence at the old scar or former treatment site.

D. **Skin assessment related to indwelling catheters/access devices**

Effort must be made to inspect the insertion site of any indwelling catheter and/or implanted vascular access device (VAD) on a routine basis. The patient and family must receive proper education regarding the care and management of the specific device. Return demonstrations are encouraged. Home health nursing should be used if the patient and family are not capable of performing the maintenance care. Calendars are often helpful and serve as reminders of when to flush and cleanse catheters. Centrally placed catheters usually stay in place from 6 weeks, if temporary, to 1 year, if tunneled. Pick lines may remain for several weeks until no longer needed.

E. **Dry skin and rashes**

Simple dry skin affects a large general population and, in particular, the elderly. Certain kidney- and liver-related diseases likewise produce dry skin. Pruritus is caused by the dermal/epidermal nerve endings and is mediated by histamine and other substances. Rashes can occur because of allergic reactions to the environment, medication, or disease-related causes. In addition, cancer and cancer therapy can produce dry skin and rashes. Certain antineoplastic agents cause pruritus without rash manifestation.

Chemotherapy skin reactions range from dry skin to local erythema, edema, and urticaria at the access site. Previous studies showed that doxorubicin, daunorubicin, cytarabine, L-asparaginase, paclitaxel, docetaxel, and cisplatin caused hypersensitivity most often (Cancernet PDQ, 2000). Premedication with mediating agents is strongly advised. The increased cytotoxic effect of combined-modality cancer therapy almost always causes increased skin and mucosal reactions.

Pruritus and rash is often the first sign of hypersensitivity. In graft-versus-host disease after bone marrow transplant, the skin involvement is substantially increased and manifests itself as severe dryness to a pruritic erythematous rash (Cancernet PDQ, 2000).

F. **Mucosal changes**

1. **Xerostomia** is a condition found mostly in patients receiving radiation to the head and neck area. The oral mucosa shows excessive dryness, and there is absence of saliva.
2. **Stomatitis** is an exposure of the underlying tissue because of damaged mucosa. If untreated, these areas will form open lesions and painful ulcers.
3. **Moniliasis** is an opportunistic yeast infection caused by the *Candida albicans* organism. Patient undergoing head and neck, oral, and esophageal cancer treatments most often are affected by this infection.
4. **Dysphagia and odynophagia** are difficult and painful swallowing often experienced by patients undergoing head and neck, esophageal, and lung cancer therapy. Stomatitis and xerostomia are commonly the underlying causes (Hassey DK, Dunn Bucholtz J, Iwamoto, et al. *Nursing care in radiation oncology.* 2nd ed. Philadelphia: WB Saunders, 1997).
5. **Viral inflammation** caused by herpes simplex can cause painful oral, tongue, pharyngeal, nasal, and esophageal chancre sores. It is usually a sign of a

stressed or depressed immune system.

6. **Vaginal and rectal mucosa and perineum.** Cancer treatment–related symptoms include severe vaginal and mucosal dryness, yeast infections, proctitis, and perineal skin-integrity changes, including fissures and ulcers.

G. **Intervention and treatments**

1. **Dry skin:** use fragrance-free, moisture-rich skin lotion; use pH neutral cleansers.
2. **Rashes:** Investigate and treat the underlying cause. If unable to eliminate cause, use a systemic or local mediating agent such as steroids.
3. **Erythema:** dry desquamation: use aloe-containing topical ointments or petroleum jelly (Vaseline)-based products.
4. **Moist desquamation:** clean with running water or sterile saline solution, and then apply Hydrogel-type dressing or sulfadiazine (Silvadene) cream at least once a day.
5. **Xerostomia:** frequent mouth rinses, proper hydration, citrus juices, discourage dry foods and smoking. Artificial salvia is helpful in extreme cases to lubricate the oral cavity.
6. **Stomatitis/mucositis:** recommended are frequent non–alcohol-containing mouth rinses and hydration. A cocktail composed of equal amounts of Maalox nystatin (Mycostatin) suspension (10,000 units/mL), and diphenhydramine (Benadryl) liquid used to swish and swallow is helpful when used every 2 to 4 hours as needed. Sucralfate suspension (10 mg) used 2 hours after meals coats the oral and esophageal mucosa and promotes healing.
7. **Viral chancre sores:** treat with systemic antiviral agents. Provide local relief with lidocaine-containing gels.
8. **Moniliasis:** treat with antifungal agents topically or systemically.
9. **Infection of the skin:** treat local cellulitis with broad-spectrum antibiotic. Carefully inspect VAD for signs of infection, since there is an increased risk for generalized sepsis, especially in the immune-suppressed patient.
10. **Wound care:** Frequent assessment of wound healing is essential. Observe for signs and symptoms of infection and approximation of wound margins. Teach the patient and family wound-management techniques, especially when sutures and staples are still present.

V. **Psychosocial distress**

The diagnosis of cancer causes psychological distress to every patient. This distress is manifested in different ways by each person and is the result of multiple factors, which include

- Fear of dying
- Changes in body integrity and comfort
- Changes in self-concept and disruption of future plans
- Inability to maintain equilibrium
- Lack of fulfillment of social roles and activities
- Inability to adapt to new physical social environments (Cohen F, Adler NE, eds. *Health psychology: a handbook.* San Francisco: Jossey-Bass, 1979:217–254)

The oncology nurse is obligated to address these factors through assessment and development to a plan of care. Holland (1997) wrote, “management of a patient's psychological state is vital to the care of every patient at all stages of the disease, irrespective of the disease stage.” The oncology nurses' objectives are to assist patients with their adjustment through the spectrum of diagnosis, treatment, disease recurrence, and end of life.

Psychological distress in patients with cancer can range from common feelings of sadness, loss, and fear to severe psychiatric disorders. Often people are reluctant to discuss the distress they are experiencing. Symptoms that help nurses to pinpoint troubled patients are many, but they are also symptoms that may result from cancer, its treatments, or its side effects. When care is provided by a multidisciplinary team, each team member provides information that will assist in diagnosing and treating psychological distress.

A. **Key assessment points include the following**

1. **Age.** A person's age will identify developmental tasks in which the person may be engaged (i.e., school, work, parenting).
2. **Occupation.** Knowing a person's occupation will alert the nurse to possible disruption that the disease and treatment may cause.
3. **Education.** Knowing educational level allows the nurse to formulate a teaching plan tailored to the patient's understanding.
4. **Marital status/family social support.** The diagnosis and treatment of cancer affects every person in the patient's family (*Oncol Nurs Forum* 2000;27:843–848). It is vital to know whom the patient depends on for physical and psychological support. A high level of social support is associated with decreased demands of illness (*Res Nurs Health* 1990;13:153–161).
5. **Financial concerns.** The lack of a job or the inability to work is a major source of stress and worry. Patients may be unable to pay for costly medications.
6. **Previous coping strategies.** Patients who identify how they have coped in the past with stress situations may be able to use successful strategies in their current situation. History of prior psychiatric disorder, substance abuse, or recent bereavement may indicate a person at higher risk for psychological distress associated with cancer diagnosis (*Oncology* 1999;13:1293–1300).
7. **Body image.** Surgery (mastectomy, -ostomy, impotence), chemotherapy (alopecia), or radiation (skin changes) can cause significant changes in the function and appearance of the body. Patients vary greatly in their ability to cope with these changes.
8. **Concentration.** Anxiety and depression interfere with a person's ability to concentrate and process information.
9. **Appetite, activity level, and sleep patterns.** Although these are affected by cancer and treatment, disruptions in any of these areas may be caused by anxiety and depression.
10. **Spirituality.** Patients with cancer are concerned about value of life and their morality (*Oncol Nurs Forum* 2000;27:633–639). They may be facing death, and many patients' relationship with God is important and strong at the end stage of life (*Oncol Nurs Forum* 2000;27:817–823).

    The assessment of the patient's psychosocial condition should be ongoing because responses and situations change over time (*Qual Life Res* 1994;3:27–141). Memorial Sloan Kettering has developed a distress scale (similar to a pain-rating scale) that can be used at each patient contact to identify quickly the need for assessment and intervention (*Oncology* 1997;11:109–114).

    In the 1980s, a multicenter study by the Psychosocial Collaborative Oncology Group found that 51% of patients with cancer had symptoms consistent with psychiatric diagnosis, most commonly depression or anxiety (*JAMA* 1985;249:751–757). These patients benefit from a referral to a mental health professional. Signs and symptoms that would prompt a referral are feelings of helplessness, hopelessness, worthlessness, poor self-esteem, guilt, a desire to end life, immobilizing anxiety, inability to comply with therapy, and anger that interferes with relationships (*Oncology* 1997;11:109–114, 1997).

B. When addressing a patient's psychosocial issues, the nurse must be able to assist with some of the “fixable issues,” which may ease the situation. Examples of this follow.

1. **Altered body image.** Assist patients in obtaining hairpieces, turbans, and prosthetic devices. Refer patients to support groups and programs.
2. **Financial issues.** Ensure that applications for disability, Medicaid, drug-assistance programs, and community agency programs are completed in a timely fashion. Refer to social workers for complex social needs.
3. **Physical symptoms.** Pain, insomnia, fatigue, and malnutrition contribute to psychosocial distress. Correcting these problems gives the patient more energy to concentrate on psychosocial issues.

   Once a psychosocial disturbance has been identified, the nurse develops a plan of care. For mildly anxious or depressed patients, acknowledging the problem and attentive listening may be sufficient (*Oncology (Huntingt)* 1999;13:1293–1301). For patients who are distressed by specific situations (i.e., lack of funds to pay for medications, job loss), the nurse can refer the person to the appropriate community agencies or enlist the services of a social worker. Patients' social needs can become complex (i.e., homelessness, lack of utilities, family dysfunction), and the social worker's expertise is vital to solving these problems.

   The oncology nurse must be familiar with resources in the institution and community that can assist patients with the common concerns of transportation, financial resources, disability, and emotional support. The nurse also must refer patients to members of the health team who have expertise in managing complex problems.

VI. **Oncology nurse as an educator**

One area that often causes anxiety in patients and family is the lack of knowledge regarding diagnosis, treatment, and side-effect management. In each stage of life with cancer, patients' have different informational needs. The newly diagnosed patient and the patient entering a hospice program both will need information that assists them in making difficult decisions and anticipating problems. Patients will need information to help them cope with physical and psychological changes caused by the treatment and/or cancer. The oncology nurse should be familiar with the patient's diagnosis, stage, and purpose of treatment. He or she

should include the following in the teaching plan.

- Type of cancer
- Stage (including specific sites involved)
- Diagnostic testing
- Treatment and purpose

Adjuvant/neoadjuvant

Curative

Palliative

- Treatment procedures and schedules
- Clinical trials–informed consent
- Expected side effects
- Management of emergency situations
- Institutional and community resources

Anxiety and lack of previous experience will interfere with the patient's ability to retain information. The nurse should have a variety of teaching tools available for reinforcement. As more patients have access to the Internet, it will become an important source of information. The nurse must be familiar with various sites and the accuracy of information, because quality and accuracy are not consistent.

The nurse will evaluate patients undergoing therapy with chemotherapy agents, radiation, immunotherapy, surgery, and a combination of these. It is important that the nurse understand the principle and the sequence of these treatments and reinforce them to the patient. Generally the intent of treatment falls into one of the following categories.

- Curative (neoadjuvant/adjuvant)
- Palliative

A. **Role of oncology nurse in clinical research**

   In addition, some patients will be asked to enroll in various clinical trials. The nurse must be able to provide information to ensure that the patient is making an informed decision regarding participation. Furthermore, the nurse must be familiar with the clinical trial schema to ensure compliance.

B. **Resources**

   Cancer resources are readily available in most cancer-treatment centers. In addition, the advent of the Internet has provided myriad cancer-related information for both the practitioner and the patient. This information can be overwhelming, confusing, and contradictory. The patient will look to the nurse to help clarify this information, especially when treatment options are discussed. Legitimate and helpful Internet sites are sponsored by the National Institutes of Health (NIH), the National Cancer Institute (NCI), and the American Cancer Society (ACS), as well as the American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS).

   The care of the cancer patient provides an ongoing challenge for the oncology nurse. It is important to remain up to date with new treatment symptom management strategies to provide the cancer patient with the best care available.

C. **Ambulatory oncology telephone triage**

   The oncology nurse working in an outpatient care setting must possess the necessary skills to assess and perform triage with patient telephone calls according to the individual patient needs. These skills include professional telephone etiquette as well as knowledge regarding the disease process and its treatment options. Most often the patient calls for help with symptom management. The nurse must be competent in answering questions and giving appropriate directions. Specific standards of care must be developed by the physician and the nurse involved in daily telephone triage. They should include assessment and treatment of the following.

   - Fever/neutropenia
   - Thrombocytopenia
   - Anemia
   - Nausea/vomiting
   - Pain
   - Constipation/diarrhea
   - Other symptoms related to a specific cancer diagnosis or trademark

   In addition, the nurse must recognize the importance of his or her role in providing direction, assistance and psychological support to the patient and the family.

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CHAPTER 29. HOSPICE CARE

Colleen R. Gilmore

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“You matter because you are, you matter to the last moment of your life, and we will do all we can not only to help you die peacefully, but to live until you die.” Cicely Saunders, M.D.

Hospice is a special way of caring for patients who are terminal. When treatment, chemotherapy, radiation, and surgery will no longer slow the patient's illness or provide comfort, the hospice team can assist the physician in caring for the dying patient and helping the family cope with their loved one's final days. Hospice is a philosophy of care, not a “place to die.” Hospice care is most often provided in the home, but it can be provided in nursing homes or inpatient settings as well.

I. History of hospice

The concept of hospice was first developed in the middle of the nineteenth century by a Catholic order, the Sisters of Charity, in Ireland. The sisters found terminally ill people dying in horrible conditions at home, without adequate care from family members. They created clean places where patients could come to die. With the help of national health funds and private philanthropy, the hospice movement spread and flourished in England. By the 1960s, there were 25 hospices in England.

Cicely Saunders, a nurse trained in social work, cared for dying patients in a London hospital. One patient described to her a place he would like to be for his final days. He left a bequest to the hospital for the establishment of a hospice. Saunders was inspired by the patient and went to medical school. After graduation, she helped open St. Christopher's Hospice in South London in 1967. St. Christopher's was unique for its windows, garden, home-like furnishings, many activities for patients, attention to small details, and for the absence of heroic measures prolonging the dying process. In 1969, St. Christopher's initiated a home-care hospice program.

Dr. Saunders presented the concept of hospice care at Yale University in 1974. The first American hospice later opened in New Haven, Connecticut. In 1979, the National Hospice Organization was formed in the United States, and in 1983, the Health Care Finance Administration established the Medicare hospice benefit. In 1987, palliative medicine was first recognized as a specialty in Britain. In 1988, the International Hospice Institute helped form the Academy of Hospice Physicians, now known as the American Academy of Hospice and Palliative Medicine.

II. The hospice team

The hospice team is an integral part of the hospice philosophy. The team includes a medical director, registered nurses, social workers, chaplains, health aides, volunteers, and other allied health professionals. The focus of the team is not only the patient, but also the entire family. The patient is viewed as the “captain of the ship”; he helps to shape the “crew” that will accompany him on his journey. Members of the hospice team commonly meet at least weekly to discuss the patient and family. All team members provide input from their specialty in an effort to deliver the best interdisciplinary holistic care as possible. The team members draw strength and support from one another. Monthly support-group meetings with the spiritual counselor and/or social worker may be very beneficial for the team members.

A. The medical director

The medical director provides medical supervision to patients in the hospice program, communicates with other attending physicians, fellows, and residents, and provides educational opportunities for medical students who rotate through the hospice program. The medical director does not replace the patient's primary physician; rather, she or he assists the primary physician with the plan of care and with medical decision making as needed. The medical director is available 24 hours a day, 7 days a week, to give medical orders in the event the primary physician is unavailable to the patient.

B. The registered nurse

A registered nurse is always assigned to a patient and family. Sometimes the hospice nurse is described as the “eyes and ears” for the physician. Often the patients are too weak to be transported to see their physicians. In such cases, the nurse continually communicates with and assesses the patient through home visits and telephone calls and takes orders from the primary physician or medical director to maintain the patient's comfort. The nurse also provides education and training to the patient's family and caregivers. “Family” is defined broadly as any person who is close to the patient and has made a commitment to care for him or her.

The registered nurse and the family come up with a primary care plan, which sets forth the frequency and types of services needed by the patient. The nurse always does a medication review on admission to make sure the patient and family understand the medication dosages, schedule, and side effects. The nurse assesses needs for comfort measures and orders needed home medical equipment such as a hospital bed, oxygen, air mattress, wheelchair, and/or bedside commode. A registered nurse is on call 24 hours a day, 7 days a week. If necessary, an on-call nurse will visit the patient at any time of the day or night. The nurse assists the physician in determining whether a patient needs to be admitted as an inpatient for symptom management.

C. The social worker

Every hospice patient has a psychosocial assessment by a social worker [a master of Social Work (M.S.W.)] trained in hospice. Social workers provide support and grief counseling for patients and families, and assess risk for complicated grief reactions. Social workers assess the patient's mental status and provide the patient with the opportunity to do a life review. They encourage the patient and family to share their feelings and discuss their thoughts on death and dying, their fears and regrets, and other things they never had an opportunity to talk about. Social workers help the family with financial and estate planning, advance directives, and funeral planning. Social workers make referrals to social service agencies, assist patients in nursing home placement, or arrange private-duty nursing care for those who remain at home.

D. The hospice chaplain

The hospice chaplain's role is to provide spiritual support and counseling for the patient and family. The chaplain meets with the patient and family and performs a spiritual assessment. Hospice chaplains are ecumenical and nondenominational. Some patients will decline chaplain services because they feel close to and comfortable with their own pastor, rabbi, or spiritual leader. Other patients are estranged from their religion of origin and are open to discussing their spiritual questions with the chaplain. The hospice chaplain can assist with funeral planning. He or she can also offer other religious ceremonies such as

weddings. The chaplain may lead memorial services for patients' families and for the hospice staff who cared for the patients during the year.

E. **The home health aide**

Home health aides are certified nurses' aides who receive special training through the hospice program. They provide physical care to the patient in the home or residential nursing facility. They assist with bathing, mouth care, turning, and skin care. They teach family members and nursing facility staff about the patient's physical care. They spend a lot of time giving physical touch and comfort to the patient and psychological comfort to the family. Home health aides assist family members in getting the patient up, sometimes with a Hoyer lift. If the patient is not bed-bound, the home health aides assist the patient in getting in and out of the shower or tub. They encourage independence, but as the patient's functioning declines, they gradually provide more physical care. Their companionship is very important to patients and families.

F. **The hospice volunteers**

Hospice volunteers go through an intensive training program. They learn about the phases of dying; confidentiality, safety, and patient and family needs; and the hospice philosophy and team approach. Volunteers who help in the home are included in the patient's plan of care. They may read to or sit with the patient, play music, take a walk with the family, or provide brief respite care. Some hospice volunteers assist in the office by sending out bereavement mailings, compiling patient-education packets, answering phones, typing, cataloguing library books, and giving talks. Hospice volunteers are viewed as a critical part of the hospice team by staff, patients, and families.

G. **Other allied health professionals**

Depending on the patient's needs, other allied health professionals may be included on the hospice team as well. Some hospice patients may benefit from physical therapy, occupational therapy, speech therapy, or nutritional counseling. Others may need psychiatric or psychological services. Some hospices offer complementary therapies to assist with pain and symptom management and to improve the quality of life. These include massage therapy, music therapy, healing touch, pet therapy, art therapy, and aroma therapy.

III. Hospice eligibility criteria

When is hospice appropriate for a patient? One of a physician's most difficult challenges is knowing when to make a hospice referral. Many patients are referred to hospice very late in their illnesses. Sometimes the patient and family are not ready to discuss hospice until this point. Sometimes the physician is uncomfortable knowing when to raise the issue with the patient or family or when to stop treatment.

Under Medicare, Medicaid, and most private insurance plans, a patient is eligible for hospice if his physician and the hospice medical director certify that he is terminal and has 6 months or less to live. The patient and caregivers must agree to the philosophy of hospice. That is, they must agree that the focus is on managing symptoms of the disease without the use of life-prolonging measures. The patient needs to have a 24-hour caregiver or be willing to come up with a plan with the hospice team for 24-hour care. The patient could hire 24-hour private-duty nursing care, enter a long-term care facility, arrange for friends or family to take shifts in the patient's own home, or live with a family member.

The Medicare hospice benefit does not cover private-duty nursing or the cost of room and board at a nursing facility, but does cover visits by the hospice medical director, nurse, social worker, chaplain, and home health aide. The Medicare benefit also covers medications for pain and symptom management and durable medical equipment and supplies. Finally, the Medicare benefit covers two types of short-term inpatient admissions. First, hospice patients may be admitted to provide temporary respite for caregivers who are exhausted or in crisis. Second, a short-term inpatient admission may be required if a patient's pain and symptoms cannot be managed in the home. Examples of the latter would include intractable pain, uncontrolled bleeding, or seizures.

The patient's primary physician must discuss with the hospice program on a case-by-case basis what types of services may be provided to a given patient without disqualifying him or her from hospice. Some measures, such as intravenous hydration, blood transfusions, and tube feedings, paracentesis, and thoracentesis may be appropriate for palliation, but must be approved by the hospice medical director first.

IV. Bereavement care

One additional service provided by hospice programs is bereavement counseling for loved ones after the patient's death. Depending on the hospice, this service may be provided by the nurse, social worker, chaplain, or especially trained volunteers. Bereavement services include periodic mailings, phone calls, and home visits. Some hospices offer bereavement support groups, and some host annual memorial services. Bereavement services are available for 1 year after the patient's death. If the family requires additional counseling services, the hospice may choose to provide extended services or refer them to other resources in the community.

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CHAPTER 30. BLOOD TRANSFUSION IN THE PRACTICE OF ONCOLOGY

Lawrence T. Goodnoughxs

Red blood cells
Transfusion therapy
General considerations
Complications of transfusion
Infections
Plasma therapy
Special blood products
Platelet transfusions
Overview
Platelet transfusion practices
Risks of platelet transfusion
Product contamination
Platelet growth factors
Suggested Readings

I. Red blood cells

The therapeutic goal of a blood transfusion is to increase oxygen delivery according to the physiologic need of the recipient. The usual response to an acute reduction in [Hgb] in the normovolemic state is to increase cardiac output (Fig. 30.1) to maintain adequate oxygen delivery. The normal whole-body oxygen-extraction ratio (the ratio of oxygen consumption to oxygen delivery) is 20% to 25%. The oxygen-extraction ratio approaches 50% when myocardial lactate production occurs, indicating anaerobic metabolism. The observations that the critical extraction ratio and anaerobic threshold occur at a different [Hgb] in different physiologic states suggest that the oxygen-extraction ratio represents a reasonable indicator of the adequacy of oxygen delivery and, therefore, need for transfusion.

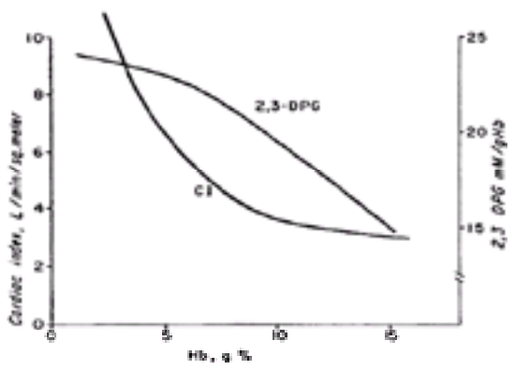

FIG. 30.1. Effect of anemia on cardiac index and diphosphoglycerate (DPG). (Reprinted from Finch CA, Lenfant C. *N Engl J Med* 1972;286:407–415, with permission.)

The benefits of transfusion are difficult to define and measure with precision. In a multiinstitutional Canadian study by Hebert et al., 418 critical care patients were to receive red-cell transfusions when the [Hgb] decreased to less than 7.0 g/dL, with [Hgb] maintenance in the range of 7.0 to 9.0 g/dL, and 420 patients to receive transfusions when the [Hgb] was less than 10.0 g/dLr, with [Hgb] levels maintained in the range of 10.0 to 12.0 g/dL. The 30-day mortality rates were not different in the two groups (18.7% vs. 23.3%; $p = 0.11$), indicating that a transfusion threshold as low as 7.0 g/dL is as safe as a higher transfusion threshold of 10.0 g/dL in critical care patients. Clearly, more data are needed to determine when transfusion in this setting is beneficial.

Data on morbidity also are unclear. Silent perioperative myocardial ischemia has been observed in patients undergoing noncardiac as well as cardiac surgery. Hemoglobin levels ranging from 6.0 g to 10.0 g/dL, a range in which indicators other than [Hgb] may identify patients who may benefit from blood, therefore must be the most closely scrutinized. A study of elderly patients who were undergoing elective, noncardiac surgery found that intraoperative or postoperative myocardial ischemia was more likely to occur in patients with hematocrits less than 28%, particularly in the presence of tachycardia. In the absence of a physiologic need in a stable, nonbleeding patient, an increase in [Hgb] level alone is not a good reason to give a transfusion.

Published data related to the benefit of transfusion on patient functional status are scant. Some investigators have studied possible benefits to the transfusion of autologous blood. No relation between [Hgb] and length of hospital stay was found for 332 patients who underwent total hip arthroplasty. There was no overall correlation between hematocrit value and exercise capacity in a randomized prospective trial of two transfusion strategies in 39 patients undergoing elective myocardial revascularization. No significant differences in postoperative exercise endurance were found between these patients who received transfusions to maintain a hematocrit of 32% compared with patients who received transfusions only if the hematocrit was less than 25%. There also were no documented effects in terms of length of hospital stay, rehabilitation, return to work, or health care costs as a consequence of transfusion. Whether blood transfusion is associated with a clinically significant immunomodulatory effect (e.g., perioperative infections) is controversial.

Guidelines for blood transfusion have been issued by several organizations including a National Institutes of Health consensus conference on perioperative transfusion of red cells, the American College of Physicians, the American Society of Anesthesiologists, and the Canadian Medical Association. These guidelines recommend that blood not be transfused prophylactically and suggest that in patients who are not critically ill, the threshold for transfusion should be a hemoglobin level of 6.0 to 8.0 g/dL. Adherence to these guidelines has raised questions about whether transfusion is now underused. A [Hgb] level of 8.0 g/dL seems an appropriate threshold for transfusion in surgical patients with no risk factors for ischemia, whereas a threshold of 10.0 g/dL can be justified for patients who are considered at risk. However, prophylactic transfusion of blood (i.e., in anticipation of blood loss) cannot be endorsed, particularly because studies have found that overuse of transfusion in critically ill patients may be associated with less favorable outcomes. It is unlikely that any level of hemoglobin can be used as a universal threshold for transfusion.

II. Transfusion therapy

A. General considerations

The transfusion of blood or blood components has inherent risks, summarized in Table 30.1. Informed consent (a dialogue of relative benefits, risks, and alternatives regarding the transfusion between patient and physician) is mandatory, and in many institutions is accompanied by a consent form that documents the conversation. Alternatives in the elective transfusion setting may include autologous (patient's own) or directed (from a donor known to and selected by the patient) blood. In all cases, patients should be evaluated for treatable anemias (e.g., iron, folate, B_{12}, erythropoietin) before blood transfusion.

			Estimated Frequency of Occurrence per Million Units (per Actual Unit)	Deaths Reported per Million Units
I	Infectious			
	Virus			
	Hepatitis A	1	(1/1,000,000)	0
	Hepatitis B	7–32	(1/30,000–1/250,000)	0–0.14
	Hepatitis C	4–36	(1/30,000–1/150,000)	0.5–17
	HIV	0.4–5	(1/200,000–1/2,000,000)	0.5–5
	HTLV	0.5–4	(1/250,000–1/2,000,000)	0
	Parvovirus	100	(1/10,000)	0
	Bacteria			
	Red cells	2	(1/500,000)	0.1–0.25
	Platelets	83	(1/12,000)	21
II	Acute hemolytic transfusion reactions	1–4	(1/250,000–1,000,000)	0.67
III	Delayed hemolytic transfusion reactions	1,000	(1/1,000)	0.1
IV	Transfusion-Related Acute Lung Injury (TRALI)	200	(1/5,000)	0.2

Modified from Goodnough et al. *N. Engl J Med* 1999;340:438, with permission.
HIV, human immunodeficiency virus; HTLV, human T-cell lymphoma virus.

TABLE 30.1. SOME ESTIMATED RISKS OF BLOOD TRANSFUSION

Details regarding the administration of blood and blood products, including risks, side effects, and indications, are available in the Circular of Information for Blood and Blood Products, issued jointly by the American Red Cross, America's Blood Centers, and the American Association of Blood Banks under the direction of the Food and Drug Administration (FDA), and is available from every hospital transfusion service. Administration of blood must be preceded by an identification check of the patient (three different criteria, such as name, birth date, and hospital number or social security number), matching the same information on the blood unit label, immediately before infusing the blood unit. The blood must be infused through a dedicated intravenous line with no other concurrent drugs or fluids, except 0.9% NaCl (normal saline). Vital signs are recorded immediately before transfusion and within 5 to 10 minutes after starting, during which the patient is observed carefully, and at regular intervals (e.g., hourly) thereafter. Each blood unit should be administered within 4 hours. A standard macroaggregate filter (170 to 260 μm) is used to prevent infusion of fibrin, cell clumps, and debris.

The laboratory blood type and screen tests the patient's red blood cells (RBCs) for the A, B, and D (Rh) antigen and also screens the serum for the presence of alloantibody against other (minor) RBC antigens. Such alloantibodies are present in approximately 2% of patients, through previous exposure from pregnancy or transfusion. Blood cross-match refers to *in vitro* testing of the patient's serum against donor RBCs to confirm compatibility between the blood unit selected and the patient.

B. **Complications of transfusion**

1. **Transfusion reactions** are defined by the transfusion service to alert medical personnel regarding potential problems with the transfusion. These are defined as a temperature elevation of greater than 1°C; the appearance of symptoms (e.g., shortness of breath, nausea/vomiting, pruritus, pain at infusion site, back pain, palpitations) or signs (changes in vital signs, rash, hives, edema, or stridor) indicating a change in the patient's clinical status. The transfusion is stopped immediately, and a physician is notified to assess the patient's status. The transfusion is terminated if for any reason it is determined that the patient's change in clinical status is significant and is possibly related to the transfusion. The blood bag and patient blood samples and urine are sent to the blood bank, where patient and blood-unit identification are reverified; blood group and antibody screen are repeated; serum and urine are inspected for signs of hemolysis; and blood-bag content is cultured. The patient's blood should be drawn for blood culture if fever or blood pressure changes were part of the transfusion reaction.
2. **Nonhemolytic febrile-associated transfusion reactions (FATRs)** are characterized by fever and accompanied variably by chills, pruritus, rash, or hives. They occur in 0.5% to 2% of RBC transfusions and in 8% to 30% of platelet transfusions. Within certain populations such as multiparous women and frequently (or chronically) transfused patients, the prevalence can be higher. These reactions are generally mild and occur during the latter part of the transfusion. The mechanisms are related to antibodies against donor leukocyte antigens and/or donor plasma proteins, soluble cytokines (interleukins, tumor necrosis factor), or both. Symptoms are treated with acetaminophen (650 mg) for fever and diphenhydramine (25 to 50 mg) p.o. or i.v. Occasionally, rigors and chills may require meperidine (25 to 50 mg i.v.). Epinephrine and glucocorticoids are rarely needed. The transfusion may be continued at the discretion of the physician, particularly in patients with prolonged transfusions with mild reactions. Some patients may benefit from prophylactic treatment shortly before transfusion, to avoid reactions altogether. Bedside leukodepletion filters can be tried in patients with a history of two or more reactions, but prevent only 50% of reactions, because they affect only reactions due to antibodies against leukocytes. Anaphylactic reactions can be seen in patients with immunoglobulin A (IgA) deficiency who have anti-IgA antibodies and receive blood products (all of which contain IgA).
3. **Acute hemolytic transfusion reactions are caused** by preformed antibodies (IgM antibodies against A or B antigens, or complement-fixing IgG antibodies against minor RBC antigens, such as Kidd) in the patient and are characterized by intravascular hemolysis soon after beginning the transfusion. Hypotension, fever, nausea/vomiting, and back and/or chest pain may develop, along with hemoglobinuria, renal failure, and disseminated intravascular coagulation (DIC). If such a reaction is suspected, the transfusion should be stopped immediately and terminated. Treatment includes resuscitative measures, support of intravascular volume, and protection of renal function with i.v. fluids, along with sodium bicarbonate therapy to alkalinize the urine.
4. **Delayed transfusion reactions** are usually detected 7 to 21 days after RBC transfusion. They are related to the primary or anamnestic IgG response on exposure to minor RBC antigens, the latter seen particularly in patients previously exposed to such antigens through pregnancy or previous blood transfusion. Clinical manifestations may include icterus or jaundice (due to accelerated intravascular RBC destruction), a failure to increment expected Hgb (1 g/dL per unit) levels after RBC transfusion, or most commonly, the appearance of a new alloantibody on antibody screen before subsequent transfusion. Occasionally the reactions can be clinically severe, with renal impairment and even reported deaths (Table 30.1). Treatment in these cases is the same as for acute reactions.
5. **Transfusion-related acute lung injury (TRALI)** is an underrecognized and serious reaction to plasma transfusion, most commonly due to a high-titer anti–human leukocyte antigen (HLA) antibody from a donor (usually a multiparous woman) that reacts to the HLA haplotype on leukocytes. The clinical manifestations are noncardiogenic pulmonary edema that can lead to profound respiratory distress and a radiographic picture consistent with acute respiratory distress syndrome. Treatment is supportive, including diuresis and mechanical ventilation.
6. **Volume overload** with symptoms and signs of congestive heart failure can be seen in patients with cardiopulmonary compromise, particularly in elderly patients with substantial anemia who already have expanded plasma volume. Diuretic therapy should be used in such patients prophylactically to minimize this complication.

C. **Infections**

1. **Human immunodeficiency virus infection.** Since the recognition that human immunodeficiency virus (HIV) infection is transmissible by blood, major arithmetic advances in blood safety have been made, particularly in the risk of posttransfusion hepatitis. With the implementation of nucleic acid testing (NAT) for direct detection of viral (HIV and hepatitis C) contamination, a further reduction (estimated at 50%) in risk is anticipated for these agents. The current estimated risk for HIV and hepatitis C transmission is $1:7 \times 10^{6}$ and 1:250,000, respectively. **The risk of fatality from acute hemolytic transfusion reaction (usually due to ABO incompatibility secondary to patient or blood unit misidentification or bacterial contamination of blood products) is approximately $1:1.5 \times 10^{11}$ which now exceeds the estimated risk from viral transmission.** Nevertheless, the prudent use of transfusions is important because blood is a scarce resource and because of possible, unknown future blood risks.
2. **Cytomegalovirus infection.** Cytomegalovirus (CMV) infection has been a substantial cause of morbidity and mortality for immunocompromised oncology patients. Patients who receive allogeneic bone marrow/stem cell transplantation are at risk because of cytotoxic preparative regimens, immunosuppressive therapy (cyclosporine and corticosteroid), and/or graft-versus-host disease (GVHD). Up to 60% of this patient population will experience CMV infection, with half of them developing CMV disease. Even with the use of CMV-negative blood products, CMV seroconversion has been reported in 1% to 4% of CMV-negative donor–recipient transplant patients; a recent analysis of our own program identified CMV viremia in only one (2.5%) of 39 CMV-negative donor–recipient pairs undergoing allogeneic peripheral stem cell transplantation. Of note, 59 patients undergoing allogeneic peripheral blood stem cell transplant who participated in an investigational study of prophylactic granulocyte infusions from their stem cell donors showed that CMV-positive granulocytes did not alter the risk of viremia when compared with CMV-negative granulocytes (34.5% vs. 26.6% incidence of CMV viremia, respectively).

   CMV infection and CMV disease are much less common in patients undergoing conventional chemotherapy or autologous bone marrow/stem cell transplantation, and are not thought to be a significant clinical problem, except with CD-34 selected stem cell transplants.

   A randomized, controlled clinical trial in allogeneic bone marrow transplant patients compared the value of CMV-seronegative blood products with unscreened blood products that were subjected to bedside leukofiltration. Four (1.3%) of 252 patients in the CMV-seronegative cohort developed CMV infection, with no CMV disease or fatalities; six (2.4%) of 250 patients in the leukoreduced cohort developed CMV disease, of whom five patients died.

The filtered cohort had an increased probability of developing CMV disease by day 100 (2.4% vs. none; $p = 0.03$). Even when the investigators eliminated CMV infections that occurred within 21 days of transplant, two cases of fatal CMV disease occurred in the filtered arm compared with none in the leukoreduced arm. The conclusion by the authors of this study that leukoreduced blood products are “CMV safe,” remains controversial. In a recent consensus conference held by the Canadian Blood Service, seven of 10 panelists concluded that patients considered at risk for CMV disease should receive CMV-seronegative products, even when blood components are leukoreduced.

Transfusion-associated GVHD is a syndrome in which donor lymphocytes that share an HLA haplotype with the patient's lymphocytes successfully engraft and attack the host (patient) with clinical manifestations of rash, pancytopenia, and liver and gastrointestinal damage (diarrhea). This appears to be unique to immunocompromised patients such as solid organ or bone marrow transplant patients, and patients with certain malignancies (Hodgkin disease, non-Hodgkin lymphoma, leukemia, multiple myeloma), particularly in those undergoing intensive chemotherapy (e.g., fludarabine or myeloablative therapy). Interestingly, a patient with HIV infection has not yet been reported to have this complication, probably because of the suppressive effect of HIV infection on donor lymphocytes. Mortality is in excess of 80%. This complication can be prevented by irradiation of blood products (see later) for patients at risk. For the same reason, directed blood transfusions from any blood relative of the transfusion recipient also must be irradiated.

Posttransfusion purpura is a rare complication, which is manifested by a profound thrombocytopenia that starts 7 to 10 days after blood transfusion. This disorder is described in the thrombocytopenia section in the chapter.

D. **Plasma therapy**

Plasma therapy should be administered to patients who have abnormal prothrombin time (PT) or partial thromboplastin time (PTT) assays and clinically significant hemorrhage. The most common setting is in patients with liver disease who have multiple coagulation deficiencies, along with consumptive elements due to impaired reticuloendothelial system (RES) clearance of substances activating the coagulation system. Another setting is in vitamin K deficiency. Vitamin K is derived from dietary sources and from intestinal bacteria, so that deficiency is caused by poor dietary intake combined with antibiotic therapy (e.g., intubated or cachectic patients treated with prolonged and multiple antibiotic therapy). Another presentation is in patients with coumadin overdose. Parenteral vitamin K (10 mg s.q. or i.v. daily) administration is the first treatment consideration in both patients with liver disease (impaired enterohepatic circulation of bile salts leading to deficiency of vitamin K and the vitamin K–dependent coagulation factors II, VII, IX, and X) and patients with coumadin overdose. For patients with life-threatening or otherwise substantial hemorrhage, plasma therapy is given at an initial dosage of 15 mL/kg, which will provide approximately an additional 25% to 35% level of each coagulation factor.

E. **Special blood products**

1. **Solvent–detergent plasma.** Efforts to inactivate viruses in plasma have proceeded rapidly, and one technique is now licensed for use in the United States. Treatment of plasma with a solvent–detergent (SD) process provides a means to inactivate all viruses with lipid envelopes, including HIV and hepatitis B and C viruses. The process, accomplished on a commercial scale by pooling plasma from 2,500 donors, yields units of standard size (200 mL) that are refrozen for distribution. The cost of a 200-mL unit of pooled plasma treated with the SD process is 2 to 5 times as high as the cost of a 250-mL unit of untreated plasma from a single donor. The contents of the plasma appear to be unchanged, except that procoagulant activity is reduced by about 15% and that levels of large multimers of von Willebrand factor and some other factors, including protein S, are decreased by more than 50%.

   The pooling of plasma from so many donors as part of the SD process has aroused concern about the possible transmission of nonenveloped viruses that are not inactivated by the process. The manufacturer and distributor have attempted to allay fears about the transmission of hepatitis A virus by documenting the presence of antibodies against this virus in their product. The transmission of parvovirus B19 is a potential problem for some transfusion recipients, such as patients with sickle cell disease or thalassemia, but it has not been reported among European recipients of plasma treated with the SD process. However, if an HIV-like nonenveloped virus were to evolve, it could be present at an undetectably low frequency in donors (e.g., 1 in 100 million) and yet present a threat in a pooled product.

   The recent identification of a potential pathogen, T.T. virus, illustrates the validity of the concern about pooled blood products. This nonenveloped virus is present in 1% to 7.5% of blood donors in the United States and is transmissible by blood. Although it is not known to cause disease, the virus has been described in a preliminary report as present in 15% of patients with cryptogenic cirrhosis and in 27% of patients with idiopathic fulminant hepatic failure.

SD plasma has subsequently been shown to have diminished levels of antitrypsin and absent antiplasmin activity, suggesting that this product may not be so effective as fresh frozen plasma (FFP) for the treatment of bleeding in patients with systemic activation of proteolytic cascades, such as DIC, sepsis, and large-volume transfusion.

Washed RBCs are rarely indicated, except for patients with severe reactions to plasma or platelets, such as patients with IgA deficiency.

Irradiation of blood products eliminates engraftment by immunologically competent donor lymphocytes and is recommended for immunocompromised patients (high-dose chemotherapy regimens, immunosuppressive therapy in allogeneic transplantation, or fludarabine therapy), and any patient receiving directed transfusions from a blood relative.

Leukoreduced blood products [99.9% of white blood cells (WBCs) removed] have been recommended for the following patients: (a) patients with previous FATR not prevented by acetaminophen and diphenhydramine therapy; (b) patients undergoing red cell exchange transfusions; (c) patients for whom cross-match compatible blood is difficult to obtain; (d) patients who are candidates for solid organ (kidney, heart, lung) or stem cell (aplastic anemia) transplantation; and (e) patients who should receive CMV-negative blood (e.g., platelets) in which CMV-seronegative products are unavailable (Table 30.2). A recognized problem with bedside leukofiltration is that some filters activate the kinin system in the blood infused, and patients taking angiotensin-converting enzyme (ACE) inhibitors have difficulty metabolizing these activated kinins. The clinical manifestations include vital sign instability, particularly hypotension. Bedside leukodepletion filters should therefore be avoided in patients' inhibitors with cardiovascular compromise treated with ACE inhibitors. Universal, prestorage leukoreduction of red blood cells (but not platelets) is being implemented in the United States.

Established indications
Prevention of recurrent nonhemolytic febrile transfusion reactions to red blood cell transfusions
Prevention or delay of alloimmunization to leukocyte antigens in selected patients who are candidates for transplantation or transfusion on a long-term basis
Indications under review
Prevention of the platelet-refractory state caused by alloimmunization
Prevention of recurrent febrile reactions during platelet transfusions
Prevention of cytomegalovirus transmission by cellular blood components
Not indicated for
Prevention of transfusion-associated graft-versus-host disease
Prevention of transfusion-related acute lung injury due to the passive administration of antileukocyte antibody
Patients who are expected to have only limited transfusion exposure
Acellular blood components (fresh frozen plasma, cryoprecipitate)

From Luse TA, et al. Ann Intern Med 1992;117:191–192, with permission.

TABLE 30.2. INDICATIONS FOR LEUKOCYTE REDUCED BLOOD COMPONENTS

III. **Platelet transfusions**

A. **Overview**

The evolution of intensive chemotherapy regimens in oncology and bone marrow/stem cell transplantation programs has resulted in increased demand for platelet products in patients with severe thrombocytopenia or for bleeding complications. The use of single-donor apheresis products has increased substantially, from 365,000 units in 1989 to 904,000 units in 1997. The use of these blood components has been driven in part by the need for alternative platelet inventories to support cardiac surgery and transplantation programs, but also in part by promotion of the use of leukoreduced platelet products.

However, issues related to the handling of the apheresis donor, the higher costs of apheresis platelets compared with pooled platelet concentrates, the results of the TRAP (Transfusion-Related Alloimmunization to Platelets) study, and emerging technologies have caused renewed interest in platelet transfusion practices. Issues include reevaluation of the platelet threshold for prophylactic transfusion, modification of platelet transfusion dose, the potential role of thrombopoietin therapy, and current investigational and pharmacologic options for the treatment of cancer-related thrombocytopenia.

B. **Platelet transfusion practices**

1. **Threshold for transfusion.** Several studies have evaluated prophylactic platelet transfusion thresholds for patients who are thrombocytopenic due to myelosuppressive therapy. One study found that most patients undergoing stem cell transplantation were transfused prophylactically with platelets when their platelet counts were between 10,000/mm^3 and 20,000/mm^3, indicating that a threshold of 20,000/mm^3 was most common. Only 9% of hemorrhagic events reported in this study occurred when platelet counts were less than 10,000/mm^3.

   Two prospective, randomized studies evaluated the relative merits of platelet-transfusion thresholds of 10,000/mm^3 or 20,000/mm^3 for leukemia patients undergoing chemotherapy. One found that the lower transfusion threshold was associated with 22% fewer platelet transfusions. No differences between the two patient cohorts were seen when hemorrhagic complications, number of red cell transfusions, duration of hospital stay, or mortality was analyzed. In a second study, a platelet threshold of 10,000 mm^3 was safe and effective when compared with a threshold of 20,000/mm^3. Two (1.9%) of the 105 patients in this study died of hemorrhagic complications; each patient had a platelet count greater than 30,000/mm^3 at time of death.

2. **Platelet dose.** Standards of the American Association of Blood Banks require that 75% of apheresis products contain more than 3×10^{11} platelets and that 75% of platelet concentrates contain more than 5.5×10^{10} platelets; however, there is no consensus for a standardized platelet-transfusion dose. Platelet doses used in several clinical trials indicate a broad range of platelet doses. In an evaluation of our own hospital-based apheresis program, 32% of products contained 3 to 4×10^{11} platelets, and 32% of products contained 4 to 5×10^{11} platelets. Leukoreduction of apheresis platelets or platelet concentrates has been shown to result in approximately 20% loss of platelets.

   Mathematical modeling has suggested that “low dose” platelet therapy would be more beneficial in thrombocytopenic patients who are receiving prophylactic platelet transfusions. A fixed platelet requirement for hemostasis is estimated to be 7,100/mm^3/day, and platelet consumption above this threshold is mainly due to platelet senescence. For patients made thrombocytopenic through myeloablative therapy, platelet survival decreases with an increasing degree of thrombocytopenia. Thus platelet survival is 5 to 7 days in patients with platelet counts in the normal range, but only 1 to 2 days in patients with platelet counts between 10,000/mm^3 and 20,000/mm^3, levels at which most thrombocytopenic patients are maintained for prophylaxis against hemorrhage. The mathematical model predicts that “low dose” platelet therapy would provide a 22% decrease in donor exposures (and total number of platelets) while maintaining patients at a platelet threshold greater than 10,000/mm^3, even with a shorter transfusion-free interval and a greater relative risk per day of receiving additional transfusions.

   A randomized clinical trial was conducted to address the issue of “high dose” platelet therapy. Standard, high, and very high platelet doses (4.6×10^{11}, 6.5×10^{11}, and 8.9×10^{11} platelets, respectively) were administered to patients receiving prophylactic platelet transfusions. The high and very high platelet-dose cohorts had greater platelet-count incremental increases and prolonged time to next transfusion when compared with the standard platelet-dose cohort. Of interest was that the estimate of platelet half-life (i.e., slopes) for the patient cohorts was not different for posttransfusion platelet counts ranging from approximately 50,000/mm^3 to 110,000/mm^3 (Fig. 30.2). These data suggest that the *in vivo* life span of transfused platelets cannot be normalized in this setting, even at higher platelet counts. Further studies of platelet transfusion dosage strategies are needed.

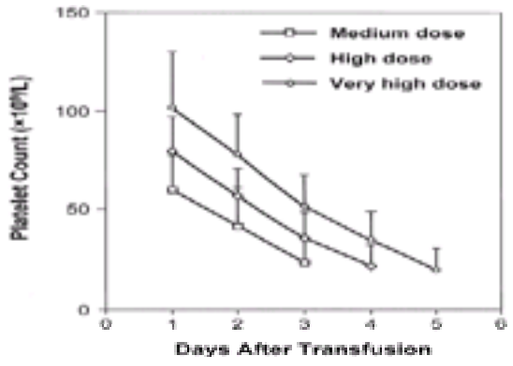

FIG. 30.2. Platelet count and platelet decline after transfusion. The half-life of platelets (i.e., slope of the curve) after transfusion of medium, high, and very high platelet doses is the same for all groups over a 5-day posttransfusion interval (medium, high, and very high doses correspond to a mean number of platelets per kg of body weight of 0.10, 0.15 and 0.22×10^{11}, respectively). (From Norol F, et al. *Blood* 1998;92:1448–1453, with permission.)

3. **Patient response.** Not only is platelet dosage nonstandardized and variable, but patient response to platelet transfusion also varies. When thrombocytopenic patients undergoing hematopoietic stem cell transplantation were analyzed for platelet corrected count increment (CCI) after transfusion, a bell-shaped or polynomial distribution was found, and patient-specific factors accounted for the polynomial distribution. Factors usually associated with patient response to platelets (history of previous transfusion, pregnancy, the presence of HLA or platelet-specific antibodies) did not significantly correlate with CCI. These findings suggest that prevention of refractoriness to platelet transfusion by the administration of leukoreduced platelets is not clinically important. Rather, patient-specific variables such as disease status (advanced rather than early), conditioning regimen (including total body irradiation or not), progenitor cell source (bone marrow rather than peripheral stem cell), and type of transplant (allogeneic vs. autologous) are significant predictors of platelet refractoriness in patients undergoing stem cell transplantation.

   In summary, platelet transfusion dose and patient response to transfusion vary. Furthermore, thrombocytopenic patients can be safely maintained at prophylactic transfusion thresholds of 10,000 cells/mm^3. Finally, the likelihood of hemorrhagic complications correlates poorly with the degree of thrombocytopenia in patients undergoing myeloablative chemotherapy. These findings, the results of the TRAP study, and our observations indicate that the use of specialized products (apheresis platelets and leukodepleted platelets) needs reassessment in the light of emerging technologies.

C. **Risks of platelet transfusion**

Risks of transfusion-transmitted diseases are the same as for red cells and are summarized in Table 30.1. The infectious risks of transfusion should decrease further with nucleic acid testing (NAT), which shortens window periods of infectivity by at least 50%, which will further reduce the risks of posttransfusion hepatitis C and HIV.

D. **Product contamination**

The risk of platelet-related sepsis is estimated to be 1:12,000 for apheresis platelets but is greater with transfusions of pooled platelet concentrates from multiple donors (e.g., 1:2,000 after receiving six concentrates). Because of the increasing risk of bacterial overgrowth with time, the shelf life of platelets stored at 20°C to 24°C is limited to 5 days. In descending order, the organisms most commonly implicated in fatalities (as reported to the FDA) are *Staphylococcus aureus, Klebsiella pneumoniae, Serratia marcescens,* and *Staphylococcus epidermidis*.

The clinical presentation of bacterially contaminated platelet infection can range from mild fever (which may be indistinguishable from febrile, nonhemolytic transfusion reactions) to acute sepsis, hypotension, and death. Sepsis caused by transfusion of contaminated platelets is underrecognized in part because the organisms found in platelet contamination are frequently the same as those implicated in “catheter” or “line” sepsis. The overall mortality rate of identified platelet-associated sepsis is 26%.

There is no widely accepted test for the detection of bacterially contaminated blood products. The most promising approach is the use of psoralen and

ultraviolet light to sterilize blood products. In the clinical setting, any patient in whom fever develops within 6 hours of platelet infusion should be evaluated for possible bacterial contamination of the component, and initiation of empiric antibiotic therapy should be considered. Because of their storage at room temperature, platelets are more prone to bacterial infection than are other blood products.

FATRs occur in only 0.5% of red cell transfusions; of these, 18% and 8% of patients experience a second or third FATR, respectively. Approximately 18% of platelet transfusions are associated with FATR, although the prevalence of platelet-associated FATR can be as high as 30% in frequently transfused populations such as oncology patients. Reactions characterized as severe occur in only 2% of platelet transfusions, and bedside leukofiltration has not been found to reduce the overall prevalence of FATR. Bedside leukoreduction filters are now recognized to cause significant hypotensive events by activation of the bradykinin/kininogen systems, particularly in patients taking ACE inhibitors.

TRAP was studied in a multicenter trial of newly diagnosed patients with leukemia. The study found that clinical platelet refractoriness associated with HLA antibody seropositivity was reduced from 13% of patients transfused with unprocessed platelet concentrates, to 3% to 5% of patients receiving leukoreduced apheresis platelets, leukoreduced platelet concentrates, or psoralen/UV-B–treated platelets. Although this difference achieved statistical significance, no important clinical differences were found between the patient cohorts, including prevalence of transfusion reactions, hemorrhagic events, mortality, length of hospital stay, number of platelet transfusions, or number of red cell transfusions.

IV. Platelet growth factors

Owing to the biologic nature of platelet products, the need for available donors, and the problems associated with platelet use, there is a need for pharmacologic options to manage cancer-related thrombocytopenia and prevent its attendant morbidity and mortality. At this time, marketed and investigational treatment options include interleukin-11 (IL-11) and recombinant human thrombopoietin (rhTPO), respectively.

These pharmacologic options offer the possibility of preventing thrombocytopenic bleeding in the hematology/oncology population. Although rhIL-11 is modestly effective in increasing platelet counts in patients who are thrombocytopenic after chemotherapy, treatment can be accompanied by significant adverse effects. Ongoing trials of rhTPO will help to determine the most effective treatment schedule and aid in targeting indications for this emerging hematopoietic growth factor.

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CHAPTER 31. NUTRITIONAL SUPPORT FOR THE CANCER PATIENT

Carolina C. Javier

Introduction: Identification and assessment of patients at nutritional risk
Nutritional assessment
Patient history and examination
Anthropometric assessment
Assessment of protein status
Immune function
Subjective global assessment
Interventions and nutritional therapy
Oral nutrition
Dietary supplements
Enteral feeding
Total parenteral nutrition

I. Introduction: Identification and assessment of patients at nutritional risk

Nutrition plays a supportive role in the care of the patient with cancer, whether the goal of therapy is curative or palliative. Nutritional interventions will maintain and preserve body composition and lean body mass, support functional status, and enhance the quality of life. Proactive assessments of nutritional status are essential to assure success in intervention and to improve patient outcome. Treatment modalities could have an impact on the nutritional status of the patient and could increase the risk for weight loss and malnutrition. Oncology dietitians play a key role in optimizing nutrition for the cancer patient through counseling and education of patients and their families, and other members of the health care team. The assessment and nutritional surveillance of the patient with cancer can help meet therapeutic goals.

II. Nutritional assessment

Nutritional assessment is an essential component in the nutritional care of the patient with cancer, because it will provide an estimate of body composition, such as fat, skeletal muscle protein, and visceral protein. It will likewise identify patients who are at risk of cancer-induced malnutrition and determine the magnitude of nutritional depletion in patients who are already malnourished (*CA Cancer J Clin* 1998;48:69–80).

A. Patient history and examination

Information that pertains to the patient's medical history and physical examination will reveal usual body weight, any recent weight change, or inclusion of new or special diets. Unintentional weight loss of 10% or more of body weight within the previous 6 months could mean a significant nutritional deficit and is a good indicator of clinical outcome. Signs of malnutrition such as muscle wasting, loss of muscle strength, and depletion of fat stores may be revealed by a physical examination (*CA Cancer J Clin* 1998;48:69–80). However, body weight alone is insufficient as a nutritional assessment tool and will fail to show important changes in disease or therapy-related caloric intake or metabolic rate (Calabresi P, Schein PS, eds. *Medical oncology: basic principles and clinical management of cancer.* 2nd ed. New York: McGraw-Hill, 1993:1151–1172).

In addition, detailed information should be obtained regarding change in appetite, food intake, gastrointestinal problems, and concomitant disease.

B. Anthropometric assessment

Anthropometric measurements are often used in the assessment of nutritional status, particularly when a chronic imbalance occurs between protein and energy intake. Such disturbances change the patterns of physical growth and the relative proportions of body tissues such as fat, muscle, and total body water (Gibson RS. *Principles of nutritional assessment.* New York: Oxford University Press, 1990). The measurement of the triceps skinfold is used to calculate an estimation of fat stores, whereas the midarm muscle circumference (includes the basic anthropometrics of weight and height) assesses lean body mass.

MMC (cm) = Arm circumference (cm) – 0.314 × TSF (mm)

where MMC is the midarm muscle circumference, and TSF is the triceps skinfold thickness (*Support Care Cancer* 1997;5:376–380).

Standards for age and gender have been established; however, there are wide variations among individuals, and interobserver measurement variability is considerable.

Anthropometric measurements may be markedly affected by nonnutritional factors and are rarely performed in the routine clinical setting.

C. Assessment of protein status

Serum protein concentrations such as retinol-binding protein, transferrin, prealbumin, and albumin can be used to assess the degree of visceral protein depletion.

The relation between malnutrition and serum protein levels is related to the patient's hydration status and the half-life of the individual protein (*CA Cancer J Clin* 1998;48:69–80).

Visceral protein status is frequently assessed by the measurement of one or more of the serum proteins (Gibson RS. *Principles of nutritional assessment.* New York: Oxford University Press, 1990) (Table 31.1). One of the first organs to be affected by protein malnutrition is the liver, which is the main site of synthesis for most of these serum proteins.

Protein	Half-Life	Body Pool Size (g/kg Body Weight)
Serum albumin	14–20 d	3–5
Serum transferrin	8–10 d	<0.1 g
Serum thyroxine-binding pre-albumin (TBPA)	2–3 d	0.01
Serum retinol-binding protein (RBP)	12 h	0.002

TABLE 31.1. SERUM PROTEINS OF HEPATIC ORIGIN

The synthesis of serum proteins is impaired by the limited supply of protein substrates, resulting in a decline in serum protein concentrations. Many nonnutritional factors influence the concentration of serum proteins (Table 31.2) and reduce their specificity and sensitivity (*Am J Clin Nutr* 1982;35:1159–1165; *Br Med Bull* 1981;37:11–17).

Inadequate protein intake resulting from low dietary intakes, anorexia, unbalanced diets, hypocaloric intravenous infusions
Altered metabolism generated by trauma, stress, sepsis, and hypoxia
Specific deficiency of plasma proteins caused by protein-losing enteropathy and liver disease
Reduced protein synthesis resulting from inadequate energy intake, electrolyte deficiency, trace element deficiencies (e.g., iron and zinc), vitamin deficiency (e.g., vitamin A)
Pregnancy induces changes in the amount and distribution of body fluids
Capillary permeability changes
Drugs (e.g., oral contraceptive agents)
Strenuous exercise

Adapted from Jeejeebhoy *Br Med Bull* 1981;37:11–17, with permission.

TABLE 31.2. FACTORS AFFECTING SERUM PROTEIN CONCENTRATIONS

Total serum protein is easily measured and has been used as an index of visceral protein status in several national nutrition surveys; however, it is a rather insensitive index of protein status (Gibson RS. *Principles of nutritional assessment.* New York: Oxford University Press, 1990). For example, normal limits of total serum protein concentration are maintained initially despite a restricted protein intake, with significant depletion when clinical signs of protein malnutrition become apparent. This marked decrease in the serum albumin concentrations, which represent 50% to 60% of the total serum protein, is the cause of this decline.

Serum albumin reflects changes within the intravascular space and not the total visceral protein pool. Serum albumin is not very sensitive to short-term changes in protein status; it has a long half-life of 14 to 20 days (Table 31.1) (Gibson RS. *Principles of nutritional assessment.* New York: Oxford University Press, 1990; *Br Med Bull* 1981;37:11–17). Reduced catabolism largely compensates for reductions in hepatic synthesis of serum albumin.

Each transferrin molecule binds with two molecules of iron, and thus serves as an iron-transport protein. Transferrin responds more rapidly to changes in protein status because of its shorter half-life and smaller body pool than albumin. Like serum albumin concentrations, serum transferrin concentrations are affected by a variety of factors, including gastrointestinal, renal, and liver disease (Gibson RS. *Principles of nutritional assessment.* New York: Oxford University Press, 1990).

The nutritional status of the patient also can be defined by using objective data. The Prognostic Nutritional Index (PNI) has been shown to predict clinical outcome in cancer patients. The PNI is based on serum albumin level, serum transferrin level, delayed cutaneous hypersensitivity, and triceps skinfold thickness (*Am J Surg* 1980;139:160–167; *J Parenter Nutr* 1987; 11:109S).

D. **Immune function**

Tests of immunocompetence are sometimes used as functional indices of protein status; however, their sensitivity and specificity are low. Nutritional deficiencies can impair nearly all aspects of the immune system, and no single measurement can assess adequacy of the immune response. Examples of immunologic tests include lymphocyte count, measurement of thymus-dependent lymphocytes, and delayed cutaneous hypersensitivity (Gibson RS. *Principles of nutritional assessment.* New York: Oxford University Press, 1990).

E. **Subjective global assessment**

Subjective global assessment (SGA) of nutritional status includes relevant history data (dynamic weight loss, dietary intake, specific symptoms, performance status, primary disease, and metabolic demand) as well as clinical data (subjective estimate of fat/protein stores.) The use of a standardized, simple, and validated assessment method such as Detsky's SGA is recommended (Table 31.3) for further specific studies. (*J Parenter Nutr* 1987;11:109S; *Nutrition* 1991;7:35–38; *J Parenter Enteral Nutr* 1987;1:8–13). The nutritional assessment tools used for clinical routine are summarized in Table 31.4 (*Semin Oncol* 1994;21:770–778).

A. History
Weight change (loss in 1, 3, 6 months, change in past 2 weeks)
Dietary intake change (relative to normal, type of diet)
GI symptoms (persisting >2 wk)
Functional capacity (ECOG 0–4)
Disease and relation to nutritional requirements (primary diagnosis, stage, metabolic stress)
B. Physical
Subcutaneous fat, muscle wasting, edema, ascites
C. SGA rating
A, well nourished
B, moderately malnourished
C, severely malnourished

*Modified SGA used at Fox Chase Cancer Center (short version).
GI, gastrointestinal; ECOG, Eastern Cooperative Oncology Group.

TABLE 31.3. FACTORS CONSIDERED IN SUBJECTIVE GLOBAL ASSESSMENT (SGA) OF NUTRITIONAL STATUS

Minimal screening assessment
Present weight in relation to ideal weight (weight/height index)
Weight change (% weight change per time interval)
Serum albumin
Complete assessment
History
Dietary data (food records, recall methods)
Concomitant disease
Physical examination
Body fat, muscle wasting
Specific nutritional deficiencies
Anthropometrics
Triceps skin fold (caliper method)
Midarm muscle circumference
Laboratory tests
Creatinine/height index
Serum transferrin or albumin
Immune function
Total lymphocyte count
Delayed hypersensitivity skin tests
Subjective global assessment, clinical experience
Appositional assessment
Bioelectrical impedance analysis

TABLE 31.4. SYNOPSIS OF NUTRITIONAL ASSESSMENT PARAMETERS

III. Interventions and nutritional therapy

An estimate of current energy and protein balance is useful in providing nutritional intervention.

Nitrogen metabolism. The measurement of the nitrogen balance can document the effectiveness of nutritional therapy; nitrogen balance is calculated by the formula (*Am J Pub Health* 1973;63:1).

$$\text{Nitrogen balance} = \frac{\text{protein intake}}{6.25} - (\text{urinary urea nitrogen} + 4)$$

The apparent net protein utilization is generated by using the relationship

$$\text{Net protein Utilization (apparent)} = \frac{\frac{\text{protein intake}}{6.25} - \text{urinary urea nitrogen} + 2 - \text{obligatory nitrogen loss}}{\frac{\text{protein intake}}{6.25}}$$

The obligatory nitrogen loss is roughly equal to 0.1 g/kg of body weight.

Calorie expenditure. The calculation of basal energy expenditure (BEE) is preformed by using the following formula: (*J Parenter Nutr* 1977;1:11)

For men: BEE = 66 + (13.7 × W) + (5 × H) – (6.8 × A);
For women: BEE = 655 + (9.6 × W) + (1.7 × H) – (4.7 × A),

where W is the actual weight in kilograms; H is the height in centimeters; and A is the age in years. By using the value for BEE, the caloric intakes can be expressed as a multiple of BEE:

$$\text{Kilocalorie intake as percentage of BEE} = \frac{\text{Caloric intake}}{\text{Basal energy expenditure}} \times 100$$

Calorie-intake evaluation. Table 31.5 (Alpers DH, Stenson WF, et al. *Manual of nutritional therapeutics.* 3rd ed. Boston: Little, Brown, 1995) provides the figures for a rough estimation of protein and calorie requirements for all hospitalized patients. An evaluation of caloric intake also can be determined by using Table 31.6 (Alpers DH, Stenson WF, et al. *Manual of nutritional therapeutics.* 3rd ed. Boston: Little, Brown, 1995). Guidelines for making decisions for nutritional therapy based on energy and protein balance are given in Table 31.7 (*J Parenter Enter Nutr* 1977;1:11).

Degree of Stress	Caloric Requirements (kcal/kg[a]/day)	Protein Requirements (g/kg[a]/day)
None	25	0.8
Mild metabolic stress	35	1.0
Moderate–severe metabolic stress	45	1.5

[a]Desired body weight.

TABLE 31.5. RAPID ESTIMATION OF PROTEIN AND CALORIE REQUIREMENTS OF ADULT PATIENTS

Protein and Calorie Balance	Nutrition Plan
Negative	
Long period of support anticipated	Increase intake now
Short period of support anticipated	Delay intensive therapy; minimize losses until acute illness subsides; reevaluate frequently
Zero	Delay intensive therapy; minimize losses until acute illness subsides; reevaluate frequently
Positive	Try to maintain 500–1,000 kcal and 15–30 g protein/day over requirement

TABLE 31.6. NUTRITION PLANNING FOR PATIENTS WITH MODERATE TO SEVERE PROTEIN–CALORIE MALNUTRITION

A. Energy requirements	Kilocalories required (per 24 h)
Type of therapy	
Parenteral anabolic	1.75 × BEE
Oral anabolic	1.50 × BEE
Oral maintenance	1.20 × BEE

B. Prescriptions for anabolism[a]	Protein (g/day)	Kilocalories (kcal/day)
Type of therapy		
Oral protein sparing	1.5 × weight[b]	
Total parenteral nutrition	(1.2–1.5) × weight	40 × weight
Oral hyperalimentation	(1.2–1.5) × weight	35 × weight

Reprinted from Nutritional and metabolic assessment of the hospitalized patient. *J Parenter Nutr* 1977;1:11, with permission.
[a]Levels of protein intake are to be adjusted according to blood urea nitrogen values and nitrogen balance.
[b]Weight, actual weight in kilograms.
BEE, basal energy expenditure.

TABLE 31.7. NUTRITIONAL THERAPY

A. Oral nutrition

The preferred method for providing nutrition for patients who are able to eat is by oral diet, which can be modified according to the physiologic and anatomic constraints of their illness. For nutritional support considerations for individuals with daily energy deficits (e.g., patients with anorexia and resulting weight loss, dysphagia), see Table 31.8 (National Cancer Institute. *Eating hints for cancer patients.* 1998) and Table 31.9.

Potential Problem	Intervention
Anorexia	Small frequent meals seasoned according to individual taste Snacks of nutrient-dense liquids such as instant breakfast, milkshakes, or commercial supplements can provide significant protein and calories and are easily consumed (See Table 31.9)
Dry mouth/thick saliva	Encourage good oral hygiene Artificial saliva and use of a straw may facilitate swallowing Petroleum jelly applied to the lips may help prevent drying Avoid coarse foods; some patients may require a liquid diet
Dysphagia	Encourage a soft, more liquid diet and easy-to-swallow foods Small frequent meals Use liquid nutritional formulas Determine the appropriate consistency of food and fluids or any special swallowing techniques given by the speech therapist
Radiation esophagitis	Soft bland diet, using creamy, lukewarm, or cool foods Avoid coarse, dry, or scratchy textured foods Avoid tart and acidic fruits and juices, alcohol, and irritating spices

TABLE 31.8. NUTRITIONAL SUPPORT CONSIDERATIONS FOR INDIVIDUALS WITH DAILY ENERGY DEFICITS

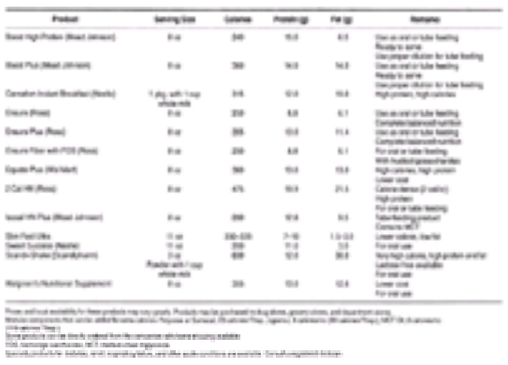

TABLE 31.9. EXAMPLES OF COMMONLY USED NUTRITIONAL PRODUCTS

B. **Dietary supplements**

Nutrients, vitamins, and minerals that are essential for human health, as well as a variety of nonessential nutrients, such as phytochemicals, hormones, and herbs, are used as dietary supplements; however, these should never replace whole foods. The American Cancer Society (ACS) warns against massive doses of any dietary supplement, recommends supplements that are close to the Daily Percentage Value for most vitamins and minerals, and states that there is no substitute for a well-balanced diet that follows the United States Department of Agriculture (USDA) Food Pyramid (American Cancer Society. *Alternative methods: dietary and herbal remedies, dietary supplements.* Atlanta: American Cancer Society, 1997). The Percentage Daily Value (DV) on food labels, formerly known as The Recommended Daily Allowances, is the average daily dietary intake level that is adequate to meet the nutrient requirements of nearly all (97% to 98%) individuals in a specific life stage and gender group (*J Am Diet Assoc* 2000;100:637–640; Food and Nutrition Board, Institute of Medicine. *Recommended daily allowances.* 10th ed. Washington, DC: National Academy Press, 1989). In order to account for differences in need and ability for absorption, the DV is set considerably higher than the estimated average requirement. Any recommendations for nutritional supplementation at doses higher than twice the DV should be individualized and are dependent on each individual's dietary and disease status. The American Dietetic Association recommends getting all the nutrients needed from the diet first and then considering supplementation only if it is adequately researched (*J Am Diet Assoc* 1996;96:73–77).

C. **Enteral feeding**

Enteral feeding refers to the provision of nutrients, either to supplement oral intake, or as the sole source of nutrition, delivered via catheter or tube to the gastrointestinal tract for absorption. Enteral feeding is preferred to parenteral feeding because it preserves the gastrointestinal architecture and prevents bacterial translocation from the gut. Enteral feeding has the advantage of delivering nutrients beyond areas of obstruction, at rates that can maximize nutrient absorption. Nutrients should be administered distal to the ligament of Treitz to avoid complications of aspiration pneumonia and gastric ileus. For short-term feeding, a nasoduodenal tube may be used. If there is a need for long-term enteral support, the preferred method is either a gastrostomy or jejunostomy tube, which can be placed either surgically or endoscopically. Nutritionally complete enteral-feeding formulas as well as specialized modular products to meet specific disease-related nutrient requirements are commercially available (Shils ME, Olson JA, Shike M, eds. *Modern nutrition in health and disease.* 8th ed. Philadelphia: Lea & Febiger, 1994:182–183).

D. **Total parenteral nutrition**

Providing nutritional support by the parenteral route is an important option for patients for whom oral or enteral nutrition is unsuitable. The hyperosmolar total parenteral nutrition (TPN) solutions require central venous access to reduce complications of venous thrombosis and phlebitis. Inherent complications, such as pneumothorax, occur infrequently (*J Clin Oncol* 1984;2:534–538). Parenteral nutrition is more expensive than enteral or oral nutrition, and adherence to specific guidelines is of utmost importance to minimize complications. Some studies on the use of TPN in cancer patients demonstrated improvement in body weight and total body fat content. Specific minerals, trace elements, and vitamins can be provided with TPN, but TPN does not stop the catabolic process of cancer cachexia, as nitrogen losses continue for patients receiving TPN, or alter the increased protein turnover and the process of lipolysis. When appropriately selected, certain cancer patients receiving TPN have shown significant decreases in morbidity and mortality. This includes patients with severe malnutrition receiving perioperative TPN and bone marrow transplant recipients (*Nutr Clin Pract* 1994;9:91–100). The American Society of Parenteral and Enteral Nutrition has recommended TPN supplementation in patients expected to have inadequate oral or enteral nutritional intake for more than 10 to 14 days (*J Parenter Enter Nutr* 1980;10:441–445).

CHAPTER 32. PSYCHOSOCIAL ISSUES IN ONCOLOGY

Teresa L. Deshields

Assessment of psychiatric disorders
Major depression
Anxiety disorders
Distinguishing psychological distress from psychiatric disorders
Psychosocial factors contributing to adjustment
Management of psychological distress
Case coordination
Spiritual support
Education and information
Peer support
Support groups
Smoking-cessation support
Family support
Individual support
Psychotropic medication management
Evaluating treatment refusal
General summary
Suggested Readings

Psychosocial issues (particularly those related to prevention and detection of cancer and compliance with treatment) have been the object of heightened attention in oncology since the 1970s. This movement has been matched by the maturation of psycho-oncology, which became recognized as a discipline in the 1980s (the International Psycho-Oncology Society was founded in 1984). As the treatment of cancer has advanced, survival rates have climbed, leading to more attention to quality of life, which encompasses a set of issues that is heavily influenced by psychosocial factors. Likewise, as more treatment is delivered on an outpatient basis, the home environment intrudes increasingly on treatment, again making psychosocial issues more a concern for medical providers.

Several topics are addressed in this chapter. The assessment of psychiatric disorders is covered because these problems are often missed by medical providers, yet they can have a significant negative effect on treatment compliance and on quality of life. Attention is paid to the distinction between psychological distress and psychiatric disorders. Whereas the former is more common, the latter is more disruptive and requires more aggressive intervention. An overview is included of psychosocial factors that affect patient adjustment. The chapter also reviews interventions to address psychological distress or psychiatric disorders. Finally, some attention is given to the issue of treatment refusal, exploring the role of psychological factors in this phenomenon.

I. Assessment of psychiatric disorders

The most common psychiatric difficulties in cancer patients are depression and anxiety. Depression is more common, in general, with the most frequent diagnoses being Major Depression and Adjustment Disorder with Depressed Mood. When Diagnostic and Statistical Manual (DSM) criteria (see later) are used in making a diagnosis, 28% of cancer patients have been found to be suffering from depression (*Psychiatry Clin Neurosci* 1996;50:309–312). For patients who are struggling with psychological difficulties, a psychiatrist or psychologist can clarify the diagnosis(es) and make treatment recommendations.

A. **Major depression** is diagnosed by using criteria established by the DSM-IV-TR of the American Psychiatric Association. The criteria for this diagnosis are listed in Table 32.1.

The symptom constellation must be present for ≥2 weeks
One of these symptoms is required
Depressed mood
Diminished interest in activities
At least four of these symptoms are required
Change in appetite or weight
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue
Feelings of worthlessness or guilt
Impaired ability to concentrate
Suicidal ideation, plan, or attempt

TABLE 32.1. DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSION

It is noteworthy that a number of the symptoms that make up the diagnostic criteria for Major Depression may be confounded with symptoms of cancer or side effects of treatment. Those that may be particularly confusing include sleep difficulties (particularly hypersomnia), loss of appetite, fatigue, and problems with concentration. This overlap has led some to propose that the diagnosis of depression in cancer patients must rely almost exclusively on the presence of psychological symptoms of depression. These symptoms also may be somewhat problematic, as there is confounding here as well. Many cancer patients report feelings of guilt, primarily related to perceived burden on family members, but at times for personal health behaviors that the patient links to development of cancer (e.g., smoking). Many patients complain of cognitive/memory difficulties after chemotherapy, popularizing labels such as “chemo brain” or “chemo fog.” Critical symptoms to look for in cancer patients are feelings of hopelessness (which may complicate decisions about treatment), excessive guilt (perhaps related to feeling like a burden), perception of being punished (often associated with religious beliefs), and suicidal ideation.

Depression is more common in specific types of cancer (pancreatic, lung), in the face of poor prognosis, and when pain is present. Individuals with a history of mood disorder are at greater risk for development of depression after a cancer diagnosis, as are those with a family history of depression. Other risk factors include alcohol or substance abuse, younger age, female sex, and socioeconomic pressure.

Several factors make an individual with cancer more at risk for suicide. Several of these are related to psychiatric status, such as history of suicide attempts, history of psychiatric disorder, current depression, feelings of hopelessness, feelings of helplessness or feeling out of control, and delirium. Several of these are related to medical status, such as advanced stage of cancer, poor prognosis, and presence of exhaustion, fatigue, or pain. Suicidal behavior may be more overt or may be more subtle (e.g., medication errors, treatment refusal). In the presence of behaviors that suggest suicidal risk, a frank discussion with the patient can clarify psychological or psychosocial factors contributing to the behavior.

The diagnostic criteria for **Adjustment Disorders** are more lenient, requiring an activating event to which the patient is adjusting but fewer psychological symptoms. The activating event can be the cancer diagnosis or some aspect of treatment. Some patients have a more difficult adjustment in the transition to survivorship. The clinical symptoms must begin within 3 months of the activating event. The diagnostic criteria for Adjustment Disorder are listed in Table 32.2.

The symptoms develop within 3 months after an identifiable stressor
The symptoms are clinically significant, as demonstrated by
Marked distress in excess of what would be expected
Significant social or occupational impairment
The symptoms are not explainable as bereavement
The symptoms do not last >6 months after the resolution of the stressor and its consequences

TABLE 32.2. DIAGNOSTIC CRITERIA FOR ADJUSTMENT DISORDER

Adjustment Disorders are classified by these subtypes: with Depressed Mood, with Anxiety, and with Mixed Anxiety and Depressed Mood. It is more common for an individual with cancer to meet the diagnostic criteria for an Adjustment Disorder than those for Major Depression. These disorders will often respond to less aggressive interventions. The patient should be included in a discussion of psychosocial interventions to identify one or more that are more palatable to the patient and thus more likely to be utilized.

B. **Anxiety disorders** may take various forms. Particular forms that may occur after a cancer diagnosis include Generalized Anxiety Disorder, Posttraumatic Stress Disorder, and Specific Phobia. Generalized Anxiety Disorder is characterized by excessive anxiety and uncontrollable worry, to the extent of significant disruption of functioning. These patients are generally able to acknowledge being “worry warts.” They may appear to be generally fretful or pessimistic.

   Posttraumatic Stress Disorder develops after exposure to circumstances that involved actual or threatened physical harm or death. The latest version of the DSM (IV-TR) included diagnosis of a life-threatening illness as a traumatic event that could be associated with development of Posttraumatic Stress Disorder. The characteristic features are persistent rumination about the event(s) [cancer diagnosis, specific treatment (e.g., stem cell transplantation)], intense distress in response to reminders of the event(s), and persistent avoidance of stimuli associated with the event(s). The affected individual is often generally agitated, as evidenced by sleep difficulties or irritability.

   Specific phobias may develop with a focus on a particular aspect of treatment, such as chemotherapy. This problem is more commonly seen in anticipatory nausea, when a patient receives chemotherapy, and worsening nausea develops. The nausea may progress to the point of occurring before chemotherapy administration and can progress to occurring in the absence of chemotherapy, but in response to cues associated with chemotherapy (particular smells, sight of the hospital, etc.).

II. **Distinguishing psychological distress from psychiatric disorders**

Although learning of a cancer diagnosis is distressing for virtually every patient, this level of distress does not usually advance to the degree required for diagnosis of a psychiatric disorder. The psycho-oncology literature contributes to some confusion on this point. For example, incidence figures for depression may or may not be based on DSM diagnostic criteria. Many articles use other standards for reporting depression, including patient self-report, scores on self-report instruments (which usually indicate prevalence of supporting symptoms without linking to DSM criteria), or treatment-provider ratings.

The importance of distinguishing psychological distress from psychiatric disorders is linked to the different approaches to treatment. Psychiatric disorders require more aggressive management, most commonly psychotropic medication management and psychotherapy (usually with a cognitive–behavioral approach). These disorders must be addressed because of concomitant difficulties, such as increased risk of suicide, greater likelihood of poor treatment adherence, and greater disruption in quality of life. Recognition of a psychiatric disorder justifies a strong response from the medical provider, particularly requesting psychiatric or psychologic consultation and following up with the patient to ensure that treatment is implemented to address the problem directly. Psychological distress often resolves with time. Patients who are distressed may be reassured by learning that their distress will likely improve with the passage of time, but may also appreciate information about and/or referral to support services, including resources for education, support groups, self-help books, and supportive counseling. Some patients may need encouragement from their medical providers to access resources for psychosocial support, believing that they should be “strong enough” to face their cancer diagnosis or treatment on their own. Normalizing the need for support can make it more palatable for many patients. Patients also will generally appreciate the attention that a treatment provider pays to how they are coping, even if they are resistant to following up on referrals for support.

III. **Psychosocial factors contributing to adjustment**

Many psychosocial factors contribute positively or negatively to overall patient adjustment. Some of these are demographic (age, gender, socioeconomic status), whereas some are more social. There is some evidence supporting the clinical lore that younger patients have greater difficulty with emotional adjustment to cancer. This seems most likely related to the disabilities of illness being more disruptive at earlier developmental stages. The typical tasks of life at a younger age, most notably establishing a career and raising small children, certainly are affected by the cancer diagnosis and treatment. Older patients also are more likely to have peers who have been diagnosed with or treated for cancer. Self-image issues, particularly those related to appearance, seem to be more important at younger ages, and these are affected variably, depending on the type of cancer. Breast cancer, gastrointestinal cancer, prostate cancer, and head/neck cancer can have great impact on physical appearance and/or self-image.

Gender issues can be important in that women are at greater risk for developing psychiatric disorders in general. It is thought that women are likely to be more comfortable speaking with their providers about psychological distress, allowing easier diagnosis. They also are more likely to be receptive to support services. Discussing psychological coping with male patients can be difficult. It is important to approach these discussions in a matter-of-fact way, normalizing the experience of distress as needed.

Socioeconomic status can affect adjustment in several ways. The barriers to treatment imposed by low socioeconomic status can be diffuse yet powerful. Transportation difficulties can undermine treatment adherence. Lack of sick leave at work can make it financially difficult, if not impossible, for patients to miss work to receive treatment. Financial worry is often reported by patients as their biggest concern and the factor contributing most to psychological distress.

A body of literature documents the health benefits of social support. Those patients who have people available to them to provide practical and emotional support cope better in general. This is a relatively easy factor to assess in patients by asking them specifically who is available to provide them with support. It also may be apparent in whether patients come to appointments alone or accompanied by others. For those older patients with cognitive difficulties, it is particularly important to encourage them to bring support individuals with them to appointments, to help them recall important information about their disease or treatment. Patients with poor social support may have greater need for psychosocial services for practical assistance through the course of treatment and may benefit emotionally from participation in a support group or supportive counseling.

A more recent area of inquiry concerns spirituality. Findings indicate that individuals who describe themselves as having a strong religious faith cope better with medical difficulties. A church community can often serve as a resource for practical support for individuals incapacitated by disease or by treatment effects. Some patients report prayer or church attendance as effective coping strategies.

IV. **Management of psychological distress**

Many interventions can be used to provide support to patients struggling with adjustment to cancer diagnosis or treatment or adjustment to survivorship. These vary in time and emotional demands on the patient. Psychosocial interventions have been found to enhance patient quality of life and improve treatment compliance. Those patients exhibiting psychological distress, but not a psychiatric disorder, may benefit from supportive interventions. Those individuals meeting criteria for a psychiatric disorder should be treated more aggressively, with multiple modalities brought to bear against the problem. Treatment options

include the following.

A. **Case coordination.** Many patients find the coordination of multiple treatments and providers to be confusing and difficult. The more complicated the regimen, the greater the likelihood of treatment noncompliance—not from the patient's active choice to curtail treatment, but from confusion, misunderstanding, or frustration.
B. **Spiritual support.** This type of support can be offered through many channels. Although most hospitals have spiritual care services available to inpatients and their family members, many patients prefer to use their own spiritual care advisors (priest, minister, etc.).
C. **Education and information.** Information about cancer and about treatment options can be reassuring to many patients; although some patients also are frightened by information, particularly that which they do not understand. It is advisable to ascertain whether patients find information to be helpful. Those who report information to be distressing can be provided information more slowly and in smaller amounts, given written information to take home to digest at their own pace, and encouraged to follow their own pace in accessing information. Patients also can be encouraged to bring to their treatment providers information that is frightening, confusing, or at odds with that given by the provider.
D. **Peer support.** Peer-support programs were among the first support services offered for cancer patients. These programs provide trained patient volunteers who serve as sources of practical information, support, and connectedness for cancer patients. There are some established national programs of this sort: Reach to Recovery through the American Cancer Society, and First Connection through the Leukemia/Lymphoma Society.
E. **Support groups.** Groups can be a powerful intervention for cancer patients. Groups usually have one of two types of focus, education or support, although combination approaches also are common. The first type (educational support groups) usually meet on a monthly basis and have an educational component, usually in the form of scheduled topics or guest speakers. Some groups are built around specific topics, such as relaxation training, anxiety management, or adjustment to a new cancer diagnosis. The second type (intensive support groups) usually meet on a weekly basis, are often closed (with participants admitted on a controlled basis), and capitalize on the interpersonal aspects of support. In these latter groups, participants share information, provide each other with ideas, and normalize experiences and reactions. They also can provide a sense of community and belonging to patients who may feel somewhat isolated by their medical experiences.
F. **Smoking-cessation support.** Assistance with smoking cessation can occur through smoking-cessation classes, individual coaching, and medication support. Although some patients may feel too overwhelmed to tackle as difficult an addiction as tobacco, others may wish to capitalize on motivation engendered by a cancer diagnosis or may feel the need to take some measure of action against the cancer.
G. **Family support.** At times, family members may need support, either involving the patient or not. Family meetings can be used to reduce confusion, clarify treatment goals, or provide support. Some programs for newly diagnosed cancer patients also will allow family members to attend, providing information and support. Support groups for family members are available in some areas and can provide the benefits of a sense of community, support from people facing similar circumstances, and the opportunity to brainstorm solutions for specific difficulties. The family may need particular support when one of its members dies. Bereavement-support services can be very useful in supporting family members through grief.
H. **Individual support.** This intervention is most useful when applied in a flexible fashion, working around treatment schedules and treatment settings. Most patients who access individual support services do so briefly (often one to two sessions), using the opportunity to ventilate, to get support, and to get ideas for coping. Cognitive–behavioral therapy is a well-established and well-researched approach to treatment of anxiety and depression, and is well suited to medical patients, given its focus on the “here and now” and its emphasis on practical behavioral change. When needed, individual therapy can be very effectively focused on specific symptoms, such as anticipatory nausea or phobic avoidance of medical procedures.
I. **Psychotropic medication management.** Many medications are available to treat anxiety and depression. Some of these medications can be helpful in managing other symptoms, such as hot flashes, nausea, and sleep disruption. Some of these medications may be contraindicated or rendered less effective in the presence of particular cancer agents. For patients who are resistant to taking psychotropic medications, it can be helpful to frame this treatment as a short-term adjunct to the cancer-treatment regimen.

V. **Evaluating treatment refusal**

Patient refusal of treatment is an obvious cause for concern in the treatment team. This may happen from the time of diagnosis or may occur at some later point in treatment. It is important to understand the reason(s) for refusal of treatment. At times, the reason is a practical one that can, perhaps, be addressed by engaging the assistance of psychosocial services. For example, financial concerns may lead some individuals to decline treatment, perhaps because of guilt associated with the perceived impact of treatment-related expenses on the family. Transportation difficulties may lead to failure to follow through with treatment, primarily because the patient cannot get to treatment appointments easily.

Treatment refusal may be related to educational issues. It is important to ensure that patients understand their diagnoses and the treatments recommended. It is particularly important to use lay language in discussions with patients. Comprehension can be verified by asking patients to repeat back what they have been told about their diagnoses or treatment recommendations. For patients with cognitive difficulties, it may help to write down for them key information about diagnosis or treatment. For the latter patients (and other patient groups, as well), it is often helpful to involve family and other support in education about their disease and treatment.

Treatment refusal can be related to depression, perhaps through a sense of hopelessness or perhaps through suicidal wishes. It is always appropriate to assess for depression in the oncology setting, but it is particularly important to identify when depression is contributing to treatment refusal. When such is the case, the depression should be treated aggressively and treatment decisions reconsidered when the depression has improved.

At times, treatment refusal may reflect a reasoned choice, logically considered by the patient. These decisions are often related to quality-of-life concerns, more likely when a patient has decided that the anticipated outcome of treatment does not merit the physical or emotional costs of treatment. When a patient has refused treatment, it is important to determine that contributing psychosocial factors affecting treatment decisions have been addressed and that depression has been ruled out as the driving force behind a treatment decision. It also may be useful to have the patient talk with a psychosocial provider, skilled at assessing motivation, to help the patient sort through the issues contributing to his or her decision. When these factors have been assessed and it is clear that treatment refusal represents a reasoned choice, it is important for the treatment team to provide palliative care.

VI. **General summary**

Psychosocial issues are intertwined with medical factors throughout the course of cancer diagnosis and treatment, but may be particularly prominent at the time of initial diagnosis, recurrence, disease progression, or treatment failure. Some research also has suggested the conclusion of treatment to be a difficult time for patients. As discussed earlier, it is common for patients to feel or to exhibit psychologic distress during the course of cancer care. Many options are available for intervention, and the patient's preference can be a primary factor in choosing which interventions to recommend or to implement. Relatively fewer patients will develop true psychiatric disorders (based on DSM criteria), but the incidence is still higher than that in the general population, with about one fourth of cancer patients affected. Those who develop a psychiatric disorder develops should be treated aggressively, as the consequences of untreated psychiatric disorders can compromise medical outcomes. When the nature or severity of a patient's psychologic difficulties is uncertain, it is always appropriate to arrange consultation with a specialist to determine the relevant diagnosis. These types of referrals work most effectively in an established multidisciplinary team, when the patient believes the psychological/psychiatric care to be integrated into the medical care. The advantage of assembling a multidisciplinary team to manage the care of cancer patients is the ability to use diverse assessment skills to identify patients' problems and to mobilize various interventions to address these problems, with minimal confusion and disruption for the patient.

SUGGESTED READINGS

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CHAPTER 33. SMOKING CESSATION: A PRACTICAL APPROACH

Mark S. Walker

Guidelines for physician intervention: ask, advise, assess, assist, arrange
Ask: assessment of smoking history
Advise patients to quit smoking
Assessment of readiness to change: the transtheoretical model
Assistance: tailored to patient's readiness to change
Arrange follow-up/routine assessment of smoking status
Suggested Readings

Adult cigarette smoking is estimated to be responsible for one of every six deaths in the United States, and more than a third of all cancer deaths annually (Orleans CT, Slade JD, eds. *Nicotine addiction: principles and management.* New York: Oxford University Press, 1993:105–128). It is the primary cause of lung (*J Natl Cancer Inst* 1999;91:675–690) and head and neck cancers (*Cancer Res* 1988;48:3282–3287), and has been proven to be a cause of bladder, kidney, and pancreatic cancers (Orleans CT, Slade JD, eds. *Nicotine addiction: principles and management.* New York: Oxford University Press, 1993:105–128; U.S. Department of Health and Human Services (USDHHS). *DHHS Publication No. (CDC) 89-8411.* Rockville, MD: DHHS, 1989). Several studies have found that among individuals with smoking-related cancers, those who continue to smoke have a higher risk of recurrence (*Arch Otolaryngol* 1983;109:746–749) or of developing a second primary tumor (*Ann Intern Med* 1993;119:383–390).

Continuing to smoke after diagnosis may diminish the effectiveness of adjuvant cancer treatment (*N Engl J Med* 1993;328:159–163; *Proc Annu Meet Am Soc Clin Oncol* 1995:1088) and increase the likelihood of complications of treatment, such as soft tissue and bone necrosis after radiation, or toxicities due to chemotherapy (Orleans CT, Slade JD, eds. *Nicotine addiction: principles and management.* New York: Oxford University Press, 1993:279–309). Continued smoking increases the risk of other serious smoking-related disease (Orleans CT, Slade JD, eds. *Nicotine addiction: principles and management.* New York: Oxford University Press, 1993:279–309) and also may lead to impaired nutrition through elevated metabolism and decreased appetite (*Br J Addict* 1991;86:549–554). Smoking also is associated with increased risk of infections among non-cancer patients (*N Engl J Med* 2000;342:681–688), a risk that is unlikely to diminish with the immunosuppression associated with chemotherapy. Clearly, quitting smoking should be a priority for cancer patients.

The U.S. Public Health Service sponsored the development of Clinical Practice Guidelines for the treatment of tobacco use and dependence (Fiore MC, Bailey WC, Cohen SJ, et al. *Treating tobacco use and dependence: clinical practice guidelines.* Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, 2000). The guidelines conclude that tobacco dependence is a chronic but treatable condition, and that treatment should be offered to every patient who smokes at every visit. Counseling and behavioral therapies were found to be consistently effective and should be used with all patients who smoke. The key elements of effective counseling are (a) problem solving/skills training, (b) intrasession support, and (c) help in securing outside social support. Bupropion SR and nicotine-replacement therapies also were found to be effective, and should be used with all patients trying to quit smoking, unless specifically contraindicated. The guidelines found that there is a strong dose–response relation between the intensity of person-to-person counseling and abstinence, and that even minimal interventions (fewer than 3 minutes) are effective. However, intensive interventions (more than 10 minutes) are more effective and should be used whenever possible. In addition, treatment delivered over multiple sessions, by multiple types of clinicians, and by multiple modalities (individual, group, telephone) are more effective than advice delivered by one clinician during a single session. Total contact of at least 30 minutes is recommended for intensive intervention, although abstinence increases with treatment intensity up to 90 minutes of total contact (Fiore MC, Bailey WC, Cohen SJ, et al. *Treating tobacco use and dependence: clinical practice guidelines.* Rockville, MD: U.S. Department of Health and Human Services. Public Health Service, 2000).

I. Guidelines for physician intervention: ask, advise, assess, assist, arrange

The Clinical Practice Guideline has recommended the use of the “5 As” model for smoking-cessation treatment in a primary care setting (Fiore MC, Bailey WC, Cohen SJ, et al. *Treating tobacco use and dependence: clinical practice guideline.* Rockville, MD: U.S. Department of Health and Human Services. Public Health Service, 2000). The five “As” are to ask patients' smoking status, advise them to quit, assess their willingness to quit, assist patients in quitting, and arrange follow-up contact regarding their efforts to quit.

A. Ask: assessment of smoking history

Except for patients who have never smoked, patients should be asked their smoking status at every medical visit, and this information should be recorded in their charts. Because individuals may relapse after months or even years of abstinence, physicians should not assume that a patient has not smoked recently. Any effective approach to helping a patient maintain abstinence requires sufficient charting to make the physician aware of changes in the patient's smoking behavior over time. Current smoking status is a minimum. However, asking the patients how much they smoke or when they last smoked may be more effective in identifying those who are in the midst of quitting and remain at high risk of relapse.

B. Advise patients to quit smoking

Every patient who smokes should be advised to quit completely. The diagnosis of cancer may represent a “teachable moment” that will make the patient more receptive to physician advice (*Prevent Med* 1999;29:133–138; *Am J Health Promotion* 1991;6:24–29), but those who believe they are unlikely to benefit from quitting may be less likely to try (*J Behav Med* 1999;22:407–418). Advice should be given nonjudgmentally, but the importance of quitting should be emphasized in terms personally relevant to the cancer patient. The physician should stress the medical dangers associated with the patient's continuing to smoke, such as the risk of occurrence (or recurrence) of smoking related cancers (*Arch Otolaryngol* 1983;109:746–9; *Ann Intern Med* 1993;119:383–390), risk of other smoking-related disease, complications of surgery (Orleans CT, Slade JD, eds. *Nicotine addiction: principles and management.* New York: Oxford University Press, 1993:279–309), and possible decreased efficacy of adjuvant treatment (*N Engl J Med* 1993;328:159–163; *Proc Annu Meet Am Soc Clin Oncol* 1995:1088). Depending on their relevance to the patient, physicians might also discuss the social and financial rewards of quitting (Fisher EB. *7 Steps to a smoke-free life.* New York: John Wiley, 1998).

C. Assessment of readiness to change: the transtheoretical model

Although all smokers should be urged to quit, it is important to assess how patients feel about quitting smoking. The Transtheoretical Model (*Am Psychol* 1992;47:1102–1114) characterizes readiness to quit smoking as progressing through five stages, from Precontemplation to Maintenance. At Precontemplation, patients have no plan to quit smoking and have made no recent efforts to quit. At Contemplation, patients are thinking of quitting some time in the next 6 months. At Preparation, patients are planning to quit in the next 30 days, and have made at least one 24-hour attempt to quit in the last year. Those at the Action stage have not smoked for less than 6 months, and those in Maintenance have stopped at least 6 months with no full-blown relapses.

Physicians should consider patients' readiness to quit in tailoring assistance to their needs. However, even patients who express no interest in quitting should be advised to quit and should be provided with brief counseling designed to increase their motivation to quit.

D. Assistance: tailored to patient's readiness to change

Many physicians may be too busy to do more than ask patients if they smoke and urge them to quit. Having self-help literature available in the office, being willing to prescribe bupropion SR or nicotine-replacement therapy, and being prepared to refer patients to more intensive treatment are ways the physicians can assist patients with modest investment of time. Physicians who are able to spend more time counseling patients to quit smoking should consider each patient's stage of readiness to quit and tailor the discussion accordingly. Following are some general issues physicians may wish to discuss, depending on

the patient's stage of change.

1. **Precontemplation.** The physician's goal for patients in this stage is to get them to start thinking about quitting smoking, to increase their awareness of their habit, and to motivate them to consider quitting. Motivation may be a key factor in whether a patient succeeds in quitting, but it also is a result of the patient's beliefs about the feasibility of quitting, and the relative costs and benefits of quitting. By exploring with patients their concerns about trying to quit, and by appropriately highlighting the costs and benefits, the physician may be able to motivate patients to try to quit. Following are some topics for discussion with patients:
   - What do they like most about smoking? What don't they like about it?
   - When are they most likely to smoke? Why then?
   - Have they ever quit? For how long? Why did they quit then?
   - What health concerns do they have about smoking?
   - What would be hardest about quitting? What would be the best thing about quitting?
2. **Contemplation.** Patients in this stage have tentative plans to quit. The goal is to get them thinking more concretely about it. Following are some issues to discuss:
   - What benefits do they get out of smoking? Patients who can identify the needs that smoking satisfies will be better equipped to meet these needs in other ways.
   - What reasons are there for them to quit? The physician should help the patient identify benefits such as improved health, financial savings, being an example to children, improved sense of taste and smell, and self-esteem resulting from success in quitting.
   - Have they quit before? How did they accomplish that? What led them to relapse? The physician should encourage the patient to take advantage of strategies that worked for them in the past, and to identify pitfalls that led to relapse.
3. **Preparation.** Patients in this stage have decided to quit in the very near future. The physician's goal is to help equip them to succeed in quitting. Following are some issues to discuss with patients as they prepare to quit smoking.
   - What roles does smoking play in their lives? Do they smoke for relaxation, because of boredom, for the taste, because of fidgetiness?
   - What external cues (situations, behaviors) and internal cues (moods) are likely to be most difficult for avoiding cigarettes?
   - What plans do they have for coping with temptation at those times? What alternative plans do they have?
   - How soon after getting up in the morning do they smoke? How much do they smoke? Those who smoke within 30 minutes of waking and/or smoke more than 1 pack per day are likely to be more dependent on nicotine (*Am J Public Health* 2000;90:1122–1127) and are more likely to benefit from pharmacotherapy.
   - Have they set a quitting date? The patient should be encouraged to set a quitting date within 2 weeks.
   - Are they willing to use nicotine-replacement therapy and/or bupropion SR? Physicians should encourage use by all patients except those with medical contraindications, those smoking fewer than 10 cigarettes/day, pregnant/breast-feeding women, and adolescent smokers (Fiore MC, Bailey WC, Cohen SJ, et al. *Treating tobacco use and dependence: clinical practice guideline.* Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, 2000).
   - Do others in their household smoke? How do they feel about the patient's quitting? Have they told friends/co-workers of their plans to quit? The patient should ask for understanding and support, and ask smoking friends and family not to smoke in their presence.
   - In addition, physicians should tell their patients to remove all cigarettes, lighters, ashtrays, and other smoking materials from their homes before quitting.
4. **Action and maintenance.** Although patients at the Action stage have quit smoking within the last 6 months, they remain at risk of relapse. The goal at this stage is to reinforce success and to engage in problem solving with respect to specific problem situations. Physicians should review the benefits of quitting and congratulate patients on their successes. They should remind patients that withdrawal symptoms generally pass within 2 weeks, but that cravings tend to fade slowly over time. Sustained abstinence is likely to involve the development of new routines and behaviors as the old smoking-related behaviors are replaced. Lapses should not be viewed as failure, but as opportunities to learn how to avoid temptation in the future, and patients should be reminded that quitting smoking is a process rather than an event. At the Maintenance stage, the goal is general problem solving, identifying any ongoing problem areas, and helping the patient avoid overconfidence.

E. **Arrange follow-up/routine assessment of smoking status**

The smoking-cessation interventions described here will help many patients achieve long-term abstinence. However, the chronic relapsing nature of tobacco dependence means that physicians cannot rely on one-time interventions or assume that success will be permanent in each case. Highly dependent patients in particular may require ongoing and repeated treatment to achieve abstinence. Patients who are attempting to quit should be contacted during the week after their planned quitting date, and this follow-up should be arranged at the time the quitting date is set. The contact may be a planned return office visit, or it may be a telephone contact initiated by the physician, but person-to-person follow-up timed in relation to the quitting attempt is critical. Additional planned or *ad hoc* contacts will enhance the likelihood of success. Finally, physicians should assess and monitor the patient's smoking on an ongoing basis as a routine part of every visit, congratulate those who remain abstinent, and use the approaches described earlier to assist patients who continue to struggle with nicotine dependence.

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CHAPTER 34. HEMATOPOIETIC GROWTH FACTORS

Kristie Blum and Benjamin Tan

Introduction
Granulocyte colony-stimulating factor
Granulocyte–macrophage colony-stimulating factor
Clinical applications of myeloid growth factors
Erythroid growth factors
Erythropoietin
Platelet and megakaryocytic growth factors
Thrombopoietin
Cytokines in clinical development
Monocyte colony-stimulating factor
Interleukin 3
Stem cell factor (c*kit* ligand, steel factor)
Interleukin 6
Interleukin 11
Interleukin 1
Granulocyte–macrophage colony-stimulating factor/interleukin-3 fusion protein (PIXY321)

I. **Introduction.** A complex interplay of interleukins and hematopoietic colony-stimulating factors (CSFs) play an important role in the maturation of the earliest hematopoietic progenitors into myeloid, erythroid, and megakaryocytic cell lines. As evolving research indicates, a single growth factor is not sufficient to induce the development of a single cell line; rather, combinations of cytokines released sequentially are responsible for hematopoietic cell differentiation. This network of cytokines not only leads to maturation of hematopoietic progenitors, but also activates mature hematopoietic cells, by triggering events such as chemotaxis, phagocytosis, or platelet aggregation.

A. **Granulocyte colony-stimulating factor.** G-CSF is a 174-amino acid glycoprotein located on chromosome 17 (Table 34.1). G-CSF induces proliferation and differentiation of cells of the neutrophil lineage. Knockout mice for the G-CSF gene develop severe neutropenia, with minimal affect on other lineages. Normally, G-CSF can be detected in serum, with a range of 20 to 100 pg/mL, but this level varies depending on the neutrophil count and the presence of inflammatory stimuli. For example, bacterial endotoxin can lead to a 20-fold increase in circulating G-CSF levels. The serum half-life of G-CSF is 1.3 to 4.2 hours, but declines with increasing neutrophil counts, suggesting that neutrophils play some role in its metabolism.

Growth Factors	Chromosome	Affected Lineage
G-CSF	17q11-22	Neutrophil
GM-CSF	5q31.1	Granulocyte, macrophage
TPO	3q26-27	Megakaryocytes
EPO	7q11-22	Erythroid
M-CSF	1p13-21	Macrophage, osteoclast
IL-1	9q12-21	Multilineage
IL-2	4q26-28	T cells
IL-3	5q31.1	Multilineage
IL-4	5q31.1	T cells, B cells, NK cells
IL-6	7p21	Multilineage
IL-11	19q13.3-13.4	Megakaryocytes
IL-12	3p12-13.2, 5q31-33	NK cells, T cells
S-CSF	12q14.3	Multilineage
PIXY 321		Recombinant fusion protein of GM-CSF and IL-3

G-CSF, granulocyte–colony-stimulating factor; GM, granulocyte–macrophage; TPO, thrombopoietin; EPO, erythropoietin; NK, natural killer; IL, interleukin.
J Clin Oncol 1995;13:1023–1035; Vincent JJ, DeVita T, Hellman S, et al., eds, *Cancer: principles and practice of oncology* (Philadelphia: Lippincott-Raven, 1997:2649–2652, with permission

TABLE 34.1. HEMATOPOIETIC GROWTH FACTORS

1. **Recombinant preparations.** Recombinant G-CSF (rHuG-CSF) is produced in *Escherichia coli.* Two formulations, filgastrim and lenogastrim, are available worldwide, although only filgastrim is available in the United States. Administration of filgastrim to humans leads to an increase in circulating neutrophils, expansion of the myeloid compartment in the bone marrow, accelerated differentiation of stem cells to mature neutrophils, and activation of mature neutrophils as evidenced by morphologic changes such as Dohle bodies and toxic granulation.
2. **Recommended dose:** Per the American Society of Clinical Oncology (ASCO) 2000 Clinical Practice Guidelines, doses of 5 µg/kg/day administered subcutaneously are recommended for all situations except peripheral blood stem cell (PBSC) mobilization (*J Clin Oncol* 2000;18:3558–3585). G-CSF may be started between 24 and 72 hours after completing chemotherapy and discontinued once the neutrophil count exceeds 10,000 (*J Clin Oncol* 2000;18:3558–3585). On discontinuation, the absolute neutrophil count (ANC) typically declines by 50% per day, returning to baseline in 4 to 5 days.
3. **Adverse effects.** Adverse events are generally mild, consisting primarily of bone pain. Bone scans after injections with (rHuG-CSF) may show a flare of metastatic bone lesions and increased tracer uptake in the axial skeleton. Additional reports exist of transient neutropenia with intravenous injections and transient dyspnea with pulmonary infiltrates on chest radiograph (CXR). Most recently, multiorgan failure occurred in a patient with sickle cell anemia who received 480 µg of rHuG-CSF after adjuvant therapy for breast cancer (*Blood* 2001;97:3998–3999). It is postulated that by increasing neutrophil adherence to endothelium, G-CSF augmented the vascular occlusion of the microcirculation observed in a typical sickle cell crisis, thereby contributing to multiorgan failure. With prolonged administration (i.e., for cyclic neutropenia), benign splenomegaly may arise, secondary to extramedullary hematopoiesis.

B. **Granulocyte–macrophage colony-stimulating factor.** GM-CSF is a 127-amino acid glycoprotein located on chromosome 5. It supports the growth and expansion of granulocytic and monocytic colonies. When combined with erythropoietin (EPO), it supports growth of myeloid, erythroid, and megakaryocytic lineages. In neutrophil/macrophage functional assays, it also enhances tumoricidal activity, superoxide production, phagocytic activity, secretion of cytokines (including G-CSF), and cell adhesion/chemotaxis. Unlike those for G-CSF, knockout mice for GM-CSF express normal numbers of neutrophils and macrophages, but instead develop pulmonary alveolar proteinosis and pneumonia, suggesting that GM-CSF has a greater role in the regulation of the local inflammatory response rather than growth/differentiation promotion. Unlike G-CSF, GM-CSF is not detected in serum even during active infection, suggesting that it is primarily produced and acts locally.

1. **Recombinant granulocyte–macrophage colony-stimulating factor.** Three preparations of rHuGM-CSF have been devised; one in bacteria (molgramostim), one in Chinese hamster ovary cells, and one in yeast (sargramostim). Only the yeast preparation is available in the United States. Clinical evaluation of the administration of rHuGM-CSF after chemotherapy yielded an increase in peripheral blood neutrophils, bands, eosinophils, monocytes, and reticulocytes.
2. **Recommended dose.** By the ASCO 2000 guidelines, 250 µg/m^2/day of GM-CSF should be used for all settings except PBSC mobilization, in which higher doses may improve stem cell mobilization (*J Clin Oncol* 2000;18:3558–3585). Subcutaneous dosing is preferred, although intravenous dosing is safe if required. GM-CSF may be administered 24 to 72 hours after chemotherapy and discontinued once the neutrophil count has recovered to 10,000.
3. **Adverse effects.** With intravenous administration, immediate, transient neutropenia may occur, most likely because of neutrophil margination and endothelial adhesion. Dyspnea, fever, myalgias, and fatigue have been reported, and weight gain, pericarditis, pleuritis, and capillary leak syndrome can occur with high doses, although rarely. In the bone marrow transplant (BMT) setting, a recently published comparison of G-CSF, GM-CSF, or combination G-CSF/GM-CSF mobilization revealed a higher incidence of fever with GM-CSF (*J Clin Oncol* 2000;18:43–53).

C. **Clinical applications of myeloid growth factors.** All of the following applications are based on the 2000 ASCO Clinical Practice Guidelines for the use of CSFs (*J Clin Oncol* 2000;18:3558–3585).

1. **Primary prophylactic CSF administration before chemotherapy.** Although primary prophylaxis has been shown to decrease the rates of febrile neutropenia (FN) by 50%, it has not been shown to prolong survival or improve response to chemotherapy, theoretically by limiting dose delays or reductions. Only in the setting of an expected incidence of febrile neutropenia greater than 40% does the cost of CSFs justify their use to reduce the costs of hospitalization and antibiotic administration. Very few first-line regimens have FN rates this high and are usually on the order of 15% to 25%. In addition to those patients receiving chemotherapy in whom the expected incidence of FN is greater than 40%, patients with preexisting neutropenia due to disease (before cycle 1 of therapy), extensive prior chemotherapy, prior pelvic irradiation, prior FN while receiving a similar regimen, or conditions enhancing risk of serious infection (i.e., poor performance status, multiple comorbidities, or active infections) may benefit from primary prophylaxis. However, in healthy patients receiving standard chemotherapy, the cost of CSFs precludes their routine use.

2. **Secondary prophylaxis.** Dose reduction should be considered after an episode of severe neutropenia, as no published data suggest an improved overall or disease-free survival by maintaining dose intensity, except in curable tumors (i.e., germ cell tumors), with CSFs.
3. **Afebrile neutropenia.** There is no role for CSFs in afebrile neutropenic patients. A large randomized trial with 138 solid tumor or lymphoma patients who were randomized to receive CSFs or placebo on the diagnosis of neutropenia demonstrated no improvement in hospitalization rates, in the number of culture-positive infections, or in the use of antibiotics (*N Engl J Med* 1997;336:1776–1780).
4. **Existing febrile neutropenia.** In uncomplicated FN (fever less than 10 days and no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan failure, fungal infection, or uncontrolled malignancy), using CSFs as an adjunct to appropriate antibiotics and supportive care does not improve outcome. CSFs should be considered only in patients with predictors of poor clinical outcome (i.e., ANC less than 100, evidence of complicated FN, age older than 65 years, or posttreatment lymphopenia).
5. **Bone marrow transplant.** CSFs may be used to mobilize PBSCs or after PBSC infusion to speed engraftment. CSFs increase peripheral blood progenitor cell concentrations by 10-fold. If administered after high-dose cyclophosphamide, the peripheral blood concentration can increase as much as 100-fold. The timing and optimal dose of CSFs during the mobilization and transplant procedures is still under investigation. Fortunately, in the allogeneic setting, CSFs do not seem to increase the incidence of graft-versus-host disease.
6. **Acute myeloid leukemia.** No evidence exists supporting an improved outcome or survival for leukemia patients receiving CSFs after induction chemotherapy, although CSFs do accelerate marrow recovery. Therefore the expense of CSFs must be weighed against those of a slight prolongation in hospitalization. CSFs may have a role in patients older than 55 years, although two recent randomized studies have conflicting results. The first, an Eastern Cooperative Group Study, found GM-CSF started on day 11, if the day 10 marrow was hypoplastic, produced a 26% decline in the rate of severe infections in patients aged 55 to 70 years, with a mild improvement in survival (*Blood* 1995;86:457). A Cancer and Leukemia Group B (CALGB) study found no difference in the rate of severe infection or early death, however, in patients older than 60 years who received GM-CSF versus placebo (*N Engl J Med* 1995;332:1671).
7. **Acute lymphoid leukemia.** All studies in ALL demonstrate that CSFs reduce the duration of neutropenia in both adults and children. The effect on response rate, incidence of severe infection, and frequency of hospitalization varies among trials. None of the trials demonstrated an improved overall survival; therefore the costs of cytokine therapy must once again be weighed against the costs of prolonged neutropenia.
8. **Myelodysplastic syndromes.** CSFs do increase the ANC in myelodysplastic syndromes (MDSs), although no data support long-term continuous use of CSFs, and there is a small chance that prolonged use may increase the risk of acute leukemia. A randomized trial comparing G-CSF with best supportive care showed a similar rate of frank AML between the two groups, but a small unexplained decline in overall survival in the refractory anemia with excess blasts (RAEB) group treated with G-CSF [*Proc Am Soc Hematol* 1993;82:768(abst)]. Therefore CSFs should be used intermittently in MDS patients with severe neutropenia or recurrent infections.
9. **Concurrent chemoradiotherapy.** Although CSFs limit prolonged neutropenia in patients receiving radiotherapy alone, no impact on overall survival has been demonstrated. In a recent Southwest Oncology Group (SWOG) study, 215 patients receiving concurrent chemotherapy and radiation therapy for small cell lung cancer were randomized to GM-CSF or placebo. They observed a significant increase in grade 3 and 4 thrombocytopenia in the GM-CSF arm, with 54% in the GM-CSF group and 35% in the placebo group. Theoretically, the megakaryocytic colony-forming units induced by the CSF may be more radiosensitive than the other colony-forming units. They also observed an increase in toxic deaths (nine vs. one), mainly due to pulmonary toxicity in the GM-CSF arm (*J Clin Oncol* 1995;13:1632–1641). Therefore CSFs should be avoided in patients receiving concomitant chemoradiotherapy, particularly with radiation to the mediastinum. However, in radiation alone, CSFs may be used to limit delays of treatment secondary to neutropenia.
10. **Granulocyte–colony-stimulating factor versus granulocyte–macrophage colony-stimulating factor.** Unlike G-CSF, in which initial phase I/II studies revealed a shortening of the duration of neutropenia and decrease in episodes of FN, the trials with GM-CSF are not so clear, with some studies revealing a decrease in infection rate and others revealing no clear benefit (*Clin Oncol Updates* 2001;4:1–13). There have been no head-to-head comparisons of G-CSF with GM-CSF. One study that compared the two agents assessed them in the treatment of nonfebrile neutropenia, with no difference in recovery time to ANC greater than 500 or in incidence of fever (*Cancer Invest* 1998;16:366–373); however, there is no clear indication for growth factors in this setting. One final study compared G-CSF, GM-CSF, and the combination of the two in PBSC harvesting. The G-CSF and the combination group had a more rapid improvement in ANC and a lower incidence of fever, hospitalization, antibiotic use, and red blood cell (RBC) transfusions than in the GM-CSF alone group (*J Clin Oncol* 2000;18:43–53). However, according to the ASCO 2000 Clinical guidelines, there are no sufficient large-scale randomized data to support the use of G-CSF over GM-CSF or vice versa in the setting of primary or secondary neutropenia prophylaxis (*J Clin Oncol* 2000;18:3558–3585).

II. **Erythroid growth factors**

A. **Erythropoietin.** Human EPO is a 193-amino acid protein, located on chromosome 7. It is produced in the kidney in response to hypoxia; its transcription is dependent on an oxygen-binding heme protein. EPO binds to a receptor that is similar to the receptors of G-CSF, GM-CSF, interleukin (IL)-2, and other cytokines, stimulating the proliferation of erythroid colony-forming units. Normally EPO levels in the serum range from 4 to 30 U/L, although in the setting of anemia (Hct less than 35%), levels can increase up to 1,000-fold.

1. **Recombinant erythropoietin.** There are two preparations of recombinant EPO (rHuEPO), both produced in Chinese hamster ovary cells; epoetin alfa and epoetin beta, with only epoetin alfa available in the United States.
2. **Recommended dose.** Currently there are no clear data favoring one dose level over another, although there seems to be a dose–response curve. The half-life of rHuEPO is from 9 to 13 hours when administered intravenously. Subcutaneous and intravenous dosing are both effective. Initial dosing recommendations range anywhere from 100 U/kg s.q. 3 times a week (TIW), increasing to 300 U/kg s.q. TIW if there is no response. However, numerous regimens have been tried, including 5,000 U/day or 40,000 U/week s.q., all with adequate response rates. It is important to note that late responses do occur occasionally 9 weeks after the initiation therapy. Finally, iron supplementation is necessary in iron-deficient patients, as they will not respond to EPO until their iron stores are replete.
3. **Clinical indications.** EPO was first tested in 1985 in renal failure patients, in whom it was effective in increasing hemoglobin levels and decreasing transfusion requirements.
   a. **Cancer-related anemia.** Cancer-related anemia is often multifactorial, due to blood loss, marrow infiltration, chemotherapy, radiation therapy, anemia of chronic disease, dietary deficiencies (i.e., iron), and hemolysis. In patients with low EPO levels in relation to the degree of anemia, EPO treatment has been extremely effective in increasing Hct, reducing transfusion requirements, and improving quality of life. In patients with anemia secondary to a variety of disorders and treatments, from MDSs to solid tumors and from transplantation to radiotherapy, response rates with EPO are often in the range of 50% (*Clin Oncol Updates* 2001;4:1–13).
   b. **Chemotherapy-induced anemia.** Several randomized trials in patients receiving cisplatin or other chemotherapeutic agents again demonstrated improvements in Hct and decreased transfusion needs. Treatment with rHuEPO in patients undergoing chemotherapy who are not yet anemic may even decrease risk of anemia and need for future transfusions (*J Clin Oncol* 1995;13:1623–1631; *J Clin Oncol* 1997;15:2715–2721).
   c. **Myelodysplastic syndromes.** Response rates to EPO in MDSs are disappointing, often in the range of 15% to 25%. Elevated baseline EPO levels and the presence of ringed sideroblasts predict a lower response. Continuing research is looking at the combinations of EPO with myeloid growth factors, hoping to improve on these numbers.
   d. **Bone marrow transplantation.** In both autologous and allogeneic transplantation, several randomized studies have found no difference in transfusion requirements of EPO- and placebo-treated patients. Therefore its use is not currently recommended in this setting.
4. **Adverse effects.** In renal failure patients with high blood volumes, diastolic blood pressure elevations and seizures were noted in 4% of treated patients. In patients with chemotherapy-induced anemia, with normal-volume status, these complications have not been noted, and adverse effects are extremely rare. The development of iron deficiency is quite common because of the consumption of available stores and decline in transfusion rate.

III. **Platelet and megakaryocytic growth factors**

A. **Thrombopoietin.** In 1994, after the discovery of a megakaryocytic growth factor receptor, the cloning of the gene encoding its ligand led to the development of thrombopoietin (TPO). TPO is a polypeptide of 353 amino acids, with an amino terminal end with 46% sequence similarity to the EPO protein and a carboxyl end that has no homology to any known proteins. The amino end is responsible for receptor binding, whereas the carboxyl end increases the bioavailability of the protein. TPO levels can be detected in the serum and vary inversely with the platelet count. Curiously, platelets themselves can bind TPO, which suggests that intermittent platelet transfusions in the thrombocytopenic patient may actually blunt the TPO response (*N Engl J Med* 1998;339:746–754).

1. **Recombinant thrombopoietin.** Two forms of recombinant human TPO (rHuTPO) are currently in clinical trials, one that is a full-length polypeptide consisting of both the carboxyl and amino terminal ends. The second is a conjugate of the amino terminal end with polyethylene glycol (PEG-rHuTPO), a synthetic polypeptide that prevents degradation of various proteins. In vitro, rHuTPO increases the size and number of megakaryocytes, stimulates nucleic polyploidy and endomitosis, upregulates expression of platelet markers (CD41 and CD61), and acts in synergy with other growth factors to stimulate growth of all types of blood progenitors. RHuTPO also sensitizes platelets to aggregating agents like adenosine diphosphate (ADP) or collagen, therefore theoretically increasing the risk of thrombosis.
2. **Recommended dosing.** The half-life of rHuTPO is longer than that of other growth factors, at 30 hours, and the addition of PEG may increase it by 10-fold. Dosing is not yet defined, as clinical trials are ongoing. TPO may need to be given early, immediately after chemotherapy, as chemotherapy initially produces a rapid decline in megakaryocytes while not affecting mature platelets (*N Engl J Med* 1998;339:746–754). Because mature platelets bind thrombopoietin, their presence may prevent an adequate endogenous TPO response until total platelet numbers are affected by the precipitate

decrease in megakaryocytic precursors. However, as TPO affects only megakaryocytic production and not platelet release, it probably will not be effective before the chemotherapeutic insult to megakaryocytes (*N Engl J Med* 1998;339:746–754).

3. **Clinical indications.** Ongoing clinical trials are evaluating the role of TPO in autologous BMT (ABMT) and chemotherapy-induced thrombocytopenia.
   a. **Chemotherapy-induced thrombocytopenia.** In current trials, platelet counts have recovered faster, and nadir counts were higher in treated patients; however, differences in platelet transfusion requirements are minimal, possibly because these trials have involved regimens that induce only moderate thrombocytopenia.
   b. **Bone marrow transplant.** In BMT, early data suggest that TPO may minimize the number of platelet transfusions in the allogeneic setting: however, similar results have not been seen with autologous transplants.
   c. **Platelet donation.** One interesting application currently being investigated is the ability of TPO to increase the platelet dose collected from a single apheresis platelet donor.
4. **Adverse events.** In current trials, side effects are few; however, most trials have excluded patients at risk for thromboembolic events, including those with a history of cardiac, pulmonary, or vascular disease.

IV. **Cytokines in clinical development**

A. **Monocyte colony-stimulating factor.** *In vitro,* this growth factor enhances growth and cytotoxicity of the macrophage lineage and also may play a role in bone metabolism, tooth development, and placental function. Mice with monocyte–colony-stimulating factor (M-CSF) deficiencies develop delayed hematopoiesis, reduced macrophage numbers, and osteopetrosis. Phase I/II trials are ongoing, with applications in the treatment of invasive fungal infections or of enhancing monocytes' capability to lyse malignant cells. Adverse events noted have been thrombocytopenia after 7 to 10 days of treatment.

B. **Interleukin 3.** IL-3 functions early in hematopoietic development, promoting the differentiation of all cell lineages. Clinical applications of this growth factor include PBSC mobilization, facilitating bone marrow engraftment, and increasing bone marrow recovery after chemotherapy, often in combination with G-CSF or GM-CSF. Toxicities include fever, headache, chills, malaise, and arthralgias.

C. **Stem cell factor (c-*kit* ligand, steel factor).** In isolation, this growth factor has little activity; however, promising results have been observed in combination with other CSFs. This factor affects multiple hematopoietic lineages, and early phase I/II trials have focused on its utility in PBSC mobilization.

D. **Interleukin 6.** IL-6 is a multifunctional cytokine, involved in the abnormal growth regulation of myeloma cells, activation of acute-phase reactants in the liver, and enhancement of hematopoietic differentiation. Current applications include accelerating platelet recovery after chemotherapy and combinations with other CSFs to accelerate neutrophil and platelet recovery. Toxicities are similar to those of other interleukins, with fever, headache, fatigue, and myalgias.

E. **Interleukin 11.** IL-11 is multifunctional, increasing acute-phase reactants, promoting megakaryocytic growth and differentiation, and increasing platelet counts. Clinical trials regarding its ability to accelerate platelet recovery after chemotherapy are being pursued. In animal models, IL-11 also has been seen to limit chemotherapy- and radiation-induced mucositis (*J Clin Oncol* 1995;13:1023–1035).

F. **Interleukin 1.** IL-1, *in vitro,* directly promotes growth of hematopoietic stem cells and induces release of other growth factors from macrophages and stromal cells. In phase I trials, hypotension has been the dose-limiting toxicity.

G. **Granulocyte–macrophage colony-stimulating factor/interleukin-3 fusion protein (PIXY321).** This synthetic cytokine is a fusion of IL-3 and GM-CSF. GM-CSF produces a rapid increase in neutrophil counts, and IL-3 promotes a slower sustained increase, with a broad spectrum of activity, affecting multiple lineages. The combination of these two drugs may prove more beneficial for chemotherapy-induced cytopenias than does either agent alone. Noted side effects in phase I/II trials include local skin reactions at the injection site.

CHAPTER 35. ONCOLOGIC IMAGING

Sanjeev Bhalla

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I. Introduction

Although x-rays were discovered a little more than 100 years ago, the role of imaging of cancer was not really explored until the 1950s. Work at that time centered mainly on conventional radiographic evaluation of pulmonary metastases. Since then, change has occurred at an exponential rate with cross-sectional techniques [computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI)] coming into play in the late 1970s and early 1980s.

The advent of helical CT in the early 1990s brought improved anatomic detail with faster scanning times. In the late 1990s, newer CT designs (four-row multidetector or multislice CT) made imaging even faster with higher spatial resolution. In the upcoming years, all of the major vendors plan to unleash eight-row and even 16-row detector designs that will allow less than 30-second scanning of the neck, chest, abdomen, and pelvis.

At the same time, MR has witnessed newer scanning techniques. Stronger magnetic gradients and new pulse sequences have allowed dynamic-contrast scans to be only slightly longer than their CT counterparts, while improving on spatial resolution. Ultrasound has managed not to fall behind with improved probes and computers that have dramatically improved spatial detail, allowing detection of lesions as small as 3 mm and guiding potential biopsy.

Positron emission tomography (PET) has shown its ability to detect lesions that may have been overlooked by CT or MRI. Its role in the workup of malignancy continues to evolve, but already it is routinely incorporated in the workup of many lung, esophageal, and cervical cancers, as well as lymphoma.

II. Choosing a modality

Clearly diagnostic imaging plays an important role in the staging of oncology patients. With the continued evolution of the field, choosing the appropriate technique can seem overwhelming. Keeping certain principles in mind can make that task easier.

The ideal imaging strategy should be

Readily available [close in distance and in time (short waiting time)
Sensitive and specific,
Safe and atraumatic for the person being imaged,
Inexpensive or at least cost-effective, and
Reproducible (for follow-up of specific lesions)

Following these guidelines may mean altering the imaging strategy for any given patient, but they will ensure safe and reliable practices. For example, at our institution, MR is used to evaluate the brain and spinal cord in neurologic malignancies. A patient who is overweight or claustrophobic may not be able to tolerate an MRI. These patients may require CT with contrast or myelography (for the nerve roots). By keeping these factors in mind, the referring physician can minimize inconvenience and discomfort for the patient.

In choosing a modality, the referring physician must be familiar with how a study is performed and what is required to achieve the expected sensitivity and specificity. As an example, abdominal CT without intravenous contrast will not be sensitive for the detection of liver lesions.

III. Computed tomography

CT is the workhorse of oncologic imaging. Because of its speed and its availability, CT is almost always the next step in evaluating a radiographic abnormality or evaluating a patient with a suspected neoplasm, yet not all CT images are the same. The oncologist must be familiar with certain technical parameters to understand their patients' images.

A. Technical parameters

1. **Collimation (slice thickness)** refers to the thickness of the x-ray beam used to obtain an axial image (Fig. 35.1). The thinner the collimation, the better the spatial resolution. For pancreatic neoplasm detection, we routinely use 3-mm-thick slices or less. If the original abdominal pelvic CT was done with a collimation of 1 cm, the pancreatic neoplasm may be very subtle or even missed. If thinner is better, why not always use thinner collimation? The answer is based on two reasons: (a) thinner collimation reduces the number of photons for any given radiation dose, so the noise is increased, and because of this (b) radiation does is increased to compensate. The collimation must be programmed by the technologist before initiating a scan and cannot be changed once the scan has been completed.

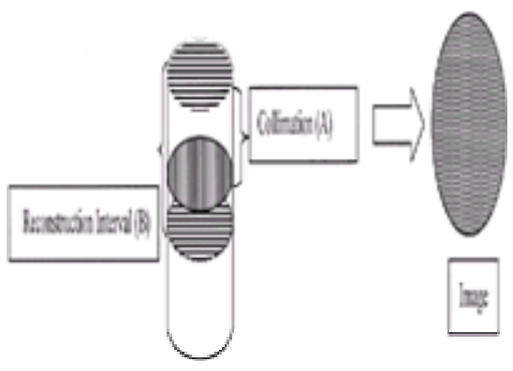

FIG. 35.1. Computed tomography (*CT*) parameters. The cylinder represents the object being scanned. The *collimation* refers to the thickness used to make one image (volume-averaging of the horizontal and vertical components gives a fine grid pattern). The *reconstruction interval* refers to the distance

from the beginning of one section to the next. The gap (distance not imaged) can be determined by B — A. In a routine abdomen/pelvis CT, the collimation is usually 5 mm, with a reconstruction interval of 8 mm. The gap is then 3 mm. These parameters vary among different protocols.

2. **Reconstruction interval** refers to the distance from the beginning of one section to the beginning of the next. This is important to realize because abdomen/pelvic CTs are usually done with a collimation of 5 mm and a reconstruction interval of 8 mm, leaving 3 mm unimaged. In the abdomen, this may be acceptable for general applications, but for many specific examinations (such as searching for a pancreatic cancer), we use contiguous slices in which the reconstruction interval is equal to the collimation.

   Other technical parameters including pitch (defined as table speed/gantry rotation divided by collimation), mA/second, kilovolt peak (kVp), and table tilt also vary according to protocol. These factors are beyond the scope of this text and a working, clinical knowledge base.

3. **Windows** refer to the viewing parameters of a scan. This variable can be changed long after the patient has gone. In brief, the image is assigned a window center, at which the gray scale is centered, and a window width, referring to the width that the gray scale (of the monitor or film) is spread over. This allows certain tissues to be highlighted. For example, at our institution, soft tissue windows are centered at 30 Hounsefield units (Hu; the value of soft tissue) with a width of 400 Hu. All tissue greater than 230 Hu [or width divided by 2 plus 30 (center)] is displayed as white, and all tissue less than –170 Hu (or center minus width divided by 2) is shown as black. So soft tissue windows do not allow lung analysis (lungs are much lower than –170 Hu) or bone analysis (bones are much higher than 230 Hu). In oncologic imaging, we routinely view soft tissue windows, lung windows, brain windows, and bone windows. Occasionally, kidney or liver windows may be used. The key is that the patient is scanned once so extra windows do not require more imaging time, and windows can be changed retrospectively. Therefore if a bone lesion is suspected 2 weeks after an abdomen/pelvic CT, the radiologist should be able to recall an examination and review it on bone windows.

B. **Contrast material**

1. **Intravenous contrast** is important in oncologic imaging because it allows the detection and characterization of lesions within solid organs: liver, kidneys, spleen, and pancreas. The pattern of enhancement may allow the differential diagnosis to be narrowed. For example, in the liver, peripheral puddling of contrast in the arterial phase with a gradual fill-in on venous phase is highly suggestive of a cavernous hemangioma. Delayed enhancement (15 minutes after contrast administration) is typical of cholangiocarcinoma or desmoplastic, fibrous metastases. For these reasons, when possible, abdomen/pelvis CT is performed **with** intravenous contrast when hepatic, splenic, pancreatic, or renal pathology is suspected. For bowel and lymph node disease, intravenous contrast can be very helpful in separating pathology from normal vessels on cross section.

   Currently, all CT intravenous contrast agents are iodine based. Two main classifications in use are low-osmolar agents (nonionic) and high-osmolar agents (ionic). The former are less irritating at the site of injection and less likely to have gastrointestinal side effects (nausea, vomiting). As well, the nonionic agents are less likely to have severe side effects in the event of an extravasation. For these reasons based on patient preference, at our institution we have changed to sole use of low-osmolar agents.

   Contraindications to intravenous dye include allergy to iodinated contrast, lack of intravenous access, and elevated creatinine. If the reaction is mild (hives), premedication may be indicated before using intravenous contrast. No universally accepted premedication protocol exists, but at our institution we use low-osmolar (nonionic) contrast after the patient has received **50 mg prednisone p.o. q6 hours, 4 times.** Some of our radiologists also like to add **diphenhydramine (Benadryl), 50 mg p.o. at the time of examination.** When reactions are more severe (bronchospasm, laryngospasm, anaphylaxis, or laryngeal edema), premedication may not be sufficient to prevent a reaction. These patients are usually referred to MR or ultrasound if possible.

   Lack of intravenous access also may prevent a contrast-enhanced CT. Although some access is better than no access, it should be remembered that certain protocols have very high flow rates (approaching 4 to 5 mL/second) and require a large-bore catheter. Therefore not all access is the same. Most of the CT protocols use a power injector, which may not be compatible with central venous lines or may require low-flow rates (1 mL/second, as an example). Protocols may need to be modified based on the type of access present.

   Poor renal function is another contraindication to the use of intravenous contrast. Contrast-induced nephropathy is fortunately rare (fewer than 1% of studies) and usually self-limited (resolving in less than 2 weeks). The mechanism is acute tubular necrosis. Occasionally, it may be irreversible. Factors that increase the potential for both contrast-induced nephropathy and irreversible renal damage include elevated creatinine, diabetes (especially type I), and dehydration.

   As discussed earlier under technical CT parameters, protocols vary in many ways. This variation includes the way contrast is administered. The flow rates and the delay in time between initiating the injection and beginning the scan are the two principal ways in which the protocols differ. Usually protocols that have an arterial phase require a rapid infusion rate (greater than 3 mL/second), which requires a peripheral intravenous line larger than a 20 gauge. The protocols with such a requirement include the dual-phase pancreas protocol, dual-phase kidney, dual-phase liver, and the pulmonary embolism protocol.

2. **Oral contrast** is important for abdomen/pelvic CT because it allows distention of bowel (so that collapsed bowel is not mistaken for pathology) and separation of bowel loops in cross section from lymph nodes. When possible, it should be given. The only absolute contraindication is potential for aspiration, but extreme nausea may be a relative one. Two types of contrast are used: water soluble (iodine based) and barium based. When bowel perforation is suspected, water-soluble agents are used, but otherwise they are used interchangeably. An iodine contrast allergy is not a contraindication to oral contrast.

C. **Clinical uses**

CT is superior to conventional radiography because of its improved contrast resolution. MR, though, has better contrast resolution than does CT. Conversely, conventional radiography has better spatial resolution than CT, which has better spatial resolution than MRI. Because it is good in both spatial and contrast resolution, CT is often the step after plain film and often the first step in evaluating suspected lesions.

1. **In the thorax,** CT is the best modality for evaluating the lung parenchyma. For suspected nodules (whether metastatic disease or primary bronchogenic carcinoma), CT is superior to plain film for quantification, detection, and characterization. For parenchymal evaluation, intravenous and oral contrast are not needed. Thin sections through a suspected anomaly may allow the detection of macroscopic fat or lamellated or solid calcification, which would indicate benign disease. Mediastinal anomalies including suspected lymphadenopathy may benefit from (but do not require) intravenous contrast material. If a mediastinal lesion is known, intravenous dye is usually given. When contraindicated, MRI might be of value. Because of its multiplanar capacity, MR is frequently used for suspected bronchogenic cysts and potential neurogenic posterior mediastinal masses.
2. **In the abdomen,** CT is used for suspected liver, kidney, pancreas, spleen, gastrointestinal, and lymph node disease. For these organs, intravenous dye is preferred. If contraindicated, strong consideration for MR is warranted. If the patient cannot receive an MR (see MR contraindications later), then a fusion of ultrasound (to evaluate solid organs) and CT (nonintravenous contrast but with oral contrast) may be indicated. Adrenal gland evaluation is routinely done by CT without intravenous contrast or with MRI. The latter may be more specific for the characterization of adrenal lesions.
3. **In the pelvis,** CT is used for evaluation of the bladder, where delayed images may be helpful. Pelvic lymphadenopathy is routinely detected by CT. MR is superior to CT in evaluating the uterus and ovaries because of its multiplanar capacity.
4. **In the neck,** CT is very good for detecting lesions in the neck, but MR may be slightly superior for the detection of smaller lesions because of its improved contrast resolution. CT is used more frequently because it can be added to a chest, abdomen, and pelvis examination without significantly altering the length of the examination.
5. **In the brain,** the role of CT is purely screening for lesions. Routinely, it is done without intravenous contrast for the detection of hemorrhage, edema, or mass effect. CT can be done quickly to address these potentially life-threatening indications. If the patient can receive an MR, no intravenous contrast should be given. MR is much better at detecting small lesions that can be easily overlooked by CT. At our institution, CT of the brain with contrast is reserved for those patients who cannot receive an MR.
6. **In musculoskeletal** applications, CT is used for the detection of fracture or for a general evaluation of the bones. When a tumor of the bone or a soft tissue neoplasm is suspected, MR is the study of choice. In clinical practice, CT is often used in conjunction with bone scintigraphy for the detection of bone metastases because whole-body MR surveillance is not yet practical.

IV. **Magnetic resonance**

MR has become a major cross-sectional modality in the evaluation of the oncologic patient. Since the 1980s, MR has seen dramatic improvement in the signal-to-noise ratio and the time required to perform an examination. These improvements have come from stronger magnets and gradients used in acquiring images. Today MR is the primary modality used for evaluation of brain and spine lesions. It is routinely used for primary bone and soft tissue tumors, and its role in the evaluation of pelvic malignancy (gynecologic and prostate cancer) continues to evolve.

A. **Technical parameters**

MR physics is well beyond the scope of this section. For the busy oncologist, a key to understanding MR is to understand that one MR examination is composed of many MR pulse-sequences. Each one may take anywhere from a few seconds to up to 7 minutes. These pulse-sequences are responsible for the length of the MR examination (which usually approaches 1 hour). Two of the most common sequences are T_1-weighted and T_2-weighted images. These images take advantage of the inherent properties of tissues to generate images. Unlike the windows on CT, T_1-weighted images are acquired separately from T_2-weighted images. A very basic approach to MR is to understand that T_1 images are used to define the anatomy, and that T_2-weighted images are used to find the pathology. Because fluid is bright on T_2, pathology is bright on these sequences. This can be made more apparent by using T_2-weighted images with fat-suppression techniques. Once an abnormality is found, it can then be localized on T_1-weighted images.

Another key thing to remember about the performance of MR is the small area that can be examined at any one time. MR is based on signal that is already rather weak. To boost the signal-to-noise ratio, a surface coil is frequently used. Without the surface coil, resolution and image quality may be sacrificed. For the head or knee, this is no problem. But for longer parts of the body (spine, torso), this requires that a coil be used for the part of the body being imaged. The result is a small field of view such as abdomen only or chest only or pelvis only. In a typical abdomen/pelvis MR, the five to six sequences must be run once in the pelvis and once in the abdomen. The result is that the study may be twice as long. If a chest/abdomen/pelvis MR is ordered, the scan will extend well beyond 1 hour. It is this limitation that requires MR to be more site specific than CT.

B. **Contrast material**

Intravenous contrast has grown in use MRI, especially in oncologic imaging. Whereas some of the older literature emphasized that MR was superior to CT because of the lack of a need for contrast, recent work has demonstrated the improved ability to detect and characterize lesions with the use of intravenous contrast. Intravenous gadolinium-based contrast agents are now routinely used. The volume is much smaller than with CT (20 mL usually vs. 125 mL), and the rate of allergic reaction much lower. Renal dysfunction is not a contraindication. Because gadolinium is a T_1-contrast agent, its use results in at least two additional sequences (pre- and postcontrast T_1-weighted images with fat suppression). Therefore, intravenous dye will increase the length of examination.

Flow rates tend to be less an issue with gadolinium, which is run at 2 mL/second at its fastest flow rates, and so intravenous access is less crucial than with CT contrast. Although allergy to gadolinium is rare, many of the patients who are allergic report an iodinated contrast allergy. Therefore when patients have a severe contrast allergy (shortness of breath, anaphylaxis) to CT contrast, some physicians will premedicate before giving gadolinium. No universally accepted premedication regimen is present, but at our institution we use the same dose: **prednisone, 50 mg p.o. q6 hours, 4 times.**

Newer contrast agents have recently been approved but have yet to make their way into our routine clinical practice. Some of these are magnesium based and others are iron-based T_2 agents. These agents still are under investigation and have yet to demonstrate their clinical utility.

Oral contrast agents also have yet to make their way into routine clinical use. Routinely, fast T_2-equivalent images are obtained, which beautifully depict the small and large bowel.

C. **Contraindications**

Certain patients are not able to have an MR scan. Pacemakers and certain metal implants are not MR compatible. The strong magnetic field may disable the pacemaker generator or may make it malfunction. Even detached leads are not MR compatible, as they may heat up in the magnetic field. Aneurysm clips are another contraindication because they may torque in the magnetic field. Certain clips, however, do not move in the magnetic field. If there is ever a doubt, most MR divisions have reference books in which this information is catalogued, and many medical suppliers have hotlines to answer such questions. Certain cardiac valves and vascular stents may require a period for endothelialization before they are MR compatible (usually 6 weeks).

Because the tube must be small enough to generate a strong magnetic field, it may not be wide enough for some patients. This diameter varies slightly from machine to machine. On occasion, certain patients may simply be too large for the MR scanner. Others may be claustrophobic. This last group may benefit from conscious sedation.

D. **Clinical uses**

Because of its multiplanar capabilities and the lack of ionizing radiation, MR seems the ideal modality. It also has the best contrast resolution. The cost, length of examination, small tube size, and magnetic field have prevented it from becoming the dominant modality of oncologic staging. It still is very useful and, in certain instances, is the primary modality for imaging. These include neuroimaging (brain, spinal cord) and musculoskeletal (joint and soft tissue processes as well as bone lesions). Because calcium is notoriously easy to miss on MR, CT may be ordered in addition to MR. This is particularly true in bone neoplasms, in which a calcified matrix may aide in the differential diagnosis.

MR also has been very good in its ability to define pelvic pathology in the uterus and ovaries, where the organs may lie in oblique planes that can be directly imaged by MR. Its role in gynecologic malignancy continues to evolve. Outside of the pelvis, CT appears to be equal to MR to define the extent of disease. Prostate MR also is superior to CT. It can be very useful in evaluating the neurovascular bundles just lateral to the prostate and the seminal vesicles. Its use as a screening tool has yet to be determined. The signal characteristics of prostate cancer do not appear to be very specific.

The role of MR in the breast also continues to evolve. Contrast-enhanced studies may play a role in the detection of mammographically occult breast cancer. Until just recently, the role has been downplayed because of the difficulty translating a lesion detected by MR into a lesion that could be sampled by conventional needle localization or core biopsy techniques. In other words, if you see it by MR, you must be able to perform a biopsy of it by MR. Newer invasive MR techniques may make this possible.

At our institution, we have found many applications in which CT and MR are equal in lesion characterization and detection. The choice of modality is then based on patient preference, physician preference, and availability of the scanner. Such applications include liver, pancreas, kidney, neck, and splenic imaging.

In the mediastinum, we have reserved MR as a problem solver. This stems from the lack of pulmonary parenchymal evaluation by MR. Because the lungs are not well evaluated by MR, we frequently begin with a CT, and if a question arises regarding a mediastinal lesion that may be solved by MR, the patient is referred to MR. Such lesions are almost always potential foregut duplication cysts that may mimic lymphadenopathy on CT. MR also is limited in its evaluation of bowel when the bowel is filled with gas because of blooming artifact from the gas. Therefore gastrointestinal suspected neoplasms usually begin with CT, which can more reliably image a greater portion of the gastrointestinal system.

V. **Ultrasound**

Like MR, ultrasound (US) has gained popularity because of its multiplanar use and lack of ionizing radiation. It is much more operator dependent than either CT or MR, and no two examinations will ever be the same. The lack of reproducibility makes it hard to use for oncologic imaging. If a patient is on a chemotherapy protocol in which specific lesions are measured, US may not allow for the reader to report confidently that the index lesion(s) was found. Conversely, US, with its near-field high resolution, is quite good at detection of lesions within solid organs and evaluation of palpable abnormalities. At many places, US may be the first line in the evaluation of suspected hepatic neoplasm.

US is limited in the presence of air and fat. Both tissues distort the sound waves and reduce image quality. As a result, US is limited in the chest (because of the lungs) and in the evaluation of the gastrointestinal tract. Endoscopic ultrasound performed in conjunction with filling of the bowel lumen with fluid has been shown to be a very valuable problem solver, however. It is rather invasive. Because of the effect of fat on sound, many of the larger patients may not benefit from US for the detection of small lesions.

A. Clinical uses

In our practice, US in oncologic imaging is used as a problem solver for the clarification of a lesion seen on CT or to follow up a single lesion on CT. US is very useful in differentiating cystic from solid lesions, which has been very useful in the kidneys and liver.

It also has been very important in the evaluation of palpable lesions, especially in the breast. Ultrasound can be used for the real-time evaluation of structures, including needles, and so we routinely use it for needle-guided biopsies in the abdomen and occasionally in the chest. Its use allows the procedure to be performed much faster and without any radiation.

VI. Nuclear medicine

The role of nuclear medicine in oncologic imaging has grown mostly because of position emission tomography (PET). The basic principle of nuclear medicine is that a chelate of a radionuclide (that gives off a known photon energy) and a compound of biologic activity is administered to a patient. The chelate travels to a predictable part of the body, and a camera (set to record the particular energy of interest) is used to acquire images. For example, a ventilation–perfusion (V/Q) scan uses xenon-133 gas that is inhaled for ventilation images and a chelate of technetium 99m–macroaggregated albumin for perfusion images. Both are trapped in the lung and allow pictures to be obtained. The radiation dose is completely independent of the number of pictures, because the camera is not radioactive. Instead, the radiation is directly related to the dose of radiopharmaceutical. The images are useful because they are based on function but are limited in their depiction of anatomy. So almost all nuclear medicine studies are read in conjunction with an anatomic analogue: chest radiographs (with V/Q scans), CT (with PET), and bone films (bone scintigram).

Many nuclear medicine studies are available today. Some, including the tagged red blood cell study (for active gastrointestinal bleeding) and V/Q imaging, are not unique to the oncologic patient. Others are now routinely used, such as bone scan and PET, and are discussed later. A third group of studies, such as octreotide scanning (somatostatin analogue) and iodine whole-body scans, have very specific oncologic applications and are too specific for this discussion.

A. Bone scintigram or bone scan

Bone scan is routinely used to evaluate potential osseous metastases. The patient is injected with a phosphonate that is taken up by osteoblasts. After a 2- to 4-hour delay, images are acquired. Although it is sensitive for neoplastic deposits, bone scan is not very specific. Correlative imaging is routinely performed to look for fractures, degenerative disease, or other lesions that may also take up the radiopharmaceutical. If the correlative imaging fails to show a lesion, the assumption is that an occult metastasis is present. Patterns of uptake may be important in narrowing the differential diagnosis. A single lesion in each rib that forms a straight line is more suggestive of trauma than of metastases. Occasionally metastatic disease is so diffuse that the bone scan is uniformly increased. This pattern is detected by realizing that the bones are so much hotter than the kidneys. This so-called “super scan” can be seen in widespread prostate and breast cancer—two neoplasms with well-known osteoblastic metastases. Bone scan also can be falsely negative in certain metastases that can be predominantly osteolytic. Two such notorious tumors include multiple myeloma and renal cell carcinoma. For these lesions, skeletal survey may be required, or MR, for a specific site of pain.

B. Positron emission tomography

PET has continued to evolve and has become a major problem-solving tool in the workup of the oncologic patient. The basic concept of PET is that a radioactively labeled agent (usually glucose) is administered. Metabolically active areas take up much of the glucose and appear “hot” on images that are taken in an axial plane, like CT. These can be reconstructed, then, into any plane. Obviously, certain tissues take up glucose normally, so lesion detection is reduced in these regions. These normally “hot” areas include the kidneys and brain. Therefore PET is not good for determining whether a lesion in the brain or kidneys is metabolically active or malignant.

In other areas, PET has clearly demonstrated its potential worth. In the thorax, PET is now used in the workup of esophageal neoplasm to look for metastases and to help characterize pulmonary lesions. A standardized uptake value (SUV) can be determined, and if elevated, it may suggest malignancy. At our institution, 1.5 to 2.0 is considered indeterminate, but a lesion greater than 2.0 is considered suggestive of malignancy. A nodule that shows increased uptake on PET warrants further workup. Not all malignant nodules are hot on PET. Slow-growing lesions may not be very glucose avid, and therefore may give a false negative. Bronchioloalveolar cell carcinoma and metastatic genitourinary cancers are two of the more common causes of false-negative examinations on PET. Not all positive studies are malignant. Some of our greatest SUV numbers have been witnessed in the setting of fungal/mycobacterial infection. Clearly PET is no substitute for history, physical examination, and comparison with old studies.

In our practice, PET is used in the evaluation of colon carcinoma, head and neck tumors, melanoma, and lymphoma (in addition to lung and esophageal neoplasms). Its role in breast cancer and gynecologic malignancy promises to expand, as it appears to be very promising in the detection of metastases from these malignancies.

In the evaluation of prostate cancer, bronchioloalveolar cell carcinoma, and pancreatic cancer, PET does not appear to have a role. These tumors are either too slow growing or are too small for detection by PET.

C. Preparation

Because a high-quality PET depends on glucose uptake in a dependable fashion, certain pretest steps must be taken. Patients must refrain from vigorous exercise before the examination to avoid excessive muscle uptake. The fasting blood glucose level must be within a normal range (less than 200 at our institution) to prevent competitive inhibition with the radioactive glucose. Diabetic patients are asked to refrain from oral hypoglycemic agents or insulin and eating after midnight. Nondiabetic patients are asked to avoid eating breakfast. In the event that pelvic pathology may need to be imaged, a Foley catheter may be placed in the bladder.

VII. Conclusion

Beyond plain film, the oncologist faces many choices in imaging patients with suspected neoplasm or in following up patients with proven neoplasms. Of the four modalities in use today, CT and nuclear medicine use ionizing radiation. MR and US do not.

All of the major modalities are changing rapidly and require a team approach if they are to be used appropriately. This usually requires a detailed history and physical examination and discussion with the radiologist. By using the radiologist as a consultant before performing the scan, the oncologist has the best shot at uncovering subtle disease and using the advanced technology to its fullest.

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APPENDIX. CHEMOTHERAPY REGIMENS

Donna M. Gamma and Kristan M. Augustin

Regimen	Drug Doses	Reference
AIDS-related malignancies		
ABV	Doxorubicin, 20 mg/m^2 i.v. Bleomycin, 10 mg/m^2 i.v. Vincristine, 1 mg i.v. Repeat every 14 d	Northfelt DW, et al. *J Clin Oncol* 1998;16:2445–2451
BV	Bleomycin, 15 IU/m^2 i.v. Vincristine, 2 mg i.v. Repeat every 3 wk	Stewart S, et al. *J Clin Oncol* 1998;16:683–691
Doxil	Doxil, 20 mg/m^2 i.v. Repeat every 2 wk	Northfelt DW, et al. *J Clin Oncol* 1998;16:2445–2451
Liposomal daunorubicin	Liposomal daunorubicin, 40 mg/m^2 i.v. Repeat every 2–4 wk	Gill PS, et al. *J Clin Oncol* 1996;14:2353–2364
Paclitaxel	Paclitaxel, 100 mg/m^2 i.v. over 3 h Repeat every 2 wk	Gill PS, et al. *J Clin Oncol* 1999;17:1876
Vinorelbine	Vinorelbine, 30 mg/m^2 i.v. bolus Repeat every 2 wk	Nasti G, et al. *J Clin Oncol* 2000;18:1550–1557
Bladder		
CISCA	Cyclophosphamide, 650 mg/m^2 i.v. day 1 Doxorubicin, 50 mg/m^2 i.v. day 2 Cisplatin, 100 mg/m^2 i.v. day 2 Repeat cycle every 21–28 d	Logothetis CJ, et al. *J Clin Oncol* 1990;8:1050–1055
Cisplatin–Docetaxel	Cisplatin, 75 mg/m^2 i.v. Docetaxel, 75 mg/m^2 i.v. Repeat cycle every 3 wk	Dimopoulos MA, et al. *Ann Oncol* 1999;10:1385–1388
CMV	Methotrexate, 30 mg/m^2 i.v. days 1, 8 Vinblastine, 4 mg/m^2 i.v. days 1, 8 Cisplatin, 100 mg/m^2 i.v. over 4 h, day 2 (¬12 h after methotrexate and vinblastine) Repeat cycle every 21 d	Harker WG, et al. *J Clin Oncol* 1985;3:1463–1470
Gemcitabine–cisplatin	Gemcitabine, 1000 mg/m^2 i.v. days 1, 8, 15 Cisplatin, 70 mg/m^2 over 1 h, day 2 Repeat every 28 d	Moore MJ, et al. *J Clin Oncol* 1999;17:2876–2881
MVAC	Methotrexate, 30 mg/m^2 i.v. days 1, 15, 22 Vinblastine, 3 mg/m^2 i.v. days 2, 15, 22 Doxorubicin, 15–30* mg/m^2 i.v. day 2 Cisplatin, 70 mg/m^2 i.v. day 2 Repeat cycle every 28 d *15 mg if >20 Gy pelvic irradation in 5 d before	Stemberg CN, et al. *Cancer* 1989;64:2448–2458

Regimen	Drug Doses	Reference
Paclitaxel–carboplatin-gemcitabine	Paclitaxel, 200 mg/m^2 i.v. day 1 Carboplatin (AUC 5) i.v. day 1 Gemcitabine, 800 mg/m^2 i.v. days 1, 8 Repeat cycle every 21 d	Hussain M, et al. *J Clin Oncol* 2001;19:2527–2533
PC	Paclitaxel, 200 mg/m^2 i.v. over 3 h, day 1 Carboplatin (AUC 6) i.v. day 1 after paclitaxel Repeat cycle every 21 d	Redman BG, et al. *J Clin Oncol* 1998;16:1844–1848
Brain		
Carmustine + XRT	Carmustine, 80 mg/m^2/d i.v. days 1–3 Repeat every 8 wk	Green SB, et al. *Cancer Treat Rep* 1983;67:121–132
PCV	Lomustine, 110 mg/m^2 p.o. day 1 Procarbazine, 60 mg/m^2/d p.o. days 8–21 Vincristine, 1.4 mg/m^2 i.v. days 8, 29 Repeat every 6 wk	Glass J, et al. *J Neurosurg* 1992;76:741–745
Procarbazine + XRT	Procarbazine, 150 mg/m^2/d (in 3–4 divided doses) p.o. days 1–28 Repeat every 8 wk	Green SB, et al. *Cancer Treat Rep* 1983;67:121–132
Temozolamide	Temozolamide, 200 mg/m^2/ d × 5 d Repeat every 28 d (1st cycle, give only 150 mg/m^2/d × 5 d; if no toxicity, then increase dose as above)	Chinot OL, et al. *J Clin Oncol* 2001;19:2449–2455
Breast		
AC	Doxorubicin, 60 mg/m^2 day 1 Cyclophosphamide, 600 mg/m^2 i.v. day 1 Repeat cycle every 21 d	Fisher B, et al. *J Clin Oncol* 1997;15:1858–1869

Regimen	Drug Doses	Reference
AT	Doxorubicin, 75 mg/m^2 i.v. q2wk × 3 cycles, then Docetaxel, 100 mg/m^2 i.v. q2wk × 3 cycles	Miller KD, et al. *J Clin Oncol* 1999;17:3033–3037
AT	Doxorubicin, 50 mg/m^2 i.v. day 1 Paclitaxel, 220 mg/m^2 i.v. day 2 Repeat cycle every 3 wk	Jassem J, et al. *J Clin Oncol* 2001;19:1707–1715
CAF or FAC	Cyclophosphamide, 500 mg/m^2 i.v. day 1 Doxorubicin, 50 mg/m^2 i.v. day 1 Fluorouracil, 500 mg/m^2 i.v. days 1 and 8 Repeat cycle every 21–28 d	Swenerton KD, et al. *Cancer Res* 1979;39:1552–1562
Capecitabine	Capecitabine, 2510 mg/m^2/d (divided into two doses) p.o. daily for 2 wk Repeat cycle every 3 wk	Blum JL, et al. *J Clin Oncol* 1999;17:485–493

FEC	Cyclophosphamide, 500 mg/m^2 i.v. day 1 Epirubicin, 100 mg/m^2 i.v. day 1 Fluorouracil, 500 mg/m^2 i.v. day 1 Repeat cycle every 21 d	Brufman G, et al. *Ann Oncol* 1997;8:155–162
CMF	Cyclophosphamide, 600 mg/m^2 i.v. day 1 Methotrexate, 40 mg/m^2 i.v. day 1 Fluorouracil, 600 mg/m^2 i.v. day 1 Repeat cycle every 21 d	Weiss RB, et al. *Am J Med* 1987;83:455–463
CNF	Cyclophosphamide, 500 mg/m^2 i.v. day 1 Fluorouracil, 500 mg/m^2 i.v. day 1 Mitoxantrone, 10 mg/m^2 i.v. day 1 Repeat cycle every 3 wk	Bennett JM, et al. *J Clin Oncol* 1988;6:1611–1620
Docetaxel, q3 wk	Docetaxel, 100 mg/m^2 i.v. over 1 h Repeat every 3 wk	Nabholtz JM, et al. *J Clin Oncol* 1999;17:1413–1424
Gemcitabine	Gemcitabine, 800 mg/m^2 i.v. over 30 min weekly for 3 wk followed by 1-wk rest Repeat cycle every 28 d	Carmichael J, et al. *J Clin Oncol* 1995;13:2731–2736
NFL	Mitoxantrone, 12 mg/m^2 i.v. day 1 Fluorouracil, 350 mg/m^2 i.v. days 1–3, given after leucovorin Leucovorin, 300 mg/m^2 i.v. over 30–60 min, days 1–3	Hainsworth JD. *Eur J Cancer Care* 1997;6:4–9

Regimen	Drug Doses	Reference
Paclitaxel, every 3 wk	Paclitaxel, 175 mg/m^2 i.v. over 3 h Repeat cycle every 21 d	Seidman AD, et al. *J Clin Oncol* 1995;13:2575–2581
Paclitaxel, weekly	Paclitaxel, 100 mg/m^2 i.v. over 1 h, weekly	Seidman AD, et al. *J Clin Oncol* 1998;16:3353–3361
Trastuzumab	Trastuzumab, 4 mg/kg load i.v. × 1, then 2 mg/kg i.v. weekly thereafter	Cobleigh MA, et al. *J Clin Oncol* 1999;17:2639–2648
Trastuzumab and docetaxel	Trastuzumab, 4 mg/kg load i.v. × 1, then 2 mg/kg i.v. weekly thereafter Docetaxel, 35 mg/m^2 i.v. day 1, then weekly thereafter (given after trastuzumab)	Meden H, et al. *Anticancer Res* 2001;21:1301–1305
Trastuzumab and paclitaxel	Trastuzumab, 4 mg/kg load i.v. × 1, then 2 mg/kg i.v. weekly thereafter Paclitaxel, 175 mg/m^2 over 3 h i.v. every 3 wk (given after trastuzumab)	Slamon DJ, et al. *N Engl J Med* 2001;344:783–792
Trastuzumab and paclitaxel (weekly)	Trastuzumab, 4 mg/kg load i.v. × 1, then 2 mg/kg i.v. weekly thereafter Paclitaxel, 90 mg/m^2 over 3 h i.v. weekly (given after trastuzumab)	Seidman AD, et al. *J Clin Oncol* 2001;19:2587–2595
Trastuzumab and vinorelbine	Trastuzumab, 4 mg/kg load i.v. × 1, then 2 mg/kg i.v. weekly thereafter, followed by Vinorelbine, 25 mg/m^2 i.v. weekly Assessment done at 8-wk intervals	Burstein HJ, et al. *J Clin Oncol* 2001;19:2722–2730

Regimen	Drug Doses	Reference
Vinorelbine	Vinorelbine, 30 mg/m^2 i.v. weekly	Fumoleau P, et al. *J Clin Oncol* 1993;11:1245–1252
Vinorelbine–doxorubicin	Vinorelbine, 25 mg/m^2 i.v. days 1, 8 Doxorubicin, 50 mg/m^2 i.v. day 1 Repeat cycle every 3 wk	Spielmann M, et al. *J Clin Oncol* 1994;12:1764–1770
Cervical		
BIP	Bleomycin, 30 U CIVI over 24 h day 1 Ifosfamide, 5 g/m^2 CIVI over 24 h day 2 Mesna, 8 g/m^2 CIVI over 36 h day 2, starting with ifosfamide Cisplatin, 50 mg/m^2 i.v. day 2 Repeat cycle every 21 d	Buxton EJ. *Acta Oncol* 1988;27:545–549
Cisplatin	Cisplatin, 100 mg/m^2 i.v. Repeat every 21 d	Bonomi P, et al. *J Clin Oncol* 1985;3:1079–1085
Cisplatin- fluorouracil- hydroxurea	Cisplatin, 50 mg/m^2 i.v. days 1, 29, then Fluorouracil, 4000 mg/m^2 i.v. over 96 h beginning on days 1, 29 Hydroxurea, 2000 mg/m^2 p.o. twice weekly 2 h before radiotherapy at weeks 1–6	Rose PG, et al. *N Engl J Med* 1999;340:1144–1153
Cisplatin–vinorelbine	Cisplatin, 80 mg/m^2 i.v. day 1 Vinorelbine, 25 mg/m^2 i.v. days 1, 8 Repeat cycle every 21 d	Pignata S, et al. *J Clin Oncol* 1999;17:756–760
CLD–BOMP	Bleomycin, 5 units/day CIVI days 1–7 Cisplatin, 10 mg/m^2 i.v. over 4 h days 1–7 Vincristine, 0.7 mg/m^2 i.v. day 7 Mitomycin-C, 7 mg/m^2 i.v. day 7 Repeat cycle every 3 wk	Shimizu Y, et al. *J Clin Oncol* 1998;16:1869–1878

Regimen	Drug Doses	Reference
Paclitaxel–cisplatin	Paclitaxel, 175 mg/m^2 i.v. over 3 h Cisplatin, 75 mg/m^2 i.v. day 2 Repeat cycle every 21 d	Papadimitriou CA, et al. *J Clin Oncol* 1999;17: 761–766
Paclitaxel–cisplatin	Paclitaxel, 135–170 mg/m^2 i.v. over 24 h, day 1 Cisplatin, 75 mg/m^2 i.v. day 2 (rate of 1 mg/min) after paclitaxel Repeat cycle every 21 d	Rose PG, et al. *J Clin Oncol* 1999;17:2676–2680
Colorectal		
Capecitabine	Capecitabine, 2500 mg/m^2/d (given as 1250 mg/m^2 b.i.d.) p.o. for 2 wk Repeat cycle every 3 wk	Hoff PM, et al. *J Clin Oncol* 2001;19:2282–2292
FLe	Fluorouracil, 450 mg/m^2/d i.v. days 1–5; then, at day 28, begin 450 mg/m^2 i.v. weekly × 1 yr Levamisole, 50 mg p.o. every 8 h for 3 d, repeated every 2 wk for 1 yr	Laurie JA, et al. *J Clin Oncol* 1989;7:1447–1456
Fluorouracil	Fluorouracil, 1000 mg/m^2/d CIVI days 1–5 Repeat cycle every 4 wk	Kemeny N, et al. *J Clin Oncol* 1990;8:313–315
Fluorouracil + leucovorin	Leucovorin, 500 mg/m^2 i.v. over 2 h Fluorouracil, 600 mg/m^2 i.v. given 1 h into leucovorin infusion Weekly for 6 wk followed by 2 wk rest	Petrelli N, et al. *J Clin Oncol* 1989;7:1419–1426
Fluorouracil + leucovorin	Leucovorin, 20 mg/m^2 i.v. days 1–5 Fluorouracil, 425 mg/m^2 i.v. after leucovorin, days 1–5 Repeat cycle at 4 wk, 8 wk, then every 5 wk thereafter	O'Connell MJ, et al. *Cancer* 1989;63:1026–1030

Regimen	Drug Doses	Reference
Irinotecan (q3 wk)	Irinotecan, 300–350 mg/m^2* i.v. over 90 min Repeat cycle every 3 wk *for patients older than 69 years of age or WHO PS 2, give 300 mg/m^2	Rougier P, et al. *Lancet* 1998;352:1407–1412

Irinotecan (weekly)	Irinotecan, 125 mg/m^2 over 90 min weekly × 4 Repeat every 6 wk	Conti JA, et al. *J Clin Oncol* 1996;14:709–715
Irinotecan–5-FU/LCV	Irinotecan, 125 mg/m^2 i.v. day 1 Leucovorin, 20 mg/m^2 i.v. day 1 Fluorouracil, 500 mg/m^2 i.v. day 1 Repeat 4 consecutive wk followed by 2 wk of rest	Saltz LB, et al. *N Engl J Med* 2000;343:905–914
Endometrial		
AP	Doxorubicin, 60 mg/m^2 i.v. day 1 (6 a.m.) Cisplatin, 60 mg/m^2 i.v. day 1 given 12 h after doxorubicin (6 p.m.) Repeat cycle every 28 d	Barrett RJ, et al. Am *J Clin Oncol* 1993;16:494–496
Cyclophosphamide–doxorubicin	Cyclophosphamide, 500 mg/m^2 i.v. day 1 Doxorubicin, 60 mg/m^2 i.v. day 1 Repeat every 3 wk	Thigpen JT, et al. *J Clin Oncol* 1994;12:1408–1414
Carboplatin–paclitaxel	Carboplatin, AUC 5–7 i.v. Paclitaxel, 175 mg/m^2 i.v. Repeat every 4 wk	Hoskins PJ, et al. *J Clin Oncol* 2001;19:4048–4053
CAP	Cisplatin, 60 mg/m^2 i.v. day 1 Doxorubicin, 50 mg/m^2 i.v. day 1 Cyclophosphamide, 600 mg/m^2 i.v. day 1 Repeat every 3–4 wk	Turbow MM, et al. *Proc ASCO* 1982;1:108
Doxorubicin	Doxorubicin, 60 mg/m^2 i.v. Repeat every 3 wk	Thigpen JT, et al. *J Clin Oncol* 1994;12:1408–1414
Gastric		
EAP	Doxorubicin, 20 mg/m^2 i.v. days 1, 7 Cisplatin, 40 mg/m^2 i.v. days 2, 8 Etoposide, 120 mg/m^2 i.v. days 4–6 Repeat cycle every 3–4 wk	Preusser P, et al. *J Clin Oncol* 1989;7:1310–1317
ELF	Leucovorin, 300 mg/m^2 i.v. over 10 min, followed by etoposide, 120 mg/m^2 i.v. over 50 min, followed by fluorouracil, 500 mg/m^2 i.v. over 10 min All agents given on days 1–3 Repeat cycle every 22–28 d	Wilke H, et al. *Invest New Drugs* 1990;8:65–70
FAM	Fluorouracil, 600 mg/m^2 i.v. days 1, 8, 29, 36 Doxorubicin, 30 mg/m^2 i.v. days 1, 29 Mitomycin, 10 mg/m^2 i.v. day 1 Repeat cycle every 8 wk	Macdonald JS, et al. *Ann Intern Med* 1980;93: 533–536
FAM-Tx	Methotrexate, 1500 mg/m^2 i.v. day 1 Fluorouracil, 1500 mg/m^2 i.v. starting 1 h after methotrexate, day 1 Leucovorin, 15 mg/m^2 p.o. q6h starting 24 h after methotrexate dose, for 72 h Doxorubicin, 30 mg/m^2 i.v. day 15 Repeat cycle every 28 d	Klein HO. *Anticancer Res* 1989;9:1025–1026

Regimen	Drug Doses	Reference
Gestational trophoblastic disease		
EMA-CO	Etoposide, 100 mg/m^2 i.v. (over 30 min) day 1, 2 Actinomycin-D, 0.5 mg IVP day 1, 2 Methotrexate, 100 mg/m^2 IVP, then 200 mg/m^2 i.v. over 12 h, day 1 Folinic acid, 15 mg i.m. or p.o. q12h × 4 doses (starting 24 h after start of methotrexate) Vincristine, 1 mg/m^2 IVP, day 8 Cyclophosphamide, 600 mg/m^2 i.v. over 30 min day 8 Repeat cycle every 2 wk	Newlands ES, et al. *Br J Obstet Gynecol* 1986; 93:63–69
Methotrexate	Methotrexate, 30–50 mg/m^2 i.m. q wk	Homseley HD, et al. *Obstet Gynecol* 1988;72:413
Head and neck		
Cisplatin–docetaxel	Cisplatin, 75 mg/m^2 i.v. day 1 Docetaxel, 75 mg/m^2 i.v. day 1 Repeat cycle every 3 wk	Specht L, et al. *Ann Oncol* 2000;11:845–849
CF	Cisplatin, 75 mg/m^2 i.v. day 1, immediately followed by Fluorouracil, 1000 mg/m^2/d CIVI for 96 h Repeat every 21 d	Cooper JS, et al. *JAMA* 1999;281:1623–1627
CF	Cisplatin, 100 mg/m^2 i.v. day 1, immediately followed by Fluorouracil, 1000 mg/m^2/d CIVI for 96 h Repeat every 21 d	Kish JA, et al. *Cancer* 1984;53:1819–1824
CF	Cisplatin, 100 mg/m^2 i.v. day 1 Fluorouracil, 1000 mg/m^2/d CIVI days 1–5 Repeat every 3 wk	Bleiberg H, et al. *Eur J Cancer* 1997;33: 1216–1220
Fluorouracil	Fluorouracil, 500 mg/m^2 i.v. daily × 5 Repeat every 5 wk	Ezdinli EZ, et al. *Cancer* 1980;46:2149–2153
Methotrexate	Methotrexate, 40 mg/m^2/ wk i.m. Increase dose by 10 mg/m^2 weekly as tolerated (expect tolerable dose of 60 mg/m^2/wk)	Taylor SG, et al. *J Clin Oncol* 1984;2:1006–1011
Paclitaxel	Paclitaxel, 250 mg/m^2 i.v. over 24 h Repeat every 3 wk	Forastiere AA, et al. *Cancer* 1998;82:2270–2274
PFL	Cisplatin, 25 mg/m^2/d CIVI × 5 days, 1–5 Fluorouracil, 800 mg/m^2/d CIVI × 5 days, d2–6 Leucovorin, 500 mg/m^2/d CIVI × 6 days, d1–6 Repeat cycle every 28 d	Dreyfuss AI, et al. *Ann Intern Med* 1990;112:167–172
TIC	Paclitaxel, 175 mg/m^2 i.v. over 3 h day 1 Ifosfamide, 1,000 mg/m^2 i.v. over 2 h days 1–3 Mesna 400 mg/m^2 i.v. before ifosfamide, and 200 mg/m^2 i.v. 4 h after ifosfamide, days 1–3 Carboplatin, (AUC 6) day 1 Repeat cycle every 3–4 wk	Shin DM, et al. *Cancer* 2001;91:1316–1323

TIP	Paclitaxel, 175 mg/m^2 i.v. over 3 h day 1 Ifosfamide, 1000 mg/m^2 i.v. over 2 h, days 1–3 Mesna, 600 mg/m^2/d divided as 400 mg/m^2 i.v. before ifosfamide and 200 mg/m^2 i.v. 4 h after ifosfamide Cisplatin, 60 mg/m^2 i.v. day 1 Repeat cycle every 3–4 wk	Shin DM, et al. *J Clin Oncol* 1998;16:1325–1330

Regimen	**Drug Doses**	**Reference**
Hepatocellular		
Doxorubicin	Doxorubicin, 60–75 mg/m^2 i.v. Repeat every 3 wk	Lai CL, et al. *Cancer* 1988;62:479–483
PIAF	Cisplatin, 20 mg/m^2/d i.v. over 1 h days 1–4 Doxorubicin, 40 mg/m^2 i.v. day 1 Interferon-a2b, 5 MU/m^2 s.q. days 1–4 Fluorouracil, 400 mg/m^2/d IVP days 1–4 Repeat q3 wk (max of six cycles)	Leung TWT, et al. *Clin Cancer Res* 1999;5: 1676–1681
Intraarterial cisplatin, doxorubicin, FUDR, and leucovorin	Doxorubicin, 30–35 mg/m^2 and Cisplatin, 100 mg/m^2 day 1 by intraarterial infusion Then floxuridine (FUDR), 60 mg/m^2/d and Leucovorin, 15 mg/m^2/d by intraarterial infusion for 4 d Repeat cycle every 5 weeks	Patt YZ, et al. *J Clin Oncol* 1994;12:1204
Leukemia		
Acute lymphoblastic leukemia		
DVPA	Induction Daunorubicin, 50 mg/m^2 i.v. days 1–3 Vincristine, 2 mg i.v. days 1, 8, 15, 22 Prednisone, 60 mg/m^2 p.o. days 1–28 L-Asparaginase, 6000 U/m^2 i.m. days 17–28 Residual disease on day 14 bone marrow Daunorubicin, 50 mg/m^2 i.v. day 15 Residual disease on day 28 bone marrow Daunorubicin, 50 mg/m^2 i.v. days 29–30 Vincristine, 2 mg i.v. days 29, 36 Prednisone, 60 mg/m^2 p.o. days 29–42 L-Asparaginase, 6000 U/m^2 i.m. days 29–35 Consolidation Treatment A (cycles 1, 3, 5, 7) Daunorubicin, 50 mg/m^2 i.v. days 1, 2 Vincristine, 2 mg i.v. days 1, 8 Prednisone, 60 mg/m^2 p.o. days 1–14 L-Asparaginase, 12000 U/m^2 i.m. days 2, 4, 7, 9, 11, and 14 Treatment B (cycles 2, 4, 6, 8) Teniposide, 165 mg/m^2 i.v. days 1, 4, 8, 11 Cytarabine, 300 mg/m^2 i.v. days 1, 4, 8, 11 Treatment C (cycle 9) Methotrexate, 690 mg/m^2 i.v. over 42 h Followed by leucovorin, 15 mg/m^2 every 6 h × 12 doses Maintenance Methotrexate, 20 mg/m^2 p.o. weekly 6-Mercaptopurine, 75 mg/m^2 p.o. daily	Linker CA, et al. *Blood* 1987;69:1242–1248
HCVAD/ MTX–HDAC	Course 1 Cyclophosphamide, 300 mg/m^2 i.v. over 2 h every 12 h × 6 doses (days 1–3) Vincristine, 2 mg i.v. (days 4 and 11) Doxorubicin, 50 mg/m^2 i.v. (day 4) Dexamethasone, 40 mg p.o. qd (days 1–4 and 9–12) Course 2 Methotrexate, 1g/m^2 over 24 h (day 1) with leucovorin rescue Cytarabine, 3 g/m^2 over 2 h every 12 h × 4 doses (days 2 and 3)	Koller CA, et al. *Leukemia* 1997;11:2039–2044

Regimen	**Drug Doses**	**Reference**
Acute myelogenous leukemia: induction		
a5+2*	Cytarabine, 100 mg/m^2/d CIVI days 1–5 Daunorubicin, 45 mg/m^2/d i.v. days 1–2 *for reinduction	Rai KR, et al. *Blood* 1981;58:1203–1212
7+3	Cytarabine, 100 mg/m^2/d CIVI days 1–7 Daunorubicin, 45 mg/m^2/d i.v. days 1–3	Rai KR, et al. *Blood* 1981;58:1203–1212
7+3+7	Cytarabine, 100 mg/m^2/d CIVI days 1–7 Daunorubicin, 50 mg/m^2/d i.v. days 1–3 Etoposide, 75 mg/m^2/d over 1 h days 1–7	Bishop JF, et al. *Blood* 1996;88:754–755
EMA-86	Mitoxantrone, 12 mg/m^2 i.v. days 1–3 Cytarabine, 500 mg/m^2/d CIVI days 1–3, 8–10 Etoposide, 200 mg/m^2/d CIVI days 8–10	Archimbaud E, et al. *J Clin Oncol* 1995;13:11–18
Gemtuzumab	Gemtuzumab, 9 mg/m^2 i.v. over 2 h Every 2 wk for 2 doses	Sievers EL, et al. *J Clin Oncol* 2001;19:3244–3251
HDAC–daunorubicin	Cytarabine, 3 g/m^2 i.v. every 12 h for 6 days Daunorubicin, 45 mg/m^2 i.v. days 1–3	Fopp M, et al. *Ann Oncol* 1997;8:251–257
Idarubicin–cytarabine	Idarubicin, 12 mg/m^2/d i.v. days 1–3 Cytarabine, 100 mg/m^2/d CIVI days 1–7	Vogler WR, et al. *J Clin Oncol* 1992;10: 1103–1111
Mitoxantrone–cytarabine	Mitoxantrone, 12 mg/m^2/d i.v. days 1–3 Cytarabine, 100 mg/m^2/d CIVI days 1–7	Arlin Z, et al. *Leukemia* 1990;4:177–183
Acute myelogenous leukemia: postremission		
Cytarabine	Cytarabine, 100 mg/m^2/d CIVI days 1–5* Repeat cycle every 28 days × 4 *For patients older than 60 years	Mayer RJ, et al. *N Engl J Med* 1994;331:896–903

HiDAC	Cytarabine, 3000 mg/m^2 i.v. over 1–3 h every 12 h days 1, 3, 5 Administer with saline, methylcellulose, or steroid eye drops OU, every 2–4 h, beginning with first and continuing 48–72 h after the last cytarabine dose × 4 Repeat cycle every 28 d	Mayer RJ, et al. *N Engl J Med* 1994;331:896–903

Regimen	Drug Doses	Reference
Acute promyelocytic leukemia		
All-*trans*-retinoic acid	All-*trans*-retinoic acid, 45 mg/m^2/d p.o. (1–2 divided doses)	Warrell RP, et al. *N Engl J Med* 1991;324:1385–1393
All-*trans*-retinoic acid – daunorubicin-cytarabine	ATRA (Vesanoid), 45 mg/m^2/d divided into two daily doses and given q12h beginning day 1 and until CR (max, 90 d), then, on day 3, start Daunorubicin, 60 mg/m^2/d i.v. × 3 d and cytarabine, 200 mg/m^2/d i.v. × 7 d	Fenaux P, et al. *Blood* 1999;94:1192–1200
Arsenic	Arsenic trioxide, 0.15 mg/kg/d i.v. daily	Soignet SL, et al. *J Clin Oncol* 2001;19:3852–3860
Chronic lymphocytic leukemia		
C + P	Chlorambucil, 30 mg/m^2 p.o. day 1 Prednisone, 80 mg p.o. days 1–5 Repeat cycle every 2 wk	Raphael B, et al. *J Clin Oncol* 1991;9:770–776
Campath-1H	Campath, 30 mg i.v. over 2 h thrice weekly Begin with an initial dose of 3 mg. If tolerated, increase dose to 10 mg, and then to a final dose of 30 mg	Osterborg A, et al. *J Clin Oncol* 1997;15:1567–1574
Chlorambucil	Chlorambucil, 0.03–0.3 mg/ kg/d p.o. for 4–12 wk	Galton DA, et al. *Br J Haematol* 1961;7:73–98
Cladribine	Cladribine, 0.1 mg/kg/d CIVI over 24 h for 7 d	Tallman MS, et al. *J Clin Oncol* 1995;13:983–988
Cladribine	Cladribine, 0.12 mg/kg/d i.v. over 2 h, days 1–5 Repeat monthly	Robak T, et al. *Br J Haematol* 2000;108:357–368
Fludarabine	Fludarabine, 25 mg/m^2 i.v. days 1–5 Repeat cycle every 28 days	Rai KR, et al. *N Engl J Med* 2000;343:1799–1801

Regimen	Drug Doses	Reference
Chronic myelogenous leukemia		
Busulfan	Busulfan, 4–6 mg/d (0.06–0.085 mg/kg/d) p.o.	Haut A, et al. *Blood* 1961;17:1–19
Hydroxyurea–interferon-a2b–cytarabine	Hydroxyurea, 50 mg/kg/d p.o. Interferon-a2b, 5 MU/m^2/d s.q. Two weeks later begin Cytarabine, 20 mg/m^2/d s.q. × 10 d q mo	Guilhot J, et al. *N Engl J Med* 1997;337:223–229
Interferon-a2a	Interferon-a2a, 5 MU/m^2/d i.m.	Talpaz M, et al. *N Engl J Med* 1986;314:1065–1069
Hairy cell leukemia		
Cladribine	Cladribine, 0.1 mg/kg/d CIVI days 1–7 One cycle only	Saven A, et al. *Blood* 1998;92:1918–1926
Pentostatin	Pentostatin, 4 mg/m^2 i.v. day 1 Repeat every 14 d	Grever M, et al. *J Clin Oncol* 1995;13:974–982
Myelodysplastic syndrome		
Cytarabine–idarubicin	Idarubicin, 12 mg/m^2/d IVP days 1–3 Cytarabine, 200 mg/m^2/d i.v. days 1–7	Heaney ML, et al. *N Engl J Med* 1999;340:1649–1660
Low-dose cytarabine	Cytarabine, 20 mg/m^2/d CIVI × 14–21 d	Griffin JD, et al. *J Clin Oncol* 1985;3:982–991
Low-dose cytarabine	Cytarabine, 10 mg/m^2/d s.q. b.i.d.	Miller KB, et al. Ann Hematol 1992;65:162–168
Lung		
Non–small cell		
Carbo-Tax	Paclitaxel, 225 mg/m^2 i.v. over 24 h, day 1, followed by carboplatin (AUC 6) i.v. Repeat every 3 wk	Schiller JH, et al. *N Engl J Med* 2002;346:92–98

Regimen	Drug Doses	Reference
Cisplatin–etoposide	Cisplatin, 60 mg/m^2 i.v. day 1 Etoposide, 100 mg/m^2/d i.v. days 4, 6, 8 Repeat cycle every 3 wk	Longeval E, et al. *Cancer* 1982;50:2751–2756
Cisplatin–paclitaxel	Paclitaxel, 135 mg/m^2 i.v. over 24 h on day 1 Cisplatin, 75 mg/m^2 i.v. day 2 Repeat every 3 wk	Schiller JH, et al. *N Engl J Med* 2002;346:92–98
Cisplatin–vinorelbine	Cisplatin, 100 mg/m^2 i.v. day 1 every 4 wk Vinorelbine, 25 mg/m^2 i.v. weekly	Wozniak AJ, et al. *J Clin Oncol* 1998;16:2459–2465
Cisplatin–vinorelbine	Cisplatin, 120 mg/m^2 i.v. days 1, 29, then every 6 wk Vinorelbine, 30 mg/m^2 i.v. weekly	LeChevalier T, et al. *J Clin Oncol* 1994;12:360–367
Docetaxel	Docetaxel, 75 mg/m^2 over 1 h i.v. Repeat every 3 wk	Fossella FV, et al. *J Clin Oncol* 2000;18:2354–2362
Docetaxel–cisplatin	Docetaxel, 75 mg/m^2 i.v. day 1 Cisplatin, 75 mg/m^2 i.v. day 1 Repeat every 3 wk	Schiller JH, et al. *N Engl J Med* 2002;346:92–98
EC	Etoposide, 100 mg/m^2 i.v. days 1–3 Carboplatin, 325 mg/m^2 i.v. day 1 Repeat every 21–28 d	Klastersky J, et al. *J Clin Oncol* 1990;8:1556–1562
EP	Etoposide, 100 mg/m^2 i.v. days 1–3 Cisplatin, 50 mg/m^2/d i.v. days 1 and 2 Repeat every 21–28 d	Skarlos DV, et al. *Ann Oncol* 1994;5:601–607
Gemcitabine–cisplatin	Gemcitabine, 1000 mg/m^2 i.v. days 1, 8, 15 Cisplatin, 100 mg/m^2 i.v. day 15 (immediately after gemcitabine) Repeat every 28 d	Abratt RP, et al. *J Clin Oncol* 1997;15:744–749
PC	Paclitaxel, 175 mg/m^2 i.v. over 3 h, day 1, followed by Cisplatin, 80 mg/m^2 i.v. day 1 Repeat every 3 wk	Giaccone G, et al. *J Clin Oncol* 1998;16:2133–2141
Vinorelbine	Vinorelbine, 30 mg/m^2 i.v. weekly	Depierre A, et al. *Am J Clin Oncol* 1991;14:115–119

Regimen	Drug Doses	Reference
Small cell		

Regimen	Drug Doses	Reference
CAV	Cyclophosphamide, 1000 mg/m^2 i.v. Doxorubicin, 40 mg/m^2 i.v. Vincristine, 1 mg/m^2 i.v. (max, 2 mg) Repeat every 21 d	Roth BJ, et al. *J Clin Oncol* 1992;10:282–291
EC	Etoposide, 100 mg/m^2/d i.v. days 1–3 Carboplatin, 300 mg/m^2 i.v. day 1 Repeat every 21 d	Skarlos DV, et al. *Ann Oncol* 1994;5:601–607
EP or PE	Etoposide, 100 mg/m^2/d i.v. days 1, 3, 5 Cisplatin, 20 mg/m^2/d i.v. days 1–5 Repeat every 4 wk	Evans WK, et al. *Cancer* 1984;53:1461–1466
Etoposide	Etoposide, 50 mg/m^2/d p.o. for days 1–21 Repeat every 28 d	Johnson DH, et al. *J Clin Oncol* 1990;8:1613–1617
Irinotecan–cisplatin	Irinotecan, 60 mg/m^2 i.v. days 1, 8, 15 Cisplatin, 60 mg/m^2 i.v. day 1	Noda K, et al. *N Engl J Med* 2002;346:85–91
Topotecan	Topotecan, 1.5 mg/m^2/d i.v. over 30 min, days 1–5 Repeat every 21 d	Von Pawel J, et al. *J Clin Oncol* 1999;17:658–667
Lymphoma		
Hodgkins		
ABVD	Doxorubicin, 25 mg/m^2 i.v. days 1, 15 Bleomycin, 10 mg/m^2 i.v. days 1, 15 Vinblastine, 6 mg/m^2 i.v. days 1, 15 Dacarbazine, 375 mg/m^2 i.v. days 1, 15 Repeat cycle every 28 d	Bonadona G, et al. *Cancer Treat Rev* 1982;9:21–35
ChlVPP	Chlorambucil, 6 mg/m^2 p.o. days 1–14 (max, 10 mg/day) Procarbazine, 100 mg/m^2/d p.o. days 1–14 (max, 150 mg/d) Prednisone, 40 mg p.o. qd, days 1–14 Vinblastine, 6 mg/m^2 i.v. days 1, 8 (max, 10 mg/d) Repeat cycle every 4 wk	Selby P, et al. *Br J Cancer* 1990;62:279–285
MOPP	Mechlorethamine, 6 mg/m^2 i.v. days 1, 8 Vincristine, 1.4 mg/m^2 i.v. days 1, 8 (max, 2 mg) Procarbazine, 100 mg/m^2 p.o. days 1–14 Prednisone, 40 mg/m^2 p.o. days 1–14 Repeat cycle every 28 d	Canellos GP, et al. *N Engl J Med* 1992;327:1478–1484
MOPP/ABV	Mechlorethamine, 6 mg/m^2 i.v. day 1 Vincristine, 1.4 mg/m^2 i.v. day 1 (max, 2 mg) Procarbazine, 100 mg/m^2 p.o. days 1–7 Prednisone, 40 mg/m^2 p.o. days 1–14 Doxorubicin, 35 mg/m^2 i.v. day 8 Bleomycin, 10 units/m^2 i.v. day 8 (given with hydrocortisone, 100 mg i.v.) Vinblastine, 6 mg/m^2 i.v. day 8 Repeat cycle every 28 d	Klimo P, et al. *Semin Hematol* 1988;25(suppl 2): 34–40
Stanford V	Doxorubicin, 25 mg/m^2 i.v. days 1, 15 Vinblastine* 6 mg/m^2 i.v. days 1, 15 Mechlorethamine, 6 mg/m^2 i.v. day 1 Vincristine,* 1.4 mg/m^2 i.v. days 8, 22 Bleomycin, 5 U/m^2 i.v. days 8, 22 Etoposide, 60 mg/m^2 i.v. days 15, 16 Prednisone, 40 mg/m^2 p.o. qod (dose tapered by 10 mg qod starting at wk 10) Sulfamethoxazole-trimethoprim DS p.o. b.i.d. Acyclovir 200 mg p.o. t.i.d. Ketoconazole 200 mg p.o. q.d. H2 blockers Daily stool softeners Repeat cycle every 28 d × 3 cycles *Patients older than 50 years: Vinblastine, 4 mg/m^2, and vincristine, 1 mg during cycle 3	Bartlett NL, et al. *J Clin Oncol* 1995;13:1080–1088
Non-Hodgkins		
Chlorambucil	Chlorambucil 0.1–0.2 mg/kg/d p.o.	Hoppe RT, et al. *Blood* 1981;58:592–598
CHOP	Cyclophosphamide, 750 mg/m^2 i.v. day 1 Doxorubicin, 50 mg/m^2 i.v. day 1 Vincristine, 1.4 mg/m^2 i.v. day 1 (max, 2 mg) Prednisone, 40 mg/m^2/d p.o. × 5 days Repeat cycle every 21 d × 8	McKelvey EM, et al. *Cancer* 1976;38:1484–1493
CHOP + rituximab	Rituximab, 375 mg/m^2 i.v. day 1 Cyclophosphamide, 750 mg/m^2 i.v. day 1 Doxorubicin, 50 mg/m^2 i.v. day 1 Vincristine, 1.4 mg/m^2 i.v. day 1 (max, 2 mg) Prednisone, 40 mg/m^2/d p.o. × 5 days Repeat cycle every 21 d × 8	Coiffer B, et al. *N Engl J Med* 2002;346:235–242
CNOP	Cyclophosphamide, 750 mg/m^2 i.v. day 1 Mitoxantrone, 10 mg/m^2 i.v. day 1 Vincristine, 1.4 mg/m^2 i.v. day 1 (max, 2 mg) Prednisone, 50 mg/m^2/d p.o. days 1–5 Repeat cycle every 21 d	Pavlovsky S, et al. *Ann Oncol* 1992;3:205–209
CVP	Cyclophosphamide, 400 mg/m^2/d p.o. days 1–5 Vincristine, 1.4 mg/m^2 (max, 2 mg) i.v. day 1 Prednisone, 100 mg/m^2/d p.o. days 1–5 Repeat every 21 d	Bagley CM, et al. *Ann Intern Med* 1972;76:227–234
CVP	Cyclophosphamide, 1000 mg/m^2 i.v. day 1 Vincristine, 1.4 mg/m^2 (max, 2 mg) i.v. day 1 Prednisone, 100 mg/m^2/d p.o. days 1–5 Repeat every 21 d	
Cyclophospha-mide	Cyclophophamide 1.5–2.5 mg/kg/d p.o.	Hoope RT, et al. *Blood* 1981;58:592–598

DHAP	Dexamethasone, 40 mg p.o. or i.v. days 1–4 Cisplatin, 100 mg/m^2/d CIVI over 24 h, d 1 Cytarabine, 2000 mg/m^2 i.v. q12h × 2 doses day 2 Repeat cycle every 3–4 wk	Velasquez WS, et al. *Blood* 1988;71:117–122

Regimen	Drug Doses	Reference
ESHAP	Etoposide, 60 mg/m^2/d i.v. days 1–4 Methylprednisolone, 500 mg/d i.v. days 1–4 Cisplatin, 25 mg/m^2/d CIVI days 1–4 Cytarabine, 2000 mg/m^2 i.v. day 5 immediately after completion of cisplatin Repeat cycle every 21 d	Rodriguez MA, et al. *J Clin Oncol* 1995;13:1734–1741
Fludarabine	Fludarabine 25 mg/m^2/d i.v. days 1–5 Repeat cycle every 28 days	Falkson Cl. *Am J Clin Oncol* 1996;19:268–270
FND	Fludarabine 25 mg/m^2/d i.v. days 1–3 Mitoxantrone 10 mg/m^2 i.v. day 1 Dexamethasone 20 mg/d i.v. or p.o. days 1–5 Repeat every 4 weeks (max, 8 courses)	McLaughlin P, et al. *J Clin Oncol* 1996;14:1262–1268
ICE	Etoposide 100 mg/m^2/d i.v. days 1–3 Carboplatin (AUC 5) i.v. day 2 (max, 800 mg) Ifosfamide 5 g/m^2 with equal amount of Mesna Given over 24 hours beginning day 2 GCSF 5 mcg/kg/d sq days 5–12	Moskowitz CH, et al. *J Clin Oncol* 1999;17:3776–3785
MINE	Mesna, 1330 mg/m^2/d over 1 h i.v. given concurrent with ifosfamide, then 500 mg p.o., 4 h after ifosfamide, days 1–3 Ifosfamide, 1330 mg/m^2 i.v. over 1 h, days 1–3 Mitoxantrone, 8 mg/m^2 i.v. day 1 Etoposide, 65 mg/m^2 i.v. days 1–3 Repeat cycle every 21–28 days (max, 6 cycles)	Rodriguez MA, et al. *Am Oncol* 1995;6:609–611
ProMACE–cytaBOM	Cyclophosphamide, 650 mg/m^2 i.v. day 1 Doxorubicin, 25 mg/m^2 i.v. day 1 Etoposide, 120 mg/m^2 i.v. day 1 Cytarabine, 300 mg/m^2 i.v. day 8 Bleomycin, 5 U/m^2 i.v. day 8 Vincristine, 1.4 mg/m^2 i.v. day 8 Methotrexate, 120 mg/m^2 i.v. day 8 Leucovorin, 25 mg/m^2 p.o. q6h × 4 doses beginning 24 h after methotrexate dose Prednisone, 60 mg/m^2/d p.o. days 1–14 Repeat cycle every 21 d	Longo DL, et al. *J Clin Oncol* 1991;9:25–38
Rituximab	Rituximab, 375 mg/m^2 i.v. weekly × 4	Davis TA, et al. *J Clin Oncol* 1999;17:1851–1857

Regimen	Drug Doses	Reference
VACOP-B	Etoposide 50 mg/m^2 i.v. day 1 and 100 mg/m^2 p.o. days 2, 3 of weeks 3, 7, 11 Doxorubicin 50 mg/m^2 i.v. weeks 1, 3, 5, 7, 9, 11 Cyclophophamide 350 mg/m^2 i.v. weeks 1, 5, 9 Vincristine 1.4 mg/m^2 i.v. weeks 2, 4, 6, 8, 10, 12 Prednisone 45 mg/m^2 p.o. QD for 1 week then QOD for 11 weeks Bleomycin 10 u/m^2 i.v. weeks 2, 4, 6, 8, 10, 12* *Hydrocortisone 100 mg i.v. given just before each dose Cotrimoxazole DS p.o. b.i.d. × 14 weeks Ketoconazole 200 mg p.o. QD × 1 week then QOD × 11 weeks Cimetidine 600 mg p.o. b.i.d. × 1 week then QOD × 11 weeks	O'Reilly SE, et al. *Ann Oncol* 1991;2:17–23
Melanoma		
CVD	Cisplatin, 20 mg/m^2/d i.v. days 2–5 Vinblastine, 1.6 mg/m^2/d i.v. days 1–5 Dacarbazine, 800 mg/m^2 i.v. day 1 Repeat every 3 wk	Legha SS, et al. *Cancer* 1989;64:2024–2029
Dacarbazine	Dacarbazine, 250 mg/m^2/d i.v. × 5 d Repeat every 21 d	Middleton MR, et al. *J Clin Oncol* 2000;18:158–166
Dacarbazine–carmustine–cisplatin–tamoxifen	Carmustine, 150 mg/m^2 i.v. day 1 Dacarbazine, 220 mg/m^2 i.v. days 1–3 and 22–24 Cisplatin, 25 mg/m^2 i.v. days 1–3 and 22–24 Tamoxifen, 160 mg/d p.o. 7 days before chemotherapy, then 40 mg/d throughout the remainder of cycle Repeat every 6 wk	Rusthoven JJ, et al. *J Clin Oncol* 1996;14:2083–2090

Regimen	Drug Doses	Reference
Interferon-a2b	Interferon-a2b, 20 MU/m^2/d i.v. qd × 5 of 7 days weekly for 4 wk, then Interferon-a2b, 10 MU/m^2 s.q. 3 × /wk for 48 wk	Kirkwood JM, et al. *J Clin Oncol* 2000;18:2444–2458
Temozolamide	Temozolamide, 200 mg/m^2/d p.o. × 5 d Repeat every 28 d	Middleton MR, et al. *J Clin Oncol* 2000;18:158–166
Multiple myeloma		
M2	Vincristine, 0.03 mg/kg i.v. day 1 Carmustine, 0.5–1 mg i.v. day 1 Cyclophosphamide, 10 mg/kg i.v. day 1 Melphalan, 0.25 mg/kg p.o. days 1–4 or 0.1 mg/kg p.o. days 1–7 or 1–10 Prednisone, 1 mg/kg/d p.o. days 1–7 Repeat cycle every 35 d	Case DC, et al. *Am J Med* 1977;63:897–903
MP	Melphalan, 8 mg/m^2 p.o. days 1–4 Prednisone, 60 mg/m^2 p.o. days 1–4 Repeat cycle every 28 d	Oken MM, et al. *Cancer* 1997;79:1561–1567
VAD	Vincristine, 0.4 mg/d CIVI days 1–4 Doxorubicin, 9 mg/m^2/d CIVI days 1–4 Dexamethasone, 40 mg p.o. q.a.m. days 1–4, 9–12, 17–20 Repeat cycle every 28–35 d	Barlogie B, et al. *N Engl J Med.* 1984;310:1353–1356

Regimen	Drug Doses	Reference
Ovarian		
Altretamine	Altretamine, 260 mg/m^2/d p.o. divided into four doses/day for 14 days of each month	Rustin GJS, et al. *J Clin Oncol* 1997;15:172–176

Carboplatin–Paclitaxel	Paclitaxel, 175 mg/m^2 i.v. over 3 h day 1 followed by carboplatin (AUC 5) day 1 Repeat cycle every 21 d	Neijt JP, et al. *J Clin Oncol* 2000;18:3084–3092
CC	Carboplatin, 300 mg/m^2 i.v. day 1 Cyclophosphamide, 600 mg/m^2 i.v. day 1 Repeat cycle every 4 wk	Alberts DS, et al. *J Clin Oncol* 1992;10:706–717
Cisplatin	Cisplatin, 100 mg/m^2 i.v. day 1 Repeat cycle every 3 wk × 6 cycles	Muggia FM, et al. *J Clin Oncol* 2000;18:106–115
CP	Cyclophosphamide, 750 mg/m^2 i.v. day 1 Cisplatin, 75 mg/m^2 i.v. day 1 Repeat cycle every 28 d	McGuire WP, et al. *N Engl J Med* 1996;334:1–6
DC	Docetaxel, 75 mg/m^2 i.v. over 1 h Carboplatin, (AUC 5) i.v. Repeat every 21 d × 6	Vasey P, et al. *Proc ASCO* 2001;20:A804
Docetaxel	Docetaxel, 100 mg/m^2 i.v. over 1 h Repeat every 3 wk	Verschraegen CR, et al. *J Clin Oncol* 2000;18: 2733–2739
Etoposide p.o.	Etoposide, 50 mg/m^2/d p.o. days 1–21 Repeat every 28 d	Rose PG, et al. *J Clin Oncol* 1998;16:405–410
Gemcitabine	Gemcitabine, 1250 mg/m^2 i.v. over 30 min days 1, 8, 15 of a 28-day cycle	Von Minckwitz G. *Ann Oncol* 1999;10:853–855

Regimen	Drug Doses	Reference
Liposomal Doxorubicin	Liposomal doxorubicin 40 mg/m^2 i.v. Repeat every 21–28 days	Campos SM, et al. *Gynecol Oncol* 2001;81:206–212
Paclitaxel	Paclitaxel, 135 mg/m^2 CIVI over 24 h Repeat every 3 wk	Trimble EL, et al. *J Clin Oncol* 1993;11:2405–2410
PAC	Cisplatin, 50 mg/m^2 i.v. day 1 Doxorubicin, 45 mg/m^2 i.v. day 1 Cyclophosphamide, 600 mg/m^2 i.v. day 1 Repeat every 28 d	Conte PF, et al. *J Clin Oncol* 1991;9:658–663
Topotecan	Topotecan, 1.5 mg/m^2/d i.v. over 30 min, days 1–5 Repeat cycle every 21 d	Brookman MA, et al. *J Clin Oncol* 1998;16:3345–3352
Pancreatic		
FAM	Fluorouracil, 600 mg/m^2 i.v. days 1, 8, 29, 36 Doxorubicin, 30 mg/m^2 i.v. days 1, 29 Mitomycin, 10 mg/m^2 i.v. day 1 Repeat cycle every 8 wk	Smith FP, et al. *Cancer* 1980;46:2014–2018
Gemcitabine	Gemcitabine, 1,000 mg/m^2 i.v. over 30 min once weekly for 7 wk, followed by a 1-wk rest period Subsequent cycles once weekly for 3 consecutive weeks per 4-wk cycle	Burris HA, et al. *J Clin Oncol* 1997;15:2403–2413
SMF	Streptozocin, 1000 mg/m^2 i.v. weeks 1, 2, 5, 6 Mitomycin, 10 mg/m^2 i.v. day 1 Fluorouracil, 600 mg/m^2 i.v. weeks 1, 2, 5, 6 Repeat cycle every 8 wk	Wiggins RG, et al. *Cancer* 1978;41:387–391
Prostate		
Docetaxel	Docetaxel, 75 mg/m^2 i.v. over 1 h Repeat every 21 d	Picus J, et al. *Semin Oncol* 1999;26(5 suppl 7):14–18

Regimen	Drug Doses	Reference
Estramustine–etoposide	Estramustine, 15 mg/kg/d p.o. × 21 d and Etoposide, 50 mg/m^2/d p.o. × 21 d Repeat every 28 d	Clark PE, et al. *Urology* 2001;57:281–285
Mitoxantrone–hydrocortisone	Mitoxantrone, 14 mg/m^2 i.v. q3 wk Hydrocortisone, 30 mg qa.m. and 10 mg qp.m.	Kantoff PW, et al. *J Clin Oncol* 1999;17:2506–2513
Mitoxantrone–prednisone	Mitoxantrone, 12 mg/m^2 i.v. day 1 Prednisone, 5 mg p.o. b.i.d. Repeat cycle every 3 wk	Tannock IF, et al. *J Clin Oncol* 1996;14:1756–1764
PE	Paclitaxel, 120 mg/m^2 CIVI over 96 h Repeat paclitaxel every 21 d Estramustine, 600 mg/m^2/d p.o. in 2–3 divided doses continuously starting 24 h before first paclitaxel Repeat cycle every 21 d	Hudes GR, et al. *J Clin Oncol* 1997;15:3156–3163
TEC	Estramustine, 10 mg/kg/d in divided doses 5 days per week (start 48 h before chemo) Paclitaxel, 60–100 mg/m^2 i.v. weekly over 1 h Carboplatin, (AUC 6) i.v. every 4 wk	Kelly WK, et al. *J Clin Oncol* 2001;19:44–53
Renal cell		
Interferon-a2a–interleukin-2	Interferon-a2a, 6 MU s.q. qd thrice weekly Interleukin-2, 18 MU/m^2/d CIVI × 5 d every 3 wk for two induction cycles and four maintenance cycles	Negrier S, et al. *N Engl J Med* 1998;338:1272–1278
Interferon-a2b	Interferon-a2b s.o. thrice weekly Week 1, 5 MU, 5 MU, 10 MU Weeks 2–11, 10 MU 3 times weekly	Med Res Cncil Renal Cell Coll. *Lancet* 1999;353: 14–17
Sarcoma		
CYVADIC	Doxorubicin, 50 mg/m^2 i.v. day 1 Cyclophosphamide, 500 mg/m^2 i.v. day 1 Dacarbazine, 250 mg/m^2 days 1–5 Vincristine, 1.5 mg/m^2 (max, 2 mg) i.v. days 1, 5 Repeat every 3 wk	Yap B-S, et al. *Cancer Treat Rep* 1980;64:93–98

Regimen	Drug Doses	Reference
CYVADIC	Cyclophosphamide, 500 mg/m^2 i.v. day 1 Vincristine, 1.4 mg/m^2 i.v. day 1 Doxorubicin, 50 mg/m^2 i.v. day 1 Dacarbazine, 400 mg/m^2 days 1–3 Repeat every 28 d	Bramwell V, et al. *J Clin Oncol* 1994;12:1137–1149
DI	Doxorubicin, 50 mg/m^2 i.v. day 1 Ifosfamide, 5000 mg/m^2 CIVI over 24 h after doxorubicin, day 1 Mesna, 600 mg/m^2 i.v. bolus before ifosfamide, then 2500 mg/m^2/d CIVI with ifosfamide, then 1250 mg/m^2 i.v. over 12 h after ifosfamide Repeat every 3 wk	Schutte J, et al. *Cancer Chemother Pharmacol* 1993;31(suppl 2): S204–209

HDMTX	8–12 gm/m^2 i.v. over 4–6 h Leucovorin, 15 mg i.v./p.o. q6 h Repeat weekly	Saeter G, et al. *J Clin Oncol* 1991;9:1766–1775
(M)AID	Mesna, 2500 mg/m^2/d CIVI, days 1–4 Doxorubicin, 15 mg/m^2/d CIVI, days 1–4 Ifosfamide, 2000 mg/m^2/d CIVI, days 1–3 Dacarbazine, 250 mg/m^2/d CIVI, days 1–4 Repeat every 3 wk	Antman K, et al. *J Clin Oncol* 1993;11:1276–1285
Testicular		
BEP	Cisplatin, 20 mg/m^2 i.v. days 1–5 Bleomycin, 30 U i.v. days 2, 9, 16 Etoposide, 100 mg/m^2 i.v. days 1–5 Repeat cycle every 3 weeks × 4	Peckham MJ, et al. *Br J Cancer* 1983;47:613–619
EP	Etoposide, 100 mg/m^2/d i.v. days 1–5 Cisplatin, 20 mg/m^2/d i.v. days 1–5 Repeat cycle every 21 d × 2	Motzer RJ, et al. *J Clin Oncol* 1995;13:2700–2704
PVB	Cisplatin, 20 mg/m^2 i.v. days 1–5 Bleomycin, 30 U i.v. days 2, 9, 16 Vinblastine, 0.15 mg/kg i.v. days 1, 2 Repeat cycle every 3 wk × 4	Williams SD, et al. *N Engl J Med* 1987;316:1435–1440
VIP	Etoposide, 75 mg/m^2/d i.v. days 1–5 Ifosfamide, 1200 mg/m^2/d i.v. days 1–5 Cisplatin, 20 mg/m^2/d i.v. days 1–5 Mesna, 400 mg/m^2 i.v. before ifosfamide, then 1200 mg/d CIVI days 1–5 Repeat cycle every 21 d	Loehrer PJ, et al. *Ann Intern Med* 1988;109:540–546

XRT, radiation therapy; CIVI, continuous intravenous infusion; CR, complete response; IVP, intravenous push.