Oncology in Primary Care

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To the memory of my parents,
Mrs. Sheila Ben-Tuvia and Professor Adam Ben-Tuvia
Michal G. Rose, MD

To Dr. Richard Kaufman
Vincent T. DeVita Jr, MD

To my wife Wendy
Theodore S. Lawrence, MD, PhD

To Alice
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We were inspired to write and edit this book by the growing number of cancer survivors and patients living with cancer who require the long-term management of primary care clinicians (PCCs) and by the absence, until now, of a practical and concise source of information on cancer care aimed specifically at the needs of PCCs.

Our associate editors—Dr. Richard C. Wender from the Department of Family and Community Medicine at Jefferson Medical College, Dr. Kevin C. Oeffinger, the director of the Long-Term Follow-Up Program at Memorial Sloan-Kettering Cancer Center, and Dr. Thomas L. Schwenk, who was the chair of Family Medicine at the University of Michigan for 25 years—provided indispensable advice as we designed this book.

Section I describes the shifting landscape of the epidemiology of cancer and the many roles PCCs play in cancer prevention and care. Section II discusses risk factors for cancer and approaches to cancer prevention. Section III is a comprehensive review of the principles of cancer screening and their applications to the individual cancers. In Section IV, we review the different ways patients with cancer present and the principles of cancer diagnosis and staging. Section V covers the management and treatment of patients with cancer, with an emphasis on symptom control, doctor–patient communication, hospice and palliative care, and the principles of antineoplastic therapy. Section VI is devoted to cancer survivorship and the role of PCCs in the management of the short- and long-term effects of cancer and its therapy. In Section VII, we cover cancers of individual sites, with emphasis on the roles the PCC plays in the diagnosis and management of each type of cancer. Our book also includes a glossary of common cancer-related terms and an annotated list of Internet and community resources for cancer care.

It is our hope that this book will improve communication between you and specialists who treat cancer, support you in your role of promoting cancer screening and prevention, and help you manage patients living with and surviving cancer, to the ultimate benefit of all patients.

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We would like to acknowledge the extraordinary support of Zia Raven in guiding this book from conception to print.

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Cancer Prevention and Care—The Evolving Role of Primary Care
CHAPTER 1

The Role of the Primary Care Clinician in Cancer Prevention and Care

Michal G. Rose, MD • Kevin C. Oeffinger, MD • Richard C. Wender, MD

KEY POINTS

- By promoting a healthy lifestyle, vaccinations, and cancer screening, PCCs play the key role in cancer prevention and early detection.
- Because of the improvement in cancer care and the aging of the population, PCCs are caring for an increasing number of cancer survivors.
- Specialists caring for patients with cancer should provide the patient and his or her PCC with an individualized survivorship plan, which includes information on the cancer and its treatment and a program for future cancer screening, surveillance, and prevention.
- PCCs and specialists must collaborate in multidisciplinary teams to prevent cancer deaths and to deliver high-quality cancer care.

NEW FRONTIERS IN THE WAR AGAINST CANCER

Cancer is the second leading cause of death in the United States and worldwide. One in two American men and one in three American women will develop cancer,1 and the American Cancer Society estimates that 577,190 people will die from cancer in the United States in 2012.2 Age-specific cancer death rates peaked in 1990 for men and in 1991 for women and since then have declined by 22.9% in men and 15.3% in women. Most of this decline in mortality occurred among the most common cancers (lung, breast, colorectal, and prostate) and is attributed to a reduction in smoking (lung), cancer screening (breast, colorectal, and prostate), and improvements in treatment (multiple cancers).1–3

The 5-year overall survival rate for all invasive cancers has increased from 50% in 1975–1977 to 67% in 1999–2005. Survival now exceeds 80% for many common cancers, including breast, prostate, testicular, thyroid, bladder and endometrial cancer, melanoma, and Hodgkin lymphoma.4 In parallel, the number of cancer survivors has quadrupled in the last four decades and now exceeds 12 million.4

Excess weight and lack of physical activity are emerging as major risk factors for cancer in the United States and other industrialized countries.2,3 Globally, the World Health Organization estimates that more than 30% of cancer deaths could be prevented by modifying risk factors alone.5 Vaccinations can prevent hepatitis B–related liver cancer, cervical cancer, and some oropharyngeal cancers; and antibiotics can prevent Helicobacter pylori–related cancers.6 Medications that prevent cancer in high-risk populations, such as tamoxifen, raloxifene, and exemestane for woman at high
PCCs continue to play a major role in the care of their patients during the active treatment phase. More than 90% of primary care physicians caring for patients with lung or colorectal cancer reported that they managed their patients’ pain, depression, and comorbid conditions; helped establish do-not-resuscitate status; and referred patients to hospice.13 More than 50% helped patients determine their treatment preferences and decide about surgery.13 A significant minority were involved in establishing goals of treatment (45.6%), deciding on radiotherapy (33.7%), deciding on chemotherapy (30.2%), and discussing clinical trials (19.3%).13 PCCs want to stay involved while patients are undergoing active cancer treatment but often feel excluded, and communication between PCCs and cancer specialists can be poor.14–18 Lack of engagement by PCCs during the active treatment phase may lessen their ability to support and advise their patients and provide effective survivorship and end-of-life care. Data on patient preferences suggest that patients prefer PCC involvement.14,19

**Cancer Diagnosis and Treatment (Tables 1-2 and 1-3)**

Most patients with symptomatic cancer present to their PCC, who initiates the cancer workup. Available data suggest that

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**TABLE 1-1**

The Roles of the Primary Care Clinician in Cancer Prevention and Early Detection

<table>
<thead>
<tr>
<th>1. Promoting healthy lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Weight control</td>
</tr>
<tr>
<td>b. Smoking cessation</td>
</tr>
<tr>
<td>c. Prevention of excess alcohol consumption</td>
</tr>
<tr>
<td>d. Preventing and treating illicit drug use</td>
</tr>
<tr>
<td>2. Providing cancer-preventing vaccinations</td>
</tr>
<tr>
<td>a. HPV</td>
</tr>
<tr>
<td>b. Hepatitis B</td>
</tr>
<tr>
<td>3. Treating infections (e.g., human immunodeficiency virus, <em>Helicobacter pylori</em>, hepatitis C)</td>
</tr>
<tr>
<td>4. Obtaining a family history and referral to genetic counseling</td>
</tr>
<tr>
<td>5. Ensuring cancer screening</td>
</tr>
<tr>
<td>6. Workup of signs and symptoms of cancer</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus.

---

**TABLE 1-2**

Potential Roles of the Primary Care Clinician in the Cancer Diagnosis Process

<table>
<thead>
<tr>
<th>1. Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cancers found by screening</td>
</tr>
<tr>
<td>b. Cancers found by workup of signs/symptoms</td>
</tr>
<tr>
<td>c. Incidentally found cancers</td>
</tr>
<tr>
<td>2. Delivering news</td>
</tr>
<tr>
<td>3. Staging</td>
</tr>
<tr>
<td>4. Coordination of care among specialists</td>
</tr>
</tbody>
</table>

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**TABLE 1-3**

Potential Roles of the Primary Care Clinician in the Active Cancer Management Phase

| 1. Managing side effects of antineoplastic drugs |
| 2. Administering antineoplastic drugs (usually oral agents) |
| 3. Promoting participation in clinical trials |
| 4. Pain management |
| 5. Assisting in treatment decisions |
| 6. Coordinating among specialists |
| 7. Providing psychosocial support |
| 8. Providing hospice/terminal care |

---

**Cancer Prevention and Screening (Table 1-1)**

Public health– and primary care–based interventions aimed at reducing smoking and promoting screening for breast, colorectal, and prostate cancer contributed significantly to the decrease in cancer mortality seen since 1990/1991. The single most important intervention in smoking cessation is counseling from a PCC,3 and the most important predictor of whether or not a patient has a cancer screening test done is whether his or her PCC recommended it.9–11 PCCs also play a key role in counseling patients about weight and nutrition. Nevertheless, much remains to be done. In 2012, 173,000 Americans will die from cancer caused by tobacco use; and excess weight, physical inactivity, and/or poor nutrition will lead to a similar number of cancer deaths.2 The 2000 National Health Interview Survey demonstrated that, although screening rates have improved in the United States, major disparities remain, and rates are especially low for people without a PCC (no “usual source of care”), the uninsured, and recent immigrants.12

---

**TABLE 1-4**

Primary Care Clinicians and Survivorship Care (Table 1-4)

As the number of long-term survivors has increased, awareness has grown that many survivors will develop health conditions secondary to their cancer therapy.20–23 Some of these conditions, such as chemotherapy-induced renal risk for breast cancer,7 are now available. At least half of all new cancer cases can be prevented or detected earlier by screening.7 The human genome project is rapidly expanding our knowledge of cancer genetic syndromes and paving the way for more personalized cancer prevention and treatment strategies.
Many patients are now living for years while receiving one or more of our rapidly growing arsenal of antineoplastic agents. Between July 2005 and December 2007, the Office of Oncology Drug Products of the U.S. Food and Drug Administration (FDA) approved 53 new indications for cancer care, 18 of which were new molecular entities.28 Many of the newer agents are oral, require less frequent visits to an oncologist, and are associated with a host of side effects that are traditionally managed by PCCs, such as hypertension, hyperlipidemia, and osteoporosis.

PCCs will play an increasingly important role in ensuring that the individual patient benefits from this progress (Table 1-5). The patient-centered medical home, with its emphasis on integrated care, care teams, accountability, and quality of care, may facilitate the expanded role of the PCC in cancer prevention and care.29,30 Community outreach programs, which promote healthy lifestyles, cancer screening, and vaccinations, are usually run by PCCs; and PCCs will be instrumental in helping patients overcome cultural, racial, and psychosocial barriers to cancer prevention and care.

### TABLE 1-4 Potential Roles of the Primary Care Clinician in Survivorship Care

| 1. | Surveillance for cancer recurrence |
| 2. | Screening for second and subsequent primary cancers |
| 3. | Screening for and managing physical and psychosocial late effects of cancer therapy |
| 4. | Counseling and psychological support |
| 5. | Prevention-focused education |
| 6. | Referral for specialized survivorship services (e.g., lymphedema program, cancer rehabilitation) |

### TABLE 1-5 Reasons for the Increasing Role of the Primary Care Clinician in Cancer Prevention and Care

| 1. | Increase in the prevalence of cancer |
| 2. | Expanding role for cancer prevention (e.g., obesity prevention/treatment) |
| 3. | Expanding role for cancer screening (e.g., lung) |
| 4. | Availability of cancer-preventing vaccines (e.g., hepatitis B, human papillomavirus) |
| 5. | Increasing knowledge of cancer genetic syndromes |
| 6. | Increased availability of medications that prevent cancer |
| 7. | More oral anticancer agents |
| 8. | More anticancer agents with metabolic and systemic effects requiring management by primary care: |
| 9. | Predicted shortage of specialists |
| 10. | Financial concerns (specialists are more expensive) |

### THE PRIMARY CARE CLINICIAN AND THE FUTURE OF CANCER PREVENTION AND CARE

Cancer is largely a disease of the elderly; and the aging of the population, coupled with improved cancer treatment, are resulting in an increase in the burden of cancer care. The number of people living with a cancer diagnosis is predicted to increase from 13.8 million in 2010 to 18.1 million in 2020.26 The direct cost of cancer care is expected to increase 39% during this period, from an estimated $124.5 billion to $172.8 billion,26 with a parallel increase in indirect costs, such as lost productivity of patients and their caregivers and premature death.27

Many patients are now living for years while receiving one or more of our rapidly growing arsenal of antineoplastic agents, such as lost productivity of patients and their caregivers and premature death.27
defining the optimal roles of the disciplines in cancer prevention, treatment, and surveillance across the continuum of care and in the different health care settings.\textsuperscript{18,33} Lack of adequate insurance coverage for coordination of care and creation of survivorship plans continues to discourage both PCCs and specialists from adopting practice patterns that better reflect the needs of patients with cancer. Finally, cancer specialists must learn to communicate more effectively with their primary care colleagues to align care goals for individual patients, and PCCs need more sources of up-to-date information.

\section*{CONCLUSION}

A health care system that strives to eliminate premature cancer deaths and deliver high-quality cancer care must be based on a foundation of high-performing PCCs working with and within multidisciplinary teams. Success in the cancer battlefield has created new challenges and responsibilities for all members of these teams. More is at stake now that we are better able to prevent, cure, and treat patients with cancer. We cannot make these accomplishments available to patients if PCCs and specialists work in silos. What is called for is a coordinated, concerted effort by all disciplines to empower the PCC to deliver the benefits of this progress to the patient.

\section*{References}


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Cancer is a leading cause of death in the United States and other economically developed countries. It is also becoming a major health problem in economically developing countries because of the growth and aging of the population and marketing-driven adoption of unhealthy lifestyle, such as smoking tobacco and the consumption of calorie dense food and alcohol. Both because of the increase in cancer risk in developing countries and because of the aging of the population caused by control of communicable diseases, there are now more deaths in the world each year from cancer than from the sum of HIV, malaria, tuberculosis, and childhood diarrhea combined.¹ The United Nations has recently highlighted the importance of prevention and management of noncommunicable diseases such as cancer as a global challenge in both humanitarian and economic terms.²

Cancer risk (incidence and mortality rates) varies substantially according to many avoidable causes of cancer and also across different regions of the world.³ Although the reasons for this geographic variation are not all known, the observation that cancer risk tends to change after migration to approximate that of the new host country after only one or two generations tells us that the international variation is not largely genetically determined.⁴ Factors in people’s everyday lives, including their use of tobacco, the qualities of foods they eat, infections they acquire, and their other habits, are the main determinants of cancer risk.⁵ For tobacco and nutritional factors, variation in exposures across different countries determines the variation in risk rather than any differences in the effects of risk factors across regions.⁶,⁷ There are some unique local and regional factors that affect cancer risk, such as food storage or preservation methods or high prevalence of particular cancer-causing infections.

This chapter highlights what is known about the causes of cancer and the ways in which primary health care clinicians can help patients either reduce their cancer risk or diagnose cancers at earlier, more curable stages. Because we live in an increasingly global culture, this chapter also describes some of the more common variations in cancer risk across the world and comments on factors clinicians in the United States should be aware of to assist patients who have immigrated from elsewhere about cancer prevention, screening, and early detection.
**SOURCES OF INFORMATION ABOUT CANCER**

Most economically developed countries have reliable data systems for monitoring deaths by cause and for estimating cancer incidence. In the United States, cancer is a reportable disease, so each state monitors and tracks cancer incidence trends. In addition, the Surveillance Epidemiology and End Results (SEER) system of cancer registries, funded by the National Cancer Institute, provides high-quality surveillance data on cancer incidence, treatment, and outcomes. However, such data systems are often incomplete in developing countries. The International Agency for Research on Cancer (IARC) has been working with all nations for many years to provide more reliable and comprehensive estimates of cancer incidence and mortality. IARC produces estimates of cancer incidence and mortality for all regions of the world. For many developing countries, those estimates are derived from extrapolations from information collected in only some localities, from nearby countries, and/or from mathematical modeling. The most recent comprehensive set of global cancer estimates (GLOBOCAN 2008) was the primary source of information on global cancers for this chapter. Because age structures vary substantially across countries and cancer risk varies with age, age-standardized rates (standardized to the 1960 world population) are used for comparisons across countries and regions. For gender-specific reproductive sites, only the gender-specific rates were used. Comparisons highlighted here are for the United States, the sum of the less developed regions (Africa, Middle East, Eastern Asia, Southeastern Asia, and Western Pacific regions), and specific regions that are “hot spots,” where cancer incidence is more than three times higher than in the United States.

### Table 2-1: Cancer Incidence and Mortality Rates in the United States as Compared to the Less Developed Regions of the World and Global Hot Spots for Selected Cancer Sites in 2008

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>United States</th>
<th>Less Developed Regions</th>
<th>United States</th>
<th>Less Developed Regions</th>
<th>Global “Hot Spots”</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>300.2</td>
<td>146.8</td>
<td>104.1</td>
<td>100.6</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>42.1</td>
<td>19.0</td>
<td>30.4</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>76.0</td>
<td>27.1</td>
<td>14.7</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Colorectum</td>
<td>29.2</td>
<td>10.7</td>
<td>8.8</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>4.1</td>
<td>15.2</td>
<td>2.0</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>83.8</td>
<td>11.9</td>
<td>9.7</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>4.5</td>
<td>13.0</td>
<td>3.6</td>
<td>12.1</td>
<td>Asia &amp; Western Pacific (5x), Africa (3x)</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>5.7</td>
<td>17.7</td>
<td>1.7</td>
<td>9.7</td>
<td>Africa (5x), Southeastern Asia (4x)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3.3</td>
<td>8.6</td>
<td>2.8</td>
<td>7.3</td>
<td>Asia &amp; Western Pacific (4x), South &amp; East Africa (3x)</td>
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<tr>
<td>Bladder</td>
<td>12.7</td>
<td>3.3</td>
<td>2.2</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>9.9</td>
<td>4.0</td>
<td>4.0</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>13.7</td>
<td>3.5</td>
<td>3.3</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>2.4</td>
<td>0.7</td>
<td>0.3</td>
<td>0.5</td>
<td></td>
</tr>
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<td>Multiple myeloma</td>
<td>3.8</td>
<td>0.8</td>
<td>1.9</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>16.5</td>
<td>5.9</td>
<td>2.5</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>8.8</td>
<td>4.9</td>
<td>5.4</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>7.0</td>
<td>2.4</td>
<td>6.2</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>12.2</td>
<td>1.9</td>
<td>2.6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Lip, oral cavity</td>
<td>5.0</td>
<td>3.6</td>
<td>0.7</td>
<td>2.0</td>
<td>Melanesia (3x)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>0.5</td>
<td>1.5</td>
<td>0.1</td>
<td>1.0</td>
<td>Asia &amp; Western Pacific (4x), South &amp; East Africa (3x)</td>
</tr>
<tr>
<td>Other pharynx</td>
<td>2.3</td>
<td>1.9</td>
<td>0.6</td>
<td>1.5</td>
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</tbody>
</table>

*Table 2-1 summarizies cancer incidence and mortality rates for the United States, the less developed regions of the world, and...*
hot spot regions (where cancer incidence exceeds US rates by more than threefold) for selected cancers. The age-adjusted death rates for all cancers are remarkably similar between the United States and the less developed regions of the world, but the incidence rates are about twice as high in the United States. One factor that increases incidence without affecting mortality is the phenomenon of “overdiagnosis,” which is the problem of the identification of cancers by screening tests when those cancers would never have become clinically manifest in the patient’s lifetime. Another factor is that in developing countries, the diagnostic methods are less sensitive for some cancers, so the site of origin can be difficult to determine without advanced imaging studies. Hence, cancer incidence and mortality in less developed regions can be misclassified for some sites, and overall rates can be underestimated. For cancer sites amenable to screening and treatment, lack of screening services and low availability of state-of-the-art therapies in less developed regions contribute to poorer survival and hence to their relatively higher mortality rates. Figure 2-1 displays the estimated numbers of newly diagnosed cancers and cancer deaths for the leading cancer sites for the United States and the world in 2008.

Figure 2-2 summarizes the trends in cancer mortality by gender for selected cancer sites in the United States over the past 80 years. There are several mortality trends that are noteworthy. Clearly, deaths from lung cancer follow the trends in tobacco use by US men and women. The persistently declining trends in stomach cancer mortality are not totally explained but are likely due principally to improved living conditions and declining *Helicobacter pylori* chronic infection. Cervical cancer declines are likely caused by increased screening and prevention by treatment of cervical dysplasia. Those and other cancer trends will be discussed in more detail in sections that follow. The combined effects of international differences in risk factors and screening result in considerable international variation in the leading cancer sites.


<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Incidence (1,000s)</th>
<th>Mortality (1,000s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>250</td>
<td>200</td>
</tr>
<tr>
<td>The World</td>
<td>0</td>
<td>500</td>
</tr>
</tbody>
</table>


- **Males**
  - Stomach: 100
  - Lung & bronchus: 80
  - Prostate: 60
  - Liver: 40
  - Colon & rectum: 20

- **Females**
  - Breast: 100
  - Uterus: 90
  - Lung & bronchus: 70
  - Stomach: 60
  - Colon & rectum: 40
across different countries. Figure 2-3 displays the leading cancer sites for men and women in different countries.

**Lung and Larynx Cancers**

In the United States, there are more deaths from lung cancer than from the sum of all cancers of the breast, prostate, and colorectum. Lung cancer is by far the leading site for cancer deaths in US women as well as men. Tobacco is the single leading cause of cancer in the United States and worldwide. In countries such as the United States and other developed nations where the tobacco epidemic began earlier and tobacco control has been a public health priority in recent decades, lung cancer rates are now declining; but in several other parts of the world, where the tobacco epidemic began latter or is still growing, lung cancer rates are increasing. Tobacco cessation
is clearly the single most important clinical service that can be offered to smokers. Screening using low-dose spiral CT has been shown to reduce risk of lung cancer mortality in current smokers and former smokers ages 55 to 74 years, who have at least a 30 pack-year history of tobacco use. Although the risks and benefits of such screening are not yet fully understood, for patients at high risk for lung cancer, early detection by this method has shown promise.

Breast Cancer

There are many known factors that contribute to breast cancer risk, including parity, the ages of menarche, menopause, and first pregnancy; the use of hormone replacement therapies and alcohol; obesity and physical activity; and family cancer history. In the United States, about 5% of breast cancer is caused by familial genetic factors that have been identified and are testable. Breast cancer incidence rates are decreasing or stabilizing in the United States and in several western countries such as Australia and the United Kingdom largely because of reduction in the use of postmenopausal hormone therapy and decreases in the number of prevalent cases detected following mammography saturation. In contrast, incidence rates are increasing in several low- and middle-income countries likely because of higher prevalence reproductive factors (late childbearing, having fewer children), physical inactivity, and obesity. Despite this, global variation in breast cancer incidence rates remains very large and seems to follow predictable patterns of higher rates in regions with lower parity, later age at first pregnancy, higher use of hormone replacement therapies, obesity, and higher use of mammography (Fig. 2-4). Mammography contributes to higher incidence because of its inherent problem of some degree of overdiagnosis. Women who migrate from low-incidence countries to the United States tend to adopt the higher US risks within a generation. All women, regardless of migration status, should be counseled about breast cancer risk factors and should be offered clinical breast exams and mammograms at least every other year beginning at age 40 years.

Colorectal Cancer

Colorectal cancer mortality rates have been declining in the United States for more than 50 years (see Fig. 2-2). The reasons for this long-term trend are not all known, but several factors seem to be contributing, including improved surgical treatment, earlier detection, nutritional improvement, less tobacco use, and the use of some medications such as nonsteroidal anti-inflammatory drugs and hormone replacement therapies, which have been shown to reduce risk. Obesity and lack of physical activity are now established risk factors for colorectal cancers, and these were in part thought to contribute to the rapidly increasing incidence rates in several European and Asian countries. The incidence of colorectal cancer is lower in less developed regions, but the mortality rates are more similar to those in the United States (see Table 2-1). Internationally, there are no particular hot spots for colorectal cancer. Migrant studies show that colorectal cancer risk increases rapidly after people migrate from low-risk to high-risk countries.

Colorectal cancer risk can be reduced by weight control and physical activity; but the most important fact to remember is that regardless of other risk factors, most colorectal cancer can be prevented by finding and removing colorectal adenomas. Colorectal screening beginning at age 50 years (or earlier if a strong family history) should be offered to everyone regardless of their risk factors or immigration status.

Stomach Cancer

Stomach cancer was the leading site for cancer deaths among US men 80 years ago, but both the incidence and mortality rates have been persistently declining since then (see Fig. 2-2).
The reasons for this persistent decline are not all known but are thought to be caused by improvements in nutrition and to declines in chronic gastric infections with *H. pylori* because of general improvements in hygiene. Stomach cancer incidence and mortality rates are three times higher in less developed parts of the world than in the United States. Stomach cancer rates are especially high in Asia and South America, so immigrants from these areas should be carefully evaluated for any chronic upper gastrointestinal (GI) symptoms that are not relieved by symptom-directed therapies.

**Prostate Cancer**
Prostate-specific antigen (PSA) screening explains the large variation in prostate cancer incidence over time and by region in the past 25 years. There is currently mixed evidence that routine screening of asymptomatic men using PSA testing will substantially reduce their risk of death from prostate cancer because an ongoing US trial is null and an ongoing European trial shows modest benefits. The U.S. Preventive Services Task Force has recommended against PSA screening based on the small benefits as compared to the documents hazards. Clearly, some men are at increased risk for this disease, such as men of African descent. Death rates from prostate cancer among men in West Africa are quite similar to those of African American men in the United States.

**Liver Cancer**
Hepatocellular cancer is caused by chronic damage to the liver by either alcohol or viruses. There is a severalfold difference in liver cancer incidence and mortality across different regions of the world. The largest reason for this variation is regional differences in chronic infection with hepatitis viruses B and C. Rates of hepatocellular cancer are now beginning to drop in countries that have implemented hepatitis B immunization programs. Immigrants from Africa, Asia, and the Western Pacific basin countries have a high likelihood of bearing chronic hepatitis B infection and hence high lifetime risk of liver cancer. In the United States, liver cancer incidence rates among Asian Americans are nearly three times as high as among Whites, so any signs or symptoms of liver disease should be carefully evaluated for liver cancer in this population.

**Cervical Cancer**
Among US women, cervical cancer was a leading cause of cancer death 80 years ago, but it is now rare (see Fig. 2-2). This historic progress has been caused by use of cervical cytology (Pap smears) for diagnosing early premalignant cervical lesions. In some parts of the world, Pap testing is not available, so cervical cancer is still the most commonly diagnosed cancer and the leading cause of cancer mortality among women, exceeding the rates of breast cancer. We now know that the major factor causing cervical cancer is chronic infection with human papillomaviruses (HPVs). The discovery of vaccines that prevent infection by about 70% of the HPV serotypes that cause cervical cancer promises to substantially reduce the burden of cervical cancer worldwide in the future, but population penetration by the vaccine is slowed by its high cost. The effects of HPV vaccination on cervical cancer incidence will not be seen until the distant future because the vaccine is only effective when delivered before sexual activity begins, and cervical cancer deaths typically occur decades later. All women, regardless of immigration status, should be offered Pap testing every 3 years; and during the decade of ages 30 to 39 years, ancillary testing for chronic HPV infection can provide additional information about future cervical cancer risk.

**Esophageal Cancer**
Esophageal cancers are caused by tobacco use and by chronic inflammation because of acid reflux. There are two counterbalancing trends in the United States in esophageal cancer: Incidence rates are decreasing for the squamous cell esophageal cancers (those that tend to occur mostly in the upper half of the esophagus) because of reduction in tobacco smoking, whereas the rates are increasing for adenocarcinomas (those that tend to occur mostly in the lower half of the esophagus) in part because of acid reflux tied to the obesity epidemic. Both incidence and mortality are substantially higher for esophageal cancer in less developed regions of the world. Micronutrient deficiencies seem to play some role in this risk, as does the ingestion of very hot beverages, but the full explanation remains unknown. In some parts of China, esophageal cancer risk is high enough that population-wide screening using upper GI endoscopy and cytology have been developed. Immigrants from Asia should be carefully evaluated for any symptoms of esophageal dysfunction.

**Uterine Corpus and Ovarian Cancers**
The major factors explaining variations in endometrial cancer risk are the use of estrogen as hormone replacement therapy and obesity (which increases circulating estrogens in postmenopausal women). Consequently, incidence rates are highest in developed countries such as the United States. All women, regardless of immigration status, who present with unexplained menstrual bleeding after the menopause should be properly examined for endometrial cancer. For ovarian cancer, there is not much international variation, and there are no early detection methods that have been shown to reduce mortality. However, a substantial proportion of ovarian cancers seems to be attributable to inherited mutations in BRCA1 or BRCA2 genes, so careful attention to family cancer history can identify BRCA1 or BRCA2 mutation carriers, who can be counseled about the advantages of prophylactic oophorectomy after they have completed their planned pregnancies.

**Pancreatic Cancer**
Little is known about the causes of pancreatic cancer, although nutritional factors such as fruit and vegetable intake and obesity seem to play small roles. Pancreatic cancer incidence and mortality rates in the United States are increasing in both men and women maybe in part because of the increase in obesity prevalence over the past decades. Incidence and mortality rates are lower in less developed regions. This difference is probably in part explainable by the difficulty to diagnose this cancer. Without advanced imaging methods, it is likely that some pancreatic cancers will be misclassified as other cancers of the abdomen. At this time, there is no known screening or clinical preventive measure for pancreatic cancer control.

**Head and Neck Cancers**
Oral and pharyngeal cancers are about as common in the United States as in less developed countries, but death rates
are higher in less developed regions. In the United States, these cancers are caused mostly by three factors: tobacco, alcohol, and chronic infection with HPV. The US trends for these cancers are not remarkable over the past 20 years, but, in fact, there are two dynamic counterbalancing underlying trends underway. Cancers caused by tobacco are declining because of the reductions in tobacco use, and cancers caused by HPV are increasing. For some forms of these cancers and for some particular exposures, risk is substantially higher in some regions of the world. Nasopharyngeal cancers (NPC) are particularly common in Asia, Africa, and the Western Pacific basin countries where incidence rates are about four times those seen in the United States. This high risk is thought to be caused by the combined effects of chronic Epstein-Barr virus infections and consumption of salt-preserved food. Immigrants from this region with symptoms consistent with NPC should be carefully evaluated. Oral cancers are about twice as high in Central and Eastern Europe as in the United States, because of the combined effects of tobacco and alcohol, and in India, where the practice of betel quid chewing leads some to high risk for oral cancers. Immigrants from Eastern Europe or India with a history of such habits should be carefully examined for oral premalignant or malignant lesions.

Other Cancers

There is little variation across regions of the world in the hematologic malignancies, and little is known about either the causes or any benefits of early detection for hematologic cancers. Rates of incidence of gall bladder cancer are particularly high among women in Chile for reasons that are not known. In fact, gall bladder cancer is the leading cancer site among women in Chile despite it being one of the rare cancers in the United States. Burkitt lymphoma continues to be common in parts of Africa, as is Kaposi sarcoma as an HIV-related malignancy. Among the urologic malignancies, international variations in kidney cancer correspond to variations in obesity rates, and international variations in bladder cancer correspond to variations in tobacco use. There have been historic high levels of bladder cancer in Egypt caused by chronic infection with schistosomiasis, but that epidemic of infection has now been substantially controlled.

Summary

In the United States, the incidence and mortality rates from the leading cancer sites (lung, breast, prostate, and colorectum) have been declining for the past 20 years because of reductions in risk, early detection, and improved treatments. Cancer rates vary considerably around the world, however, because risk factors vary and clinical practices of screening and treatment vary. Because cancer risk changes with migration, it is clear that factors in the environment—including nutrition, physical activity, and exposures to tobacco, alcohol, infections, and other carcinogens—explain the large geographic variation in cancer. Immigrants to the United States will carry lifelong higher risk for many cancers uncommon to the United States, so they will need to be assessed carefully when they present with symptoms of cancers that are common in their country of origin. Conversely, none of the screen-detected cancers (cervix, breast, colorectal) in the United States is rare enough among immigrants to justify their not being recommended for screening.

References


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Cancer Risk Factors and Prevention
The primary care clinician (PCC) is well versed in eliciting a personal and family history from patients and counseling them on how this history should guide their lifestyle choices and medical management. This, combined with a thorough physical examination, could perhaps be described as cornerstones of primary care throughout history. For many decades, clinicians have used family patterns of cancer to estimate their patients’ risks of developing cancer. Whether they knew it or not, they were performing a rudimentary form of genetic risk assessment.

We can do better now. The past 15 years have brought the addition of diagnostic genetic testing to the cancer risk assessment equation. Instead of simply estimating a patient’s risk based on family history alone, we can offer DNA testing to determine if he or she actually carries a disease-causing mutation in a cancer gene. Genetic testing has evolved from an infrequently used tool for rare genetic conditions to a commonly used instrument for patients with strong personal and/or family histories of cancer.

What is the PCC’s role in genetic risk assessment, counseling, and testing? Realistically, with an average of 18 to 19 minutes per patient in which to complete a physical examination and full patient encounter, it is both unrealistic and unfair to expect the already overburdened PCC to take on the complex role of cancer genetic counseling and testing.\(^1,2\) In addition to lack of time, PCCs do not have the education, training, or certification to take on this detailed and ever-evolving subspecialty.\(^3-5\)

Genetic testing company sales representatives, with strong financial incentives to push sales kits, encourage clinicians without formal training to order their own testing. The testing company offers these clinicians “in-house” training, but such training is not considered adequate for cancer risk assessment and genetic counseling.\(^6\) Unfortunately, for the well-meaning clinicians who take on the responsibility of ordering genetic testing, the legal liability is great. Serious, life-threatening errors have resulted from clinicians without the proper training and credentials practicing genetic counseling and testing, medical malpractice claims have been filed, and the number of lawsuits these clinicians will face is likely to mushroom as the field grows.\(^7-9\)

**KEY POINTS**

- Primary care clinicians (PCCs) are ideally suited to elicit a detailed cancer family history from their patients.
- PCCs should know the risk factors that increase hereditary cancer risk and refer patients who appear to be at increased risk to a cancer genetic counselor.
- PCCs can play a key role in referring patients for genetic services and helping them follow resulting surveillance and risk reduction recommendations.
- National screening and risk reduction guidelines are established for most hereditary cancer syndromes.
and most do not feel confident in taking a detailed family history.15,16

PCCs may be able to screen for strong cancer histories by having all patients complete a family history worksheet at each visit. Shown here is a simple worksheet that can be used to assess hereditary breast, ovarian, uterine, and colon cancer risk (Table 3-1). The information gathered here would make it possible to broadly assess if that patient requires a referral for cancer genetic counseling. It is especially important to keep in mind that paternal and maternal family histories count equally in risk assessment. However, many patients will not offer a paternal family history of breast cancer, for example, unless asked because they believe breast cancer risk can only be passed down via their mother. Clinicians are also more likely to erroneously underestimate breast cancer risk if the pertinent history is paternal.17

Patients are frequently not aware that clusters of cancers (e.g., breast/ovary/pancreas or colon/uterine/ovary/sebaceous adenomas and carcinomas) can be caused by a single gene mutation. Therefore, when one cancer is reported, the PCC should rule out related primary sites with the patient. Determining whether the patient is of Jewish ancestry is also critical in assessing hereditary breast and ovarian cancer risk. Ancestry should not be assumed based on surname, skin color, or religion practiced but must be asked of every patient.

Clinicians must be aware of several factors that can falsly lower a patient’s risk assessment. These include a small family or little family history knowledge because of poor communication, estrangement or adoption, close family members who died early of other causes, and family members who altered their cancer risks artificially (e.g., total hysterectomies at young ages, which reduces the risk of ovarian, uterine, and breast cancers). The family history also changes over time and must be updated at each visit.

It is common for patients to have vague, or very little, information about their family history. The PCC can coach patients to research their family histories through interviews with other family elders or historians, death certificates, medical records, and by searching out relatives through social networking tools (e.g., Facebook) and computer-based tools created specifically for this purpose.18–20 Key questions to answer include which family members developed cancer, the primary site of those cancers, and the ages of diagnosis. Pathology reports should be collected whenever possible to verify diagnoses because it is well known that patient report of primary site is often inaccurate.21

If any family members have had genetic testing, the patient should request a copy of the actual genetic test results from the laboratory. It is quite common for patients (and clinicians) to mistakenly interpret the meaning of genetic test results.

Note: A check mark next to any of the above should prompt the consideration of genetic counseling. If your patient reports a family history, ideally the affected family member should be seen by a genetics professional first.


CANCER RISK ASSESSMENT

Accurate risk assessment may appear simple, but it is a complicated and rapidly evolving undertaking. One study showed that PCCs have high levels of confidence in assessing breast cancer risk, although almost half (48%) incorrectly assigned a high-risk categorization to a low-risk breast cancer scenario.22 Another study showed that the minority (19%) of PCCs was able to select all of the increased risk and none of the low-risk scenarios described for possible BRCA1 and BRCA2 testing.23

There are many risk models available for assessing risk in a family.24–27 Some of these models assess the risk that the patient will develop cancer and others the risk that the patient carries a genetic mutation. At first glance, many of these models appear simple and easy to use, and it may be tempting to rely on these models, exclusively, to assess cancer risk in your patient population. However, each of these models has limitations that make it impossible to use in every situation. Clinicians who choose to rely on these models need to understand the limitations well and know which are validated, which are

### TABLE 3-1 Cancer History Checklist

<table>
<thead>
<tr>
<th>Personal History</th>
<th>Family History</th>
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<tbody>
<tr>
<td>Breast cancer diagnosed by age 60 y or a breast cancer that is “triple negative” (estrogen, progesterone, and HER2 negative).</td>
<td></td>
</tr>
<tr>
<td>Colon, uterine, or pancreatic cancer diagnosed younger than age of 50 y.</td>
<td></td>
</tr>
<tr>
<td>Ovarian/fallopian tube cancer or male breast cancer diagnosed at any age.</td>
<td></td>
</tr>
<tr>
<td>The following cancers diagnosed on the same side of the family (colon/uterine/ovarian; breast/ovarian/pancreatic/melanoma; or colon polyposis/colon cancer).</td>
<td></td>
</tr>
<tr>
<td>Jewish ancestry in combination with a history of breast, ovarian, or pancreatic cancer diagnosed at any age.</td>
<td></td>
</tr>
<tr>
<td>Greater than 15 colon or GI polyps or &gt;5 hamartomatous or juvenile polyps.</td>
<td></td>
</tr>
<tr>
<td>Known genetic mutation (e.g., BRCA, MLH1, RET, p16) or syndrome.</td>
<td></td>
</tr>
<tr>
<td>You are concerned about your personal/family history of cancer.</td>
<td></td>
</tr>
</tbody>
</table>

Patient Name: ____________________________ Patient DOB: ____________________________ Date Completed: ____________________________

Note: A check mark next to any of the above should prompt the consideration of genetic counseling. If your patient reports a family history, ideally the affected family member should be seen by a genetics professional first.
considered problematic, when a model will not work on a particular patient, or when another genetic syndrome should be considered. This is complicated. It may be easier and more accurate for the PCC to know the risk factors that increase hereditary cancer risk (Table 3-2), ask these questions and refer patients who appear to be at increased risk to a qualified genetic counselor. A list of the hereditary cancer syndromes to be considered during the cancer genetic counseling evaluation is listed in Table 3-3.

**GENETIC COUNSELING AND TESTING**

Most (91%) PCCs agree with national recommendations that patients should not undergo testing unless they obtain counseling about the risks, benefits, and consequences of the test. However, one study showed that 30% of PCCs had ordered their own genetic testing in the past year. This may be, in part, caused by the aggressive marketing by genetic testing companies. The commissions from these tests go to the sales representatives, but, unfortunately, the medical and legal liability lies solely with the PCC. This is concerning not only because risk assessment has been shown to widely be inaccurate but also because many clinicians have inaccurate information regarding health insurance coverage for testing, cancer risk in those who test positive, guidelines for managing a mutation-positive patient, and risks of genetic discrimination. Interestingly, patients do not expect their PCCs to be experts in genetics but to play a key role in referring them for genetic services.

A safer, easier, and more efficient approach is for the PCC to choose which of his or her patients need formal risk assessment and counseling and to refer them to a certified genetic counselor. There are many ways to find a genetic counselor (Table 3-4). In the past, referral to a genetic counselor was greatly dependent on whether the physician was within a 10-mile radius of a genetic counselor. Not only are there many more American Board of Genetic Counseling (ABGC)–certified genetic counselors practicing in the

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**TABLE 3-2** Risks Factors That Warrant Genetic Counseling for Hereditary Cancer Syndromes

1. Early age of onset (e.g., younger than age 50 y for breast, colon, and uterine cancer)
2. Multiple family members on the same side of the pedigree with the same cancer
3. Clustering of cancers in the family known to be caused by a single gene mutation (e.g., breast/ovarian/pancreatic; colon/uterine/ovarian; colon cancer/polyps)
4. Multiple primary cancers in one individual (e.g., breast/ovarian cancer or colon/uterine/ovarian)
5. Ethnicity (e.g., Jewish ancestry for breast/ovarian cancer syndrome)
6. Unusual presentation (e.g., breast cancer in a male, even one sebaceous carcinoma or adenoma, >15 polyps)
7. Pathology (e.g., triple negative [ER/PR/Her2] breast cancer <60 and medullary breast cancer are overrepresented in women with hereditary breast and ovarian cancer, a colon tumor with an abnormal microsatellite instability [MSI] or immunohistochemistry [IHC] result increases the risk for a hereditary colon cancer syndrome)

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**TABLE 3-3** Cancer Genetic Syndromes Considered in a Genetic Counseling Evaluation, Selected

- Ataxia telangiectasia
- Birt-Hogg-Dubé syndrome
- Cowden syndrome
- Familial adenomatous polyposis (FAP)
- Familial melanoma
- Familial paraganglioma syndrome
- Fanconi anemia
- Gorlin syndrome (nevoid basal cell carcinoma syndrome)
- Hereditary breast and ovarian cancer syndrome (BRCA1, BRCA2)
- Hereditary diffuse gastric cancer
- Hereditary leiomyomatosis and renal cell carcinoma
- Hereditary papillary cell carcinoma
- Hyperparathyroidism-jaw tumor syndrome
- Juvenile polyposis syndrome
- Li-Fraumeni syndrome
- Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC])
- Multiple endocrine neoplasia type 1
- Multiple endocrine neoplasia type 2
- MUTYH-associated polyposis
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Peutz-Jeghers syndrome
- Retinoblastoma
- von Hippel-Lindau (VHL)

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**TABLE 3-4** How to Find a Genetic Counselor for Your Patient

**GeneTests**

- gtcclinical@uwashington.edu
- A listing of US and international genetics clinics providing evaluation and genetic counseling.

**Informed Medical Decisions**

- [www.informeddna.com—(800) 975-4819](http://www.informeddna.com)
- Nationwide network of independent genetic counselors that use telephone and Internet technology to bring genetic counseling to patients and providers; covered by many insurance companies.

**National Society of Genetic Counselors**

- [www.nsgc.org—click “Find a Counselor” button—(312) 321-6834](http://www.nsgc.org)
- For a listing of genetic counselors in your area who specialize in cancer.

**NCI Cancer Genetics Services Directory**

- [www.cancer.gov/cancertopics/genetics/directory—(800) 4-CANCER](http://www.cancer.gov/cancertopics/genetics/directory)
- A free service designed to locate providers of cancer risk counseling and testing services.
United States—many of whom have outreach clinics—but there are also services available by telephone, which are largely covered by health insurance companies. Therefore, cancer genetic counseling services are now available to almost everyone.

**TEST INTERPRETATION**

When genetic testing hit the marketplace in the mid-1990s, the greatest concerns in the medical community had to do with the psychological and health insurance ramifications associated with such testing. Ironically, the risk that has proven the most problematic is the chance that the wrong genetic test is ordered and/or that the results are misinterpreted. The implications of each are far-reaching for the patient, his or her entire family, and the ordering clinician.

Many patients and clinicians falsely believe that there is simply one genetic test available for breast or ovarian cancer risk (BRCA) and one available for colon cancer risk (Lynch syndrome). Unfortunately, this is not accurate. Breast cancer is associated with mutations in many hereditary cancer genes, including p53, CHEK2, PALB2, and PTEN, in addition to BRCA1 and BRCA2. There are both cancerous (thyroid, sarcoma, pancreatic, adrenal cortical carcinomas) and non-cancerous (autism, benign skin findings, speckled genitalia) findings that can be found with many cancer mutations, and a full evaluation is needed to choose the correct testing.

Even within BRCA testing, there are many tests to order including full sequencing, the Jewish panel, familial mutation testing, and deletion/duplication analysis (BRAC Analysis Rearrangement Test [BART]). Testing for hereditary colon cancer is perhaps even more complex with MSH2, MLH1, MSH6, EpCAM, PMS2, MYH, APC, and SMAD4 representing a few of the testing options. Ordering the wrong test can result in thousands of wasted health care dollars for insurance companies; patients being stuck with large, unpaid balances; and, worst of all, patients receiving the wrong test and therefore inaccurate result interpretations.

Results can fall into a few broad categories. It is important to note that a “negative” test result can actually be interpreted in three different ways:

1. **Deleterious mutation.** When a deleterious mutation in a cancer gene is discovered, the cancer risks for the patient and his or her family are relatively straightforward. The risks associated with most genes are not precise and should be presented to patients as a risk range. When a true mutation is found, it is critical to test both parents—whenever possible—to determine from which side of the family the mutation is originating, even when the answer appears obvious.

2. **True negative.** A true negative result means that the patient has tested negative for the cancer mutation found in his or her family, which ideally has been proven to segregate with the cancer family history. In this case, the patient’s cancer risks are reduced to that of other people in the general population, and they should be counseled to follow general population guidelines for screening.

3. **Negative.** A negative result means that a mutation was not detected and, based on an assessment of the personal and family history, the cancers in the family are unlikely to be hereditary. For example, a patient is diagnosed with colon cancer at age 38 years and comes from a large family with no other cancer diagnoses and relatives who died at old ages of other causes.

4. **Uninformative negative.** This means that a patient tests negative on the cancer test ordered, but no mutation has been identified in the family. Interpretation will be based on the personal and family history. If, for example, the patient developed colon cancer at age 38 years and has a father and paternal aunt who developed colon and uterine cancers before age 40 years, a negative test result would be almost meaningless. It would simply mean that the family has a mutation that could not be identified with our current testing methods or a mutation in another cancer gene. The entire family would be followed as high risk.

5. **Variant of uncertain significance.** This result indicates that a genetic change has been found, and it is unclear if this change is deleterious or completely benign. There are several strategies to help learn more about the meaning of the variant; however, most of the time, there are few data available, and interpretation will hinge on assessment of the personal and family history. It is not advantageous or recommended to test unaffected family members for variants of uncertain significance.

**MEDICAL MANAGEMENT**

We now have clear guidelines for the management of patients who carry BRCA and Lynch syndrome mutations (Table 3-5) as well as most other hereditary cancer syndromes. However, this management is highly dependent on the patient’s age, preferences, childbearing or menopausal status, personal health, and family history. For example, a 38-year-old female BRCA1 carrier who is married, has completed her family of three children, and has a cousin who died of ovarian cancer at age 45 years may be a very good candidate for immediate prophylactic bilateral salpingo-oophorectomy (BSO). A 38-year-old female BRCA2 carrier who is engaged to be married, wants to have children, and has no family history of ovarian cancer may be a candidate for either postponing BSO for a few years or perhaps undergoing in vitro fertilization (IVF), freezing embryos, and considering preimplantation genetic diagnosis. The age-related risks, options, and pros and cons of each must be explored with each patient in depth.

Many patients are understandably overwhelmed with their positive test results and are not prepared to create a long-term plan at the time of result disclosure. It is important to encourage patients to take time to absorb the information and come back in—preferably with a support person—for 4 to 6 weeks later to discuss a plan. The genetic counselor should provide patients and their providers with support options and written information explaining their risks. The PCC can provide a referral to a psychologist for discussion, if desired, and should reiterate that the patient can outline a plan for a year and then reevaluate. The exception is a female patient older than age 40 years who tests positive for a BRCA or Lynch syndrome mutation. In that case, a prophylactic BSO (BRCA) or total hysterectomy (Lynch syndrome) should be considered immediately based on the age-related cancer risks of those gynecologic malignancies. Premenopausal prophylactic BSO will obviously cause surgical menopause, which is associated with its own risks and side effects. Patients should be counseled about these risks and the methods to counter side effects before having surgery so that they can make an informed decision. In some cases, even mutation-positive females will be good candidates for low-dose hormone replacement therapy and should be counseled based on the most current data.
Management preferences for each patient will likely change over time. Some patients are content to undergo close breast surveillance. Others will find it overly stressful, especially with the high biopsy rate associated with breast MRI, and may ultimately choose prophylactic bilateral mastectomy. Management preferences often change if the patient is diagnosed with cancer and is making surgical decisions.

**FAMILY MEMBERS**

It is the responsibility of the person ordering genetic testing not only to interpret the result for the patient but also to advise the patient about which other family members should be offered genetic counseling and testing. These recommendations are generally made in writing, and it is the responsibility of the patient, not the clinician, to contact these relatives. In fact, the clinician may commit a Health Insurance Portability and Accountability Act (HIPAA) violation if he or she shares genetic testing information with relatives without the consent of the patient.

Genetic counselors take a detailed four-generation family history and can assess which other family members are at risk to carry a mutation. This assessment must include both male and female family members not only because they are both at risk for cancer but also because they may have children who are at risk.

**COMMON CONCERNS AND MISCONCEPTIONS**

Genetic counseling and testing for hereditary cancer syndromes is still a relatively new field, and misconceptions about the field are prevalent (Table 3-6). In the 1990s, there was initial concern about health insurance discrimination of patients (particularly unaffected patients having presymptomatic testing), and, luckily, this has not been a prevalent problem. The first law to address this issue was the HIPAA
of 1996.\textsuperscript{51} It forbid exclusion, prohibited higher premiums, and banned the use of genetic information as a preexisting condition. Then, more specifically, the Genetic Information Nondiscrimination Act (GINA) of 2008 provided additional protection for patients against health insurance discrimination; however, there are gaps and this act does not protect against life or disability insurance discrimination.\textsuperscript{52} Patients must be counseled accordingly and may wish to obtain such coverage before having genetic testing. In addition, the 2010 health care reform (H.R. 4872) prohibits group health plans from denying insurance based on preexisting conditions and from increasing premiums based on health status.\textsuperscript{53}

When the field began, we were also quite concerned about the psychological impact of testing on patients. Again, the data have not shown psychological harm as a result of genetic testing.\textsuperscript{54,55} However, all patients should have pretest genetic counseling to minimize these risks, and it is critical to know that children younger than the age of 18 years should not be offered testing for adult-onset diseases for which there is no childhood intervention.\textsuperscript{56} The exception would be a family history in which family members have developed cancer at atypically early ages, warranting screening and testing in teenagers.

### TABLE 3-6 Debunking Myths in Cancer Genetic Counseling

<table>
<thead>
<tr>
<th>Myth</th>
<th>Truth</th>
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</thead>
</table>
| Myth: If your patient has genetic testing, his or her health insurance will discriminate against him or her. | |}
| Myth: Your patient’s insurance will not cover the cost of genetic counseling and testing. | Truth: Most insurance companies cover part, if not all, of the counseling and testing charges for high-risk patients. A referral may be needed. |
| Myth: Your patient has already had cancer, so testing won’t help them. | Truth: If your patient has a hereditary cancer syndrome, he or she may be at risk for a new primary cancer, testing can help him or her make better surgical and treatment decisions, and this information will be critical to his or her family members. |
| Myth: Your patient’s father’s family history doesn’t count. | Truth: Maternal and paternal family histories count equally. |
| Myth: Only Ashkenazi Jews are at risk for BRCA mutations. | Truth: BRCA mutations are seen in individuals of all ethnic backgrounds. |
| Myth: Your patient only needs genetic counseling if he or she tests positive for a mutation. | Myth: Your patient should only have this testing if she would consider bilateral mastectomies. |
| Myth: All patients considering genetic testing should be seen for pregenetic and postgenetic counseling. Negative test results are the most difficult to interpret. | Truth: Most mutation carriers do not opt for prophylactic mastectomies. There are other effective options for surveillance and risk reduction. |
| Myth: If your patient tests negative for mutations, he or she is at population risk for cancer. | Truth: This is only true for patients testing “true negative.” Results must be interpreted in light of a patient’s personal and family history. |
| Myth: Genetic tests for cancer susceptibility yield inaccurate or ambiguous results. | Myth: Patients considering genetic testing should be seen for pregenetic and postgenetic counseling. Negative test results are the most difficult to interpret. |
| Myth: The risk of cancer in patients who have a positive genetic test is not clear. | Truth: Long-term data sets now provide clear risk estimates for individuals with a hereditary cancer syndrome. |
| Myth: Clear guidelines are not available for managing patients with a hereditary cancer syndrome. | Truth: National screening and risk reduction guidelines are established for most hereditary cancer syndromes. |
| Myth: Children should be tested for adult-onset hereditary cancer syndromes. | Truth: Multiple national organizations strongly recommend postponing testing for adult-onset hereditary cancer syndromes in children and adolescents until after age 18 y. Testing children likely does more harm than good. |

### FUTURE DEVELOPMENTS

Genetics is perhaps the most rapidly evolving area of medicine and will soon impact every area of clinical practice, likely including pharmaceutical decision making and widespread surveillance recommendations. PCCs will be pivotal in determining which of their patients require a referral for genetic counseling, advising them on what family history information they should research prior to that appointment, and facilitating and documenting that referral. The PCCs will then play a critical role postcounseling and testing in helping the patient understand the results and helping to choose the short- and long-term surveillance and risk reduction plans best suited for him or her. The family physician can also guide the patient about informing other family members about their genetic risks.

Some genetic testing is now offered directly to consumers (DTC) via the Internet. Individuals contact the company directly and pay out of pocket for a saliva kit that is mailed directly to them. Unfortunately, most DTC companies will test children for adult-onset conditions even though this is not recommended.\textsuperscript{58} The quality and predictive value of such testing is suspect, and the information relayed back to the patient...
can be inaccurate and/or confusing. PCCs should review the actual test results for any patient claiming to have had genetic testing and will need to evaluate if they then need a referral to genetic counseling.

Seismic changes are expected in the field of genetic testing with the advent of whole exome sequencing in the very near future. This testing will include hundreds or thousands of genes for different conditions and will radically change the way we counsel and advise patients. The PCC should be aware of these changes and should identify genetics experts who can offer consultation on these complex matters as the field unfolds.

As the field of genetic testing grows and expands, the personal and family history obtained by the PCC, combined with the relationships that the provider has fostered over time, can and should serve as the cornerstone for the genetic revolution.

References


KEY POINTS

- Medical intervention to prevent cancer is generally targeted to individuals at increased risk of one of the common adult epithelial tumors (breast, prostate, lung, colon, skin).
- Cancer preventive agents have been U.S. FDA-approved for breast cancer (i.e., tamoxifen and raloxifene) and certain topical agents for skin cancer.
- Third generation aromatase inhibitors, such as exemestane and anastrozole, have shown promise in the prevention of ER-positive breast cancer. Exemestane is farther along, having been shown to decrease breast cancer risk in a primary breast cancer prevention trial.
- Aspirin may be appropriate as an anticancer agent for those at a high risk of colon cancer, although the potential for gastrointestinal bleeding should be closely monitored.
- Special attention to potential toxicities should be made when prescribing agents for cancer prevention in otherwise healthy individuals.

Medical interventions to prevent cancer (use of pharmaceutical agents/drugs to reduce cancer risk, i.e., “chemoprevention”) are generally targeted to individuals at increased risk of one of the common adult epithelial tumors (breast, prostate, lung, colon), which develop over a very long period of time, progressing from normal tissue through increasingly aggressive premalignant stages to invasive carcinoma. Prescribing chemopreventive agents requires special attention to potential drug toxicities because these drugs are being given to healthy people who are unlikely to tolerate adverse effects. The primary care clinician (PCC) should be familiar with these toxicities as well as the risk factors for each cancer type (Table 4-1) and should include counseling about chemoprevention in the routine care of appropriate patients.

APPROVED AND PHASE III-TESTED CHEMOPREVENTIVE AGENTS

Only a few agents have been shown to decrease the risk of common cancers, mainly the hormonally responsive tumors (breast and prostate cancer), in high-risk individuals (see Table 4-1).1–13

Breast Cancer

The first chemopreventive agent to be approved by the U.S. Food and Drug Administration (FDA) for a cancer prevention/risk reduction indication for a given cancer was tamoxifen, a selective estrogen receptor modulator (SERM) that has been widely used to treat women who already had breast cancer. In four independent tamoxifen-versus-placebo prevention trials, tamoxifen reduced breast cancer by 38% overall and estrogen receptor (ER)–positive breast cancer by 48%.4 Concerns remain, however, about the rare tamoxifen toxicities of endometrial cancers and venous thromboemboli, both primarily in postmenopausal women. The osteoporosis SERM raloxifene subsequently received U.S. FDA approval for breast cancer risk reduction when the Study of Tamoxifen and Raloxifene (STAR) trial showed that raloxifene had about equal efficacy to tamoxifen in reducing first primary cancers and did not cause endometrial cancer, making it a less toxic alternative.6–8 Despite strong clinical trial evidence, U.S. FDA approval, and endorsement by respected professional organizations,6,14–16 the acceptability of preventive tamoxifen and raloxifene to high-risk women and their PCCs has been limited.17,18 Several reasons for this reluctance include toxicities (especially tamoxifen), the number needed to be treated (NNT) to see benefits (Fig. 4-1),18,19 the lack of easily measurable surrogates (comparable to the cardiovascular [CV] biomarkers, blood pressure, or cholesterol levels) for invasive cancer risk, and the restrictive list of attributes that make a woman a good candidate for preventive therapy (premenopausal status; very high risk because of atypical ductal hyperplasia (ADH), lobular carcinoma in situ [LCIS], or ductal carcinoma in situ [DCIS]; not at risk of no history of thromboembolic disease; hysterectomy if postmenopausal).20 An interactive breast cancer risk
## TABLE 4-1  Medical Interventions Recommended or Considered for Prevention of Common Adult Cancers

<table>
<thead>
<tr>
<th>Preventive Agent</th>
<th>Prevention Trial or Epidemiologic Evidence Supporting Cancer Prevention Use (n) (eligibility)</th>
<th>Efficacy Data Experimental Agent versus Comparator</th>
<th>Side Effects Data</th>
<th>U.S. FDA Approval for Cancer Prevention Indication; or Strength of the Evidence and Recommendation for Risk Reduction</th>
<th>Recommendations Available to Primary Health Care Provider for Use in Cancer Prevention in Patients with the Following Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer Type: Breast Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen (TAM)</td>
<td>NSABP P-1: BCPT (13, 388) (&gt;60 y, 5-yr BC risk ≥1.66% per Gail model or LCIS)1,12; also IBIS-13; Overview: 4 TAM prevention trials4</td>
<td>BCPT: Invasive BC incidence: RR = 0.57 (95% CI, 0.46–0.70; p &lt; 0.001)</td>
<td>Endometrial cancer (postmenopausal women); thromboembolic disease</td>
<td>U.S. FDA approved; strong phase III clinical trial</td>
<td>Premenopausal: 5-yr BC risk ≥1.66% per NCI BC RAT, LOS-TAM is the only approved option5,6 Postmenopausal: 5-yr BC risk ≥1.66% per NCI BC RAT5,6 or LCIS; Caution: H/O DVT, PE, stroke, TIA; endometrial cancer6</td>
</tr>
<tr>
<td>RAloxiene (RAL)</td>
<td>NSABP P-2: STAR (19,747) (postmenopausal, 5-yr BC risk ≥1.66% per Gail model or LCIS)7,8</td>
<td>Invasive BC incidence (RAL versus TAM): Initial analysis: RR = 1.0 (95% CI, 0.82–1.28; p = .83)7; Updated analysis: RR = 1.24 (95% CI, 1.05–1.47; p = .01)8</td>
<td>Thromboembolic disease</td>
<td>U.S. FDA approved; strong phase III clinical trial</td>
<td>Postmenopausal: 5-yr BC risk ≥1.66% per NCI BC RAT5 or LCIS; Caution: H/O DVT, PE, stroke, TIA6</td>
</tr>
<tr>
<td>Exemestane</td>
<td>MAP.3: (4,560) (postmenopausal, 5-yr BC risk ≥1.66% per Gail model, ≥60 y; ADH, LH, LCIS, DCIS S/P total mastectomy)9</td>
<td>Invasive BC: HR = 0.35 (95% CI, 0.18–0.70; p = .002)</td>
<td>Osteoporosis, arthritis, arthralgia, myalgia; diarrhea, nausea; hot flashes</td>
<td>Not approved for prevention; strong phase III clinical trial data recently published</td>
<td>Do not recommend outside clinical trials6; given recent positive outcome in MAP.3 for postmenopausal women at increased risk, may discuss with patient, although at present time there is no U.S. FDA label indication for BC prevention; Caution: H/O osteoporosis, osteopenia, arthritis (bone), musculoskeletal side effects</td>
</tr>
<tr>
<td><strong>Cancer Type: Prostate Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finasteride (FIN)</td>
<td>SWOG. PCPT (18,882) (normal risk, ≤55 y, PSA &lt;3.0 ng/mL, DRE normal)10</td>
<td>PC incidence: 24.8% reduction (95% CI, 18.6%–30.6%; p &lt; .001) in 7-yr prevalence (13.4% FIN versus 24.4% Plac diagnosed with PC)</td>
<td>High-grade tumors (Gleason score 7–10): 37% of FIN versus 22.2% of Plac tumors; RP-high stage tumors = 1.67 (95% CI, 1.44–1.93; p &lt; .001); RP-high at risk = 1.27 (95% CI, 1.07–1.50; p = .005); Sexual function/endocrine effects (p &lt; .001, favors Plac); reduced ejaculate volume, erectile dysfunction, loss of libido, gynecomastia; Genitourinary (p &lt; .001, favors FIN); BPH, urinary urgency, frequency, retention; TURP, prostatitis, UTI</td>
<td>U.S. FDA did not approve FIN for prevention based on toxicity data: increased risk of high-grade tumors; also added warning to package insert for BPH and male pattern baldness indications11; merits discussion with patient but caution regarding high-grade tumors12</td>
<td>Not recommended for PC risk reduction</td>
</tr>
</tbody>
</table>

(continued)
### TABLE 4-1 Medical Interventions Recommended or Considered for Prevention of Common Adult Cancers (cont.)

<table>
<thead>
<tr>
<th>Preventive Agent</th>
<th>Prevention Trial or Epidemiologic Evidence Supporting Cancer Prevention Use (n) (eligibility)</th>
<th>Efficacy Data Experimental Agent versus Comparator</th>
<th>Side Effects Data</th>
<th>U.S. FDA Approval for Cancer Prevention Indication; or Strength of the Evidence and Recommendation for Risk Reduction</th>
<th>Recommendations Available to Primary Health Care Provider for Use in Cancer Prevention in Patients with the Following Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dutasteride (DUT)</strong></td>
<td>REDUCE (8,231/6,729 biopsied) (increased risk: 50–75 y, elevated PSA [2.5–10.0 ng/mL (50–60 y) or 3.0–10.0 ng/mL (&gt;60 y)]; or H/O single prostate biopsy within 6 mo)</td>
<td>PC incidence: 22.8% reduction (95% CI, 15.2%–29.8%; ( p &lt; .001 )) in 4-yr period (19.9% DUT versus 25.1% Plac diagnosed with PC)</td>
<td>High-grade tumors (Gleason score 7): 6.7% of DUT versus 6.8% of Plac tumors (( p = .81 )); Tumors (Gleason score 8, 9, 10): 0.9% of DUT versus 0.6% of Plac tumors (( p = .15 )); Tumors (Gleason score 8, 9, 10) in years 3 and 4: 0.5% (( n = 12 )) of DUT versus &lt;0.1% (( n = 1 )) of Plac (( p = .003 ))</td>
<td>Not approved (toxicity—increased risk of high-grade tumors similar to FIN; also added warning to package insert for BPH and male pattern baldness indications)</td>
<td>Not recommended for PC risk reduction</td>
</tr>
</tbody>
</table>

**Cancer Type: Colorectal Cancer**

| Aspirin | Meta-analysis of 8 RCTs for primary and secondary prevention of CVD in high-risk patients\(^{26}\) | All cancers: HR = 0.66 (0.50–0.87; \( p = .003 \)); GI cancers: HR = 0.46 (0.27–0.77; \( p = .003 \)) (benefit seen only after 5 yrs) | GI and genitourinary bleeding | In widespread use; formal U.S. FDA approval is unlikely | Discuss with patient and tailoring to individual risk (mainly GI bleeding); benefit profile; patients with increased risk of CVD may benefit most; USPSTF recommends against routine use of aspirin to prevent CRC in average-risk patients |

| Sulindac + DFMO | Phase II RCT (375) (H/O adenomas): Sulindac 150 mg + DFMO 500 mg each day\(^{27}\) | Sulindac 150 mg + DFMO 500 mg versus Plac \( \times 36 \) mo: reduced adenomas 70%, advanced adenomas 91.5% | No serious differences between arms of trial | Currently in phase II RCT: Plac versus sulindac versus DFMO versus sulindac + DFMO | Sulindac + DFMO combination not recommended for cancer prevention outside of clinical trial |

| Celecoxib | Small (77) RCT (FAP-increased risk of CRC)\(^{28}\) | Celecoxib decreased polyp number by 28% at 6 mo versus Plac | Cardiovascular disease | 1999 U.S. FDA approved for polyp number reduction in FAP; 2011 Pfizer pulled FAP indication | Celecoxib use for cancer prevention not recommended |

**Other Cancer Sites**

| Diclofenac sodium 3% | Topical application to skin in patients with actinic keratoses | Effective treatment: actinic keratoses (which are premalignant skin lesions) | GI side effects, rarely liver damage | U.S. FDA-approved gel | Recommend according to approved indication for cancer prevention by treating actinic keratoses |

| Imiquimod | Topical application to skin in patients with basal cell carcinoma, genital warts, actinic keratoses | Effective treatment of actinic keratoses (premalignant skin lesions) | Redness, itching, burning, bleeding of treated area; flaking, scaling, dryness, thickening of skin; swelling, stinging, pain in the treated area; blisters, scabs, bumps on the skin; headache, diarrhea, back pain; tiredness | U.S. FDA-approved cream | Recommend according to approved indication for cancer prevention by treating actinic keratoses |
assessments for breast cancer risk are available on the National Cancer Institute (NCI) website (http://www.cancer.gov/bcrisktool/) for use by PCCs and women to estimate a woman’s risk of developing invasive breast cancer.\(^5\)

The third generation aromatase inhibitors (AIs) are currently receiving attention for their application to breast cancer prevention. Two AIs, exemestane and anastrozole, have progressed to phase III prevention trials in high-risk, postmenopausal women. The recently completed Mammary Prevention 3 (MAP.3) trial showed a 65% reduction in the annual incidence of invasive breast cancer and a 73% reduction in ER-positive breast cancer with exemestane versus placebo.\(^9,18\) Adverse events, primarily musculoskeletal side effects, did not impair quality of life, making exemestane promising as a breast cancer prevention agent.

Risk reduction approaches are more aggressive for women who have inherited harmful BRCA1/2 mutations and have a 60% to 80% lifetime risk of breast cancer compared to 12% in the general population (also a 14% to 40% risk of ovarian cancer vs. 1.4% in the general population).\(^21\) In addition to earlier and more frequent screening with mammography and MRI, chemoprevention and prophylactic surgery (bilateral mastectomy, salpingo-oophorectomy in young women) should be addressed.\(^22-25\) Women with a strong family history or known mutation should be referred to a genetics counselor or other specialist.

**Prostate Cancer**

Dutasteride and finasteride inhibit 5α-reductase (5-AR), the enzyme that converts testosterone to its more potent form, 5α-dihydrotestosterone. Both 5-AR inhibitors, already in use, are already in use to manage lower urinary tract symptoms of benign prostatic hyperplasia (BPH) and for male pattern baldness, were shown to reduce prostate cancer (finasteride, by 24.8% in healthy men aged 55 years or older; dutasteride, by 22.8% in men at high risk based on age 50 to 75 years, elevated prostate-specific antigen [PSA], or a recent history of a prostate biopsy).\(^10-13\) Despite preventive efficacy in these two different populations (normal, older men and high-risk, older men), both agents share the troubling side effect of an increase in high-grade tumors among men who do develop prostate cancer while on the drug. As a result, the U.S. FDA has not approved either drug for prostate cancer risk reduction and in 2010 added a cautionary warning to their approved indications for symptomatic BPH and baldness.

### Colorectal Cancer

Epidemiologic data on aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)\(^26-28\) overwhelmingly point to an inverse relationship between use of these drugs and incidence of colorectal cancer (CRC), which is overall about 40% lower in regular users.\(^28\) Aspirin use also is associated with a decrease in the incidence of adenomatous polyps, a precursor to CRC.\(^31,32\) In addition, aspirin reduces CRC incidence about 40% in individuals at increased risk because of carrying genetic variants predisposing to Lynch syndrome (hereditary nonpolyposis CRC).\(^33\) The major risks with NSAIDs are gastrointestinal and genitourinary bleeding, which increase with age. Significant increases in CV events\(^34,35\) have been seen with the cyclooxygenase-2 pathway.

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**TABLE 4-1** Medical Interventions Recommended or Considered for Prevention of Common Adult Cancers (cont.)

<table>
<thead>
<tr>
<th>Preventive Agent</th>
<th>Prevention Trial or Epidemiologic Evidence Supporting Cancer Prevention Use (n) (eligibility)</th>
<th>Efficacy Data Experimental Agent versus Comparator</th>
<th>Side Effects Data</th>
<th>U.S. FDA Approval for Cancer Prevention Indication; or Strength of the Evidence and Recommendation for Risk Reduction</th>
<th>Recommendations Available to Primary Health Care Provider for Use in Cancer Prevention in Patients with the Following Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives (OCPs)</td>
<td>Meta-analysis of 45 epidemiologic studies (23,257 ovarian cancer cases; 87,303 controls)(^18)</td>
<td>Proportional risk reductions per 5 yrs use: 29% (95% CI, 23%–34%) use that stopped &lt;10 yrs previously; 19% (14%–24%) use that stopped 10–19 yrs previously; 15% (9%–21%) use that stopped 29 yrs previously</td>
<td>Nausea, headache, breast tenderness, weight gain, irregular bleeding, mood changes; uncommonly increased blood pressure, blood clots, heart attack, and stroke, especially in women who smoke and those who are older than 35 y</td>
<td>Not approved for prevention</td>
<td>Consider OCPs as a birth control method for premenopausal women who are at increased risk of developing ovarian cancer(^29)</td>
</tr>
</tbody>
</table>

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*(This table continues in the next page)*
(COX-2) selective inhibitors, celecoxib and rofecoxib, leading to removal of the latter drug from the market. Celecoxib, once approved for polyp reduction in the rare CRC-predisposing hereditary syndrome, familial adenomatous polyposis (FAP), no longer carries this risk-reducing indication. Combinations of agents at low doses, to reduce toxicity, are promising for CRC prevention. Low-dose sulindac, an NSAID, combined with difluoromethylornithine (DFMO), reduced the incidence of adenomas in patients with a history of adenomas in a phase II trial and is now being tested in 1,340 patients in a phase III randomized controlled trial (RCT) (http://clinicaltrials.gov/ct2/show/NCT01349881?term=NCT01349881&rank=1).

At present, the strongest evidence exists for aspirin as a medical intervention for CRC prevention. In discussing aspirin for this purpose, the PCC and patient must balance the predicted cancer prevention benefits against the risks. Although overall, studies have suggested an advantageous risk—benefit profile for aspirin use to reduce colon cancer incidence—this balance varies with age and other individual risk factors. Neither aspirin nor other NSAIDs are recommended for routine use in individuals at average risk. Because aspirin is already recommended to prevent CV disease in high-risk individuals and healthy individuals incur only a small increase in risk of nonfatal bleeding complications, the benefits are likely to outweigh the risks in most individuals, particularly in patients for whom antiplatelet therapy is indicated. Coprescription of a proton pump inhibitor offers an option to reduce bleeding complications. The uncertainties of dose and duration of aspirin use for prevention should also be discussed.

Other Cancers

Effective topical medicines have been approved for prevention of nonmelanoma skin cancers (see Table 4-1). In addition, extensive research into prevention of oral cancer in individuals with leukoplakia, a premalignant lesion, has shown that vitamin A derivatives, or retinoids, retard progression to invasive cancer. However, the toxicity associated with these agents has limited their use for this purpose. Finally, observational studies have shown that use of oral contraceptives confers long-term protection against ovarian cancer, although this has never been demonstrated in clinical trials.

**References**


8. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and


The rising worldwide impact of tobacco use, which killed more than 100 million people in the 20th century, is expected to be the cause of death of one of every two smokers—a billion people in the 21st century. The increase in worldwide tobacco consumption also is estimated to result in dramatic increases in years of life lost because of premature death and years of healthy life lost because of illness and disability, with tobacco use becoming the greatest health risk worldwide by 2030.

**The Smoking Lung Cancer Lag**

Encouraging patients to quit smoking presents a major challenge for PCCs given the extended lag time between smoking initiation and the development of diseases related to long-term addiction. At least a 20-year lag time is seen in both men and women between rising tobacco consumption rates in the United States and the subsequent rise in lung cancer deaths (Fig. 5-1). Of note, the lag between smoking uptake and lung cancer deaths in women resembles that in men, although the increased tobacco consumption by women occurred decades after men because of changes in societal norms that made smoking among women more acceptable.

**Mortality, Health, and Economic Impacts of Smoking**

Tobacco use in the United States accounts for approximately 30% of all cancer deaths and 90% of all lung cancer deaths each year. Although smoking rates have decreased dramatically since the 1960s, in 2010 in the United States, 22% of American men and 17% of American women still smoked. Most people do not understand that smoking is tightly associated with many diseases other than lung cancer and emphysema.

The economic cost of smoking-related health outcomes also has a major societal impact worldwide; for example, the overall cost of cancer in the United States was $263.8 billion in 2010, with one-third of this cost attributable to smoking. An underpublicized effect of smoking is its impact on reproduction and sexual activity. Women who smoke before becoming pregnant have decreased ovarian function, produce fewer oocytes, and have lower pregnancy rates; and smoking during pregnancy is associated with a higher risk of perinatal mortality, both stillbirths and neonatal deaths (including sudden infant death syndrome [SIDS]). Men who smoke (>20 pack years’ duration) have a 70% increased risk
of erectile dysfunction, whereas those who quit smoking show enhanced erectile function and quicker arousal than men who continue to smoke.9

NICOTINE ADDICTION AND MECHANISMS

Dependence on nicotine, pharmacologically and behaviorally, is one of the hardest addictions to break and, historically, has been as difficult to overcome as addictions to heroin and cocaine.10 Nicotine works through pathways in the central, sympathetic, and parasympathetic systems (Fig. 5-2). All patients do not develop the same levels of addiction because of genetic differences, such as single-nucleotide polymorphisms (SNPs) that are associated with higher levels of craving and enhancing addiction during tobacco cessation efforts, making quitting tobacco more difficult.11–13 There are genetic differences among racial groups that may account for some of the differences in smoking behavior in population subgroups.14

TOBACCO CONTROL MEASURES

Evidence of the success of multiteried interventions for smoking cessation (e.g., policy-driven initiatives, promotion of smoke-free environments, and public advertising campaigns) is increasing, especially among those encouraged not to begin smoking, such as young people.1

No strategy is consistently more than 5% to 10% effective after 1 year of follow-up, although the cumulative effect of using multiple strategies for individual patients can promote persistent reduction in active smoking over time. In 2010, 45.3 million people in the United States aged 18 years and older smoked cigarettes, down approximately 3 million from

TABLE 5-1 Tobacco-Related Mortality by Disease or Condition

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Total Disease-Specific Deaths (^b) (Number)</th>
<th>Smoking-Related Deaths</th>
<th>Percentage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Neoplasms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung/trachea/bronchus</td>
<td>156,900</td>
<td>80</td>
<td>125,520</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,630</td>
<td>68</td>
<td>8,590</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>30,330</td>
<td>22</td>
<td>6,680</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,460</td>
<td>40</td>
<td>4,990</td>
<td></td>
</tr>
<tr>
<td>Lip/oral cavity/pharynx</td>
<td>7,620</td>
<td>64</td>
<td>4,890</td>
<td></td>
</tr>
<tr>
<td>Kidney/renal pelvis</td>
<td>12,000</td>
<td>25</td>
<td>3,040</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>3,770</td>
<td>80</td>
<td>3,010</td>
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<tr>
<td>Stomach</td>
<td>12,080</td>
<td>21</td>
<td>2,480</td>
<td></td>
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<tr>
<td>Acute myeloid leukemia</td>
<td>7,080</td>
<td>17</td>
<td>1,180</td>
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<tr>
<td>Cardiovascular Diseases</td>
<td></td>
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<tr>
<td>Ischemic heart disease</td>
<td>487,350</td>
<td>16</td>
<td>80,000</td>
<td></td>
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<tr>
<td>Cerebrovascular disease</td>
<td>159,300</td>
<td>10</td>
<td>15,930</td>
<td></td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>14,720</td>
<td>57</td>
<td>8,342</td>
<td></td>
</tr>
<tr>
<td>Respiratory Diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>102,102</td>
<td>77</td>
<td>78,990</td>
<td></td>
</tr>
<tr>
<td>Bronchitis, emphysema</td>
<td>16,260</td>
<td>86</td>
<td>13,930</td>
<td></td>
</tr>
<tr>
<td>Pneumonia, influenza</td>
<td>62,530</td>
<td>17</td>
<td>10,420</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Data were adapted from estimates from the Centers for Disease Control and Prevention 2000–2004 National Health Interview Survey responses and the 2000–2004 National Center for Health Statistics death certificate data.2

\(^b\) Rounded to the nearest 10.

COPD, chronic obstructive pulmonary disease.

2005. Women smoke less than men, and adults 25 to 44 years of age have the highest incidence of smoking. This is the age group that will benefit most from smoking cessation efforts. Societal norms and initiatives in education, advertising, changing laws, and tax increases have all played a role in discouraging individuals from continuing or beginning to smoke.

**Tobacco Control Measures Targeting Individuals**

**Oral Drugs.** Several drugs have been evaluated in addiction treatment for smoking (Table 5-2). Drugs that target the nicotinic acetylcholine receptor (nAChR), including bupropion and varenicline, have shown impressive success for short-term cessation but lesser success at 1 year (23.0% for varenicline; 14.6% for bupropion). Nortriptyline, a tricyclic antidepressant, and clonidine, approved as an antihypertensive medication, are efficacious as second-line therapies for smoking cessation. However, each of the medications mentioned in this section has side effects that should be discussed with the patient and monitored by the PCC.

**Nicotine Replacement Therapy.** Since 1984, when nicotine gum was first introduced as a prescription drug, nicotine replacement therapy (NRT) has been one of the most successful strategies for tobacco cessation. NRT use has grown exponentially since the 1990s when this class of drugs became available over the counter. NRTs now include nicotine gum, patches, lozenges, and nasal sprays. NRT, usually in combination with other cessation strategies, yields successful quit
rates ranging from 5% to 50%. Most clinical trial results suggest a success rate after 1 year of 6% to 8%, although a review of eight clinical trials found a 20% quit rate after 1 year.\(^{16}\)

**Nicotine Vaccines.** Despite a decade of research into vaccines to support cessation in smokers, no vaccine has yet been approved for this purpose. The vaccine farthest along in development (NicVAX) recently was withdrawn from the market because of failure in clinical trials.

Interventions are effective at the beginning, especially in patients who really want to quit. Using multiple strategies (e.g., nicotine patch and counseling) for longer than the traditional 1- to 3-month intervention period generally prescribed for addiction treatment will afford the best chance for long-term cessation success.\(^{16}\) In fact, smoking cessation programs can produce quit rates as high as 50% if they are extended to 1 year. Despite these findings, approximately 75% to 80% of those participating in a smoking cessation program,
even if highly motivated to quit, will return to smoking within 6 months.

**Behavioral Interventions**

Behavioral interventions for tobacco cessation have been supported by governmental and private organizations since the 1980s. They involve individual and group counseling, telephone support centers, peer counseling, and informal support groups. Such behavioral approaches are most effective in individuals who truly want to quit. Although the success rate after 6 months generally is between 3% and 5%, this is still higher than for those who try to quit on their own (after 1 year).

**Governmental and Societal Interventions**

In addition to behavioral and medical interventions, many tobacco control efforts revolve around changing the societal environment regarding tobacco use, especially in an effort to keep young people from beginning to smoke. Approximately one-half of the world’s people now live in countries that have implemented governmental controls on tobacco products, an increase of 1 billion since 2008.\(^{19}\) Regulating tobacco use and sales, restricting when and where tobacco may be consumed, and public awareness campaigns have been instrumental in reducing the use of tobacco in the United States by almost one-half since the 1960s. Labels bearing stark images that depict the dire consequences of tobacco use on cigarette packages are standard in some countries but have been rejected in the United States by a federal court after the U.S. Food and Drug Administration (FDA) issued rules to require such graphic images on cigarette packaging.\(^ {20,21}\)

In the United States, the Mental Health Parity and Addiction Equity Act of 2008 defined tobacco as an addictive substance and stipulated that tobacco use must be treated in the same manner as other addictions regarding payment by insurance companies for interventions and treatments.\(^ {22}\) Early studies using residential treatment for tobacco addiction found this approach to be successful after 6 months. This finding is particularly impressive, given that the smokers receiving residential treatment had more severe tobacco dependence compared to smokers receiving outpatient treatment.\(^ {23}\)

**WHAT THE PRIMARY CARE CLINICIAN CAN DO**

The PCC, as the interface between the patient and smoking cessation efforts, plays a critical role in tobacco control. Unfortunately, less than half of smokers who had seen a health professional in the past year reported receiving advice to quit.\(^ {24}\) Yet, advice from a health professional motivates patients to attempt to quit and increases their use of effective medications, which improve the success rate about 2 to 3 times.

The constraints on time and staff available to PCCs in clinic visits have encouraged the use of complementary and concise tools for encouraging quitting. The 1-800-QUIT NOW cessation line is available toll-free throughout the United States. The American College of Obstetricians and Gynecologists (ACOG) devised a simple and direct mnemonic device for use by PCCs in addressing smoking cessation: the “5As” (Ask, Advise, Assess, Assist, Arrange). Although originally designed for pregnant women, the 5As has gained wider acceptance, becoming part of other national guidelines, including the U.S. Surgeon General’s *Quick Reference Guide for Clinicians on Treating Tobacco Use and Dependence*.\(^ {25}\) This commonsense approach, which can be implemented by the practicing PCC in a time-efficient manner, is supported by the results of a recent systematic review, which is the largest review conducted of peer-reviewed, published smoking cessation programs and clinical trials. The results were published with a “plain-language summary.”\(^ {26}\)

The “Ten Key Guideline Recommendations” (Box 5-1) have been adapted from the 2008 clinical guidelines for clinicians on steps to take with patients to encourage smoking cessation.\(^ {24}\) The ten recommendations serve as a practical guideline for imparting knowledge and strategies to patients. The overarching goal of these recommendations is that clinicians strongly recommend the use of effective tobacco dependence counseling and medication treatments to their patients who use tobacco and that health systems, insurers, and purchasers assist clinicians in making such effective treatments available.

### ENCOURAGING YOUNG PEOPLE NOT TO BEGIN SMOKING

Although beneficial at any age, quitting smoking is especially advantageous for young smokers. Cigarette smokers who quit before age 35 years exhibit mortality rates resembling those seen in people who have never smoked.\(^ {27}\) The PCC is in a unique position of influence with young people 12 to 18 years of age, the very age range when many youths decide to begin smoking.

---

**BOX 5-1: TEN KEY GUIDELINE RECOMMENDATIONS FOR HELPING PATIENTS QUIT**

1. Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments exist.
2. Document tobacco use status and treat every tobacco user seen in a health care setting.
3. Tobacco dependence treatments are effective across a broad range of populations. Encourage every patient willing to make a quit attempt.
4. Brief tobacco dependence treatment is effective.
5. Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity.
6. Numerous effective medications are available for tobacco dependence. Clinicians also should consider the use of certain combinations of medications identified as effective.
7. Counseling and medication are effective when used by themselves; however, combining them is more effective than either alone.
8. Telephone quitline counseling is effective with diverse populations and has broad reach.
9. If a tobacco user currently is unwilling to make a quit attempt, clinicians should use the motivational treatments.
10. Tobacco dependence treatments are both clinically effective and highly cost-effective relative to interventions for other clinical disorders.
smoking. Teen smoking rates declined among middle school and high school students from 25.6% in 2006 to 23.9% in 2009, but too many teens still smoke and need guidance in this area.28

THE FUTURE OF TOBACCO CONTROL

Tobacco use is possibly the most difficult addiction to break compared to dependence on other substances that are widely distributed in the population. Addiction occurs quickly in many people, depending in part on the genetic and behavioral dispositions of the individual. Antismoking societal pressures have had a large impact on smoking rates in the United States, but more needs to be done. The PCC is uniquely situated at the apex of influencing a patient’s decision to begin smoking or a current smoker’s desire to quit. This is particularly true for young patients. The role of the PCC in tobacco control efforts has not been used to its fullest extent because of competing and more immediate health concerns among patients. Because deleterious health outcomes caused by tobacco use are not immediate, the biggest challenge to the PCC is to discuss and emphasize the future risks and consequences of smoking. Numerous strategies are available to the PCC for use in providing advice and support for patients willing to attempt smoking cessation.

References


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Approximately 20% of all cancers worldwide are associated with infectious agents, including viruses, bacteria, and parasites, which cause long-term inflammation, suppression of the immune system, or DNA damage that leads to a higher risk of cancer.\(^1\)\(^2\) Several prevention and treatment strategies are available to the primary care clinician (PCC) to reduce the incidence of infectious diseases and inflammation that are associated with specific cancers. New strategies are continuously being developed as the basic mechanisms of infection, and inflammation-related carcinogenic oncologic processes are better understood.\(^3\)

**KEY POINTS**
- Infectious diseases account for as much as 20% of cancers worldwide.
- Viruses are associated with a large percentage of cancers of the cervix, liver, vagina, anus, and pharynx.
- Vaccination can protect against many of the virus-associated cancers.
- Bacteria and parasites are associated with cancer risk, and treatments exist to reduce this risk.
- Inflammation is an underlying cause of at least one in four cancers.

**THE IMPACT ON CANCER**
Infectious diseases account for more than 13 million deaths each year, with many of these infections being associated with cancers such as cervical and liver cancers in the developing world.\(^4\) In contrast, infectious diseases in the United States and other developed countries account for less than 10% of cancers.\(^5\) Among infectious diseases, viruses account for 60% of the associations with cancer. Chronic infection and other types of chronic inflammation together underlie up to 25% of cancers. Cancer-associated inflammation can result from microbial and viral infections, exposure to allergens and toxic chemicals, autoimmune diseases, and obesity. Given their inflammatory etiology, these cancers are to a large extent preventable.

**INFECTIOUS DISEASE AND CANCER (TABLE 6-1)**
The most compelling evidence for a viral etiology of a cancer is for the human papillomavirus (HPV) and cervical cancer, with 100% of these cancers attributable to the virus.\(^6\) HPV also is associated with vaginal/vulvar (40%), anal (90%), and penile (40%) cancers, in addition to smaller fractions of cancers of the oropharynx (12%) and mouth (3%). Hepatitis B virus (HBV) and hepatitis C virus (HCV) are both associated with hepatocellular carcinoma (HCC), 54% and 31%, respectively.\(^6\) Epstein-Barr virus (EBV) is associated with Burkitt and Hodgkin lymphomas and nasopharyngeal carcinoma; and Kaposi sarcoma–associated herpesvirus (KSHV)/human herpesvirus 8 (HHV-8) is associated with Kaposi sarcoma, multicentric Castleman disease, and primary effusion lymphoma in patients with AIDS. Human T-cell leukemia virus type 1 (HTLV-1) is associated with adult T-cell lymphoma/leukemia, and the newly discovered Merkel cell polyomavirus (MCPyV) appears to be associated with Merkel cell carcinoma, a rare and aggressive type of skin cancer.\(^7\)

Among bacteria, the strongest association with cancer is between *Helicobacter pylori* and stomach cancer, with more than 50% caused by *H. pylori*, and gastric mucosa-associated lymphoid tissue (MALT), a subtype of lymphoma that frequently occurs in the stomach.\(^5\) Diagnostic testing for *H. pylori* is recommended for individuals with either active or a history of gastric or duodenal ulcers. The most common methods for testing include urea breath tests which detect an *H. pylori*–mediated breakdown substance of an ingested solution (>95% diagnostic accuracy), blood tests for specific antibodies to the bacterium, and stool tests for *H. pylori* proteins. Treatment to eradicate *H. pylori* should be targeted to patients with active or a history of ulcers, peptic or duodenal, and consists of a 7- to 14-day course of a proton pump inhibitor plus two antibiotics, such as clarithromycin.
## TABLE 6-1 Infectious Agents and Cancer

### Viruses

<table>
<thead>
<tr>
<th>Virus Name (Type)</th>
<th>Cancer Site</th>
<th>Attributable Cancers (Global Estimates) (^{5,6,10})</th>
<th>Medical Therapies (Drugs, Vaccines)</th>
<th>FDA Approved, Recommended, or in Clinical Trials</th>
<th>Indicated for Which Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV (dsDNA)</td>
<td>Cervix</td>
<td>100 492.8</td>
<td>Gardasil: HPV quadrivalent (types 6, 11, 16, 18) vaccine, recombinant Cervarix: HPV bivalent (types 16, 18) vaccine, recombinant</td>
<td>Approved</td>
<td>Girls/women ages 9–45 y for cervical cancer; CIN grades 1, 2, and 3; and AIS</td>
</tr>
<tr>
<td></td>
<td>Anus</td>
<td>90 27.4</td>
<td>Gardasil</td>
<td>Approved</td>
<td>Males/females ages 9–26 y (HPV 16, 18)</td>
</tr>
<tr>
<td></td>
<td>Vulva, vagina</td>
<td>40 16.0</td>
<td>Gardasil</td>
<td>Approved</td>
<td>Girls/women ages 9–45 y for VIN and VaIN, grades 2 and 3</td>
</tr>
<tr>
<td></td>
<td>Penis</td>
<td>40 10.5</td>
<td>Gardasil</td>
<td>Extended approval</td>
<td>Boys/men ages 9–26 y</td>
</tr>
<tr>
<td></td>
<td>Genital warts</td>
<td>NA NA</td>
<td>Gardasil</td>
<td>Extended approval</td>
<td>Girls/women ages 9–45 y and boys/men ages 9–26 y</td>
</tr>
<tr>
<td></td>
<td>Mouth</td>
<td>3 8.2</td>
<td>Gardasil</td>
<td>Extended approval</td>
<td>Girls/women ages 9–45 y and boys/men ages 9–26 y</td>
</tr>
<tr>
<td></td>
<td>Oropharynx</td>
<td>12 6.3</td>
<td>Gardasil</td>
<td>Extended approval</td>
<td>Girls/women ages 9–45 y and boys/men ages 9–26 y</td>
</tr>
<tr>
<td>HPV (DNA-RT)</td>
<td>Liver</td>
<td>54 340.0</td>
<td>Engerix-B</td>
<td>Approved</td>
<td>Immunization in infants and both men and women of all ages for infection caused by all subtypes of HBV</td>
</tr>
<tr>
<td>HCV (RNA)</td>
<td>Liver</td>
<td>31 195.0</td>
<td>Antiviral drugs, interferon-α</td>
<td>In clinical trials</td>
<td>Individuals at high risk from HCV infection</td>
</tr>
<tr>
<td>EBV (DNA)</td>
<td>Burkitt lymphoma</td>
<td>82 6.7</td>
<td>No regulatory agency–approved treatments</td>
<td>In clinical trials</td>
<td>Individuals infected and noninfected with EBV, including infants</td>
</tr>
<tr>
<td></td>
<td>Hodgkin lymphoma</td>
<td>46 28.6</td>
<td>No regulatory agency–approved treatments</td>
<td>In clinical trials</td>
<td>Individuals infected and noninfected with EBV, including infants</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngeal carcinoma</td>
<td>98 78.1</td>
<td>No regulatory agency–approved treatments</td>
<td>In clinical trials</td>
<td>Individuals infected and noninfected with EBV, including infants</td>
</tr>
<tr>
<td>KSHV/HHV-8 (DNA)</td>
<td>Kaposi sarcoma</td>
<td>100 66.2</td>
<td>Doxorubicin, interferon α-2b</td>
<td>Little ongoing vaccine research</td>
<td>NA</td>
</tr>
<tr>
<td>HTLV-1 (RNA)</td>
<td>Adult T-cell leukemia/lymphoma</td>
<td>2 3.3</td>
<td>Antiretroviral therapy</td>
<td>In clinical trials</td>
<td>NA</td>
</tr>
<tr>
<td>Merkel cell polyomavirus (DNA)</td>
<td>Merkel cell skin cancer</td>
<td>80 1.2</td>
<td>Chemotherapy or radiation therapy</td>
<td>pcDNA3-LT DNA vaccine being tested in animals</td>
<td>Primarily heavily sun-exposed, older Caucasians</td>
</tr>
</tbody>
</table>

### Nonviral Infectious Agents: Bacteria

<table>
<thead>
<tr>
<th>Name of Infecting Organisms (Type)</th>
<th>Cancer Site</th>
<th>Attributable Cancers (Global Estimates) (^{5,6} )</th>
<th>Medical Therapies (Drugs, Vaccines)</th>
<th>FDA Approved or in Clinical Trials</th>
<th>Indicated for Which Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori (gram- neg, microaerophilic)</td>
<td>Stomach</td>
<td>50 10.5</td>
<td>PPIs together with antibiotics (e.g., metronidazole, clarithromycin)</td>
<td>Vaccine in phase 1 clinical trial</td>
<td>No defined patient population</td>
</tr>
<tr>
<td>Chlamydia trachomatis (gram-neg)</td>
<td>Cervical (possible HPV cofactor)</td>
<td>Unknown Unknown</td>
<td>Antibiotics</td>
<td>Approved</td>
<td>Women with HPV infection</td>
</tr>
<tr>
<td>Chlamydia pneumoniae (obligate intracellular)</td>
<td>Lung</td>
<td>Unknown Unknown</td>
<td>Antibiotics</td>
<td>Approved</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

(continued)
and amoxicillin or metronidazole (http://www.uptodate.com /contents/patient-information-helicobacter-pylori-infection -and-treatment-beyond-the-basics). Chlamydia trachomatis, a sexually transmitted bacterium that infects the female reproductive tract, may be indirectly a cause of cervical cancer, acting as a cofactor that cooperates with HPV in the promotion of squamous cell carcinoma of the cervix regardless of HPV serotype. Weaker evidence suggests a role for bacteria in certain other cancers, such as Salmonella typhi infection and the development of gallbladder cancer, Streptococcus bovis with colon cancer, and Chlamydia pneumoniae with lung cancer.

Although parasitic infections are not common in the United States, they pose a serious problem in the developing world. With travel between developed and developing countries having become commonplace, the PCC in the United States is likely to confront occasional parasitic infections in modern practice. Some of the most common parasitic flatworms are the liver flukes Opisthorchis viverrini and Clonorchis sinensis, which are associated with cancer of the bile duct and are contracted from eating raw or undercooked freshwater fish. Schistosoma haematobium is a parasite found in the water in developing countries of sub-Saharan Africa and the Middle East, and infection with this parasite, causing the disease schistosomiasis, has been linked to bladder cancer and possibly other cancer types.

Role of the Primary Care Clinician in Reducing the Risk of Infection-Associated Cancers

Two key levels of intervening to prevent infection-associated cancers are available to the PCC: averting the infection and preventing the cancer once infection has already occurred (see Table 6-1). The preferred approach is to prevent the infection in the first place. This strategy underlies the massive efforts aimed at developing microbe-directed vaccines for use in high-risk individuals and has particular appeal for infection-associated cancers in developing countries. When vaccines are not available or in the case of already infected individuals, current approaches to prevention rely on early detection and removal of premalignant or early cancerous lesions and, in some cases, treatment with antimicrobial drugs.

Vaccine approaches are successful when administered prior to exposure to the offending agent and they are cost-effective when used in high-risk individuals. The most striking example of these benefits is seen in the ability of vaccination to reduce HPV-associated cervical cancer. Immunization programs for HPV-naïve women and girls (as young as 11 years old) and sexually active women could nearly eliminate this cancer, which has a generally negative prognosis unless diagnosed at a very early stage. Since 2006, when the U.S. Food and Drug Administration (FDA) approved the first vaccine for HPV (types 16 and 18), there has been a substantial decrease in the incidence of HPV-16 and HPV-18 related cancers, including cervical cancer. Routine application of the long-standing screening approach using the Pap-nicolau (PAP) smear has effectively reduced the incidence of cervical cancer and cancer-associated mortality and is still an important preventive strategy in women with chronic HPV infection.

Vaccination for HBV has been available since the early 1980s and is now recommended for individuals at high risk, such as health care workers. Finally, for individuals who are already infected, various antiviral drugs are useful in treatment of the infection and secondarily prevention of the associated cancer. The Centers for Disease Control and Prevention (CDC) regularly publish vaccination guidelines and other information helpful for the PCC.
INFLAMMATION AND CANCER (TABLE 6-2)

A link between chronic inflammation (both of infectious and noninfectious etiology) and cancer has been strongly suspected from studies carried out by Virchow more than 150 years ago, indicating that inflammatory cells are present within tumors and from observations that tumors frequently arise at sites of chronic inflammation. The risks of some, but not all, cancers (including cancers of the colon, liver, pancreas, and esophagus) are substantially increased in the setting of chronic inflammatory conditions. Other cancers occur less frequently in association with inflammation. Numerous inflammation-based mechanisms have been shown to contribute to carcinogenesis. Key mediators of inflammation-induced cancer include nuclear factor kappa B (NF-κB), reactive oxygen and nitrogen species, inflammatory cytokines, prostaglandins, and specific microRNAs (Fig. 6-1).15,16

One of the strongest associations between inflammation and cancer is seen in colorectal cancer (CRC), with a risk that is 10-fold greater in the presence of inflammatory bowel disease, including ulcerative colitis (UC) and Crohn disease, compared to the general population.17 Colonoscopy is used both to diagnose and screen people with UC for CRC. Guidelines on how to manage UC suggest that screening for CRC begin 8 to 12 years after diagnosis and repeat screening colonoscopy take place every 1 to 2 years thereafter.18 Surgery to remove the colon can cure UC and remove the risk of colon cancer but is recommended only for patients (1) whose disease does not respond to medical intervention, (2) who exhibit precancerous lesions in their colonic mucosa, or (3) who have had serious complications in the colon (perforation, hemorrhage, toxic megacolon). In such cases, the entire colon, including the rectum, is generally removed. Either a total proctocolectomy with ileostomy or a procedure connecting the small intestine to the anus is performed. Evidence from clinical trials for prevention of CRC has demonstrated the chemopreventive efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin) in reducing the risk of adenomas and CRC.19 NSAIDs do pose a small risk of gastrointestinal (GI) bleeding, but recent findings showing an increased risk of cardiovascular events with long-term use of some NSAIDs have tempered the enthusiasm for preventive application of these agents. Despite this, pooled analyses consistently show that this increased risk is not seen in patients with low baseline cardiovascular risk19,20 or at lower doses when combined with an investigational drug that inhibits polyamine synthesis, difluoromethylornithine (DFMO).21,22

The impact of inflammation is seen across all cancer types.23 The Health, Eating, Activity, and Lifestyle (HEAL) study, a recent prospective cohort study of women diagnosed with stage 0 to IIIA breast cancer, found that low levels of systemic C-reactive protein (CRP) and serum amyloid A, measures of low-grade chronic inflammation, were associated with increased survival from breast cancer.24 Emerging evidence suggests that inflammation related to obesity plays a key role in esophageal cancer. Recent studies have shown that visceral fat in individuals who are overweight or obese is metabolically active, producing proinflammatory cytokines. These mediators of inflammation are overexpressed in erosive esophagitis and Barrett’s esophagus, both strongly associated with esophageal cancer.25

### TABLE 6-2 Chronic Inflammation and Increased Cancer Risk

<table>
<thead>
<tr>
<th>Disease or Etiology of Inflammation</th>
<th>Type of Cancer</th>
<th>Increased Risk (X-fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoinflammatory/Noninfectious Diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Colon</td>
<td>3</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Colon</td>
<td>6</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Pancreatic</td>
<td>2–20</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Endometrial</td>
<td>1.4</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Liver</td>
<td>219</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Thyroid</td>
<td>2</td>
</tr>
<tr>
<td>α1-Anti-trypsin deficiency</td>
<td>Liver</td>
<td>20</td>
</tr>
<tr>
<td>Rheumatoid arthritis (RA)</td>
<td>Lymphoma</td>
<td>Medium versus low RA activity = eightfold increase; high versus low RA activity = 70-fold increase</td>
</tr>
<tr>
<td><strong>Bacterial Exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Gastric, MALT lymphoma</td>
<td>11</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>Ovarian</td>
<td>3</td>
</tr>
<tr>
<td>Chronic prostatitis</td>
<td>Prostate</td>
<td>2–3</td>
</tr>
<tr>
<td><strong>Chemical/Physical/Metabolic Exposures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Multiple cancers (including liver, head and neck, pancreas)</td>
<td>2–7</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Mesothelioma</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Obesity</td>
<td>Multiple cancers (including esophagus, colon, and pancreas)</td>
<td>1.3–6.5</td>
</tr>
<tr>
<td>Tobacco smoke and inhalation of other noxious chemicals</td>
<td>Multiple cancers (lung, head and neck, bladder, pancreatic, kidney, gastric, acute myeloid leukemia)</td>
<td>&gt;10 (Lung cancer: men, 16; women, 4.2)</td>
</tr>
<tr>
<td>Gastric reflux, Barrett’s esophagus</td>
<td>Esophageal</td>
<td>50–100</td>
</tr>
</tbody>
</table>

MALT, mucosa-associated lymphoid tissue.
GI bleeding. However, in otherwise healthy individuals who are candidates for risk reduction of cardiovascular disease, the benefits of aspirin are likely to outweigh its risks. Potential lifestyle interventions to reduce systemic inflammation include changing to a low-glycemic-index diet and moderate exercise (Table 6-3). The message to patients should be that cancer risk can be reduced by including anti-inflammatory choices in their diet and reducing caloric intake, participating in at least 30 minutes of moderate to vigorous exercise 3 to 5 days per week, maintaining a healthy weight, limiting excessive exposure to sunlight, limiting alcohol consumption to moderate amounts, and, most importantly for those patients who smoke, encouraging them to quit.\textsuperscript{15,27,28}

![FIGURE 6-1. The balance of inflammatory mediators determines tumor suppression or tumor formation. NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; COX-2, cyclooxygenase-2.](image)

### TABLE 6-3 Lifestyle Interventions to Reduce the Risk of Inflammation-Associated Cancers

<table>
<thead>
<tr>
<th>Lifestyle Interventions</th>
<th>Specific Recommendations</th>
<th>Inflammation-Associated Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet\textsuperscript{15}</td>
<td>Reduce fried foods and red meat, alcohol intake; increase fruits, vegetables, and spices such as tea catechins and curcumin.</td>
<td>Colon, lung, stomach, esophagus, liver</td>
</tr>
<tr>
<td>Maintaining a healthy weight\textsuperscript{27}</td>
<td>Achieve a body mass index as close to normal as possible (20–25 kg/m\textsuperscript{2}).</td>
<td>Colon, breast (in postmenopausal women), endometrium, kidneys (renal cell), esophagus (adenocarcinoma), gastric cardia, pancreas, prostate, gallbladder, and liver</td>
</tr>
<tr>
<td>Tobacco cessation\textsuperscript{27}</td>
<td>Quit if one smokes; do not begin if a nonsmoker, especially in the young.</td>
<td>Lung, esophagus, bladder, larynx, oropharynx; increased risk for most other cancers</td>
</tr>
<tr>
<td>Sunlight exposure\textsuperscript{27}</td>
<td>Wear sunscreen at all times for exposure &gt;30 min/day, especially in the young.</td>
<td>Skin, including melanoma</td>
</tr>
<tr>
<td>Physical activity\textsuperscript{28}</td>
<td>Suggest 30–60 min of moderate or vigorous activity at least 5 day/week</td>
<td>Colon, breast, and endometrial cancers; possibly ovarian, lung, and prostate cancers.</td>
</tr>
</tbody>
</table>
References


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CHAPTER 7

Chemicals and Radiation

Lindsay M. Morton, PhD • Mark P. Purdue, PhD

KEY POINTS

- Ionizing radiation and numerous chemicals are well-established carcinogens, with increased cancer risks persisting for decades following exposure.
- Survivors of cancer may have substantial ionizing radiation exposure from their previous cancer treatments. These exposures should be documented, including information on which body regions were irradiated and the age at exposure, and surveillance for subsequent malignancies should be considered for some patients, particularly those treated at younger ages. Radiation-related risks are particularly notable for tissues in or near the radiotherapy treatment fields, with some patients (e.g., children) thought to be more radiosensitive.
- Chemotherapies from previous cancer treatments also may increase risk for subsequent malignancies, particularly cytotoxic chemotherapies such as alkylating agents and platinum-based chemotherapy.
- Certain occupations can result in exposures to chemical carcinogens at much higher levels than the general population. Occupational screening questions should be incorporated into patient histories, with a more comprehensive history obtained for certain high-risk occupations. Referral to a specialist in occupational medicine may be appropriate for additional follow-up.

RADIATION

A wealth of knowledge on the carcinogenic effects of ionizing radiation has been derived from epidemiologic studies of patients exposed to diagnostic and therapeutic radiation, workers exposed to occupational radiation, radiation accidents, and survivors of the atomic bombs as well as experimental studies of animals and cell cultures. Key determinants of ionizing radiation–related cancer risks include the radiation dose, age at exposure, time since exposure, and tissue(s) exposed.

The strongest and most consistently reported associations between ionizing radiation and cancer are for malignancies of the thyroid, breast (female), brain, and skin (nonmelanoma) as well as myeloid leukemias. Other cancers associated with ionizing radiation (with lower risk estimates and/or based on more modest evidence) include those of the esophagus, stomach, colon, rectum, liver, lung, bladder, salivary glands, connective tissue, bone, and ovary. In contrast, limited or no evidence for an association exists to date for cancers of the pancreas, uterine cervix, uterus, prostate, and testis or for melanoma of skin and lymphoid malignancies.

Therapeutic Radiation

Patients undergoing radiotherapy have high-dose radiation exposures to targeted tumor tissues, but tissues outside the treatment area also are exposed to a wide range of radiation doses because of scatter. Numerous studies of patients exposed to therapeutic radiation for malignant or benign conditions (e.g., ankylosing spondylitis, peptic ulcers) have demonstrated that patients are at risk for radiation-related subsequent malignancies, particularly those arising in tissues in or near the treatment fields.

Risk for most malignancies increases linearly with increasing radiation dose. Exceptions include risk for thyroid cancer, which appears to peak at 20 to 29 Gy and declines thereafter, consistent with a cell-killing effect, and leukemia, which appears to be nonlinear, although the exact shape of the dose response is not established. Higher risks often, but not always, are seen for individuals exposed at younger ages. Elevated risks of leukemia typically peak within several years following exposure and then decline with time, whereas elevated risks for other malignancies may not be evident for at least 5 to 10 years following exposure and persist for decades.
Most studies conducted to date have included patients treated with conventional X-ray (photon) or cobalt-60 gamma ray therapy. In the last decade, newer radiotherapy techniques (e.g., intensity-modulated radiation therapy [IMRT]) and other types of radiation (e.g., proton therapy) have been introduced in clinical practice with the aim of delivering high radiation doses to targeted tissues while sparing surrounding normal tissues. Possible differences in the risks of subsequent malignancies following advanced radiotherapies are poorly understood, with concerns remaining regarding the amount of normal tissue exposed to moderate scatter in IMRT and cancer risk from secondary neutrons in particle therapy.24,25

**Other Sources of Ionizing Radiation Exposure**

Consideration of cancer risks associated with radiation exposures from other sources is most relevant for patients who did not receive radiotherapy during prior cancer treatments because the radiation doses from these exposures typically are 10 to 1,000 times lower than doses from therapeutic radiation. Other sources of ionizing radiation exposure include diagnostic medical procedures (conventional diagnostic X-rays, computed tomography [CT] scans, and fluoroscopy), occupational radiation exposures, and environmental radiation (e.g., radon in underground mines and homes). Direct study of cancer risks from low-dose ionizing radiation exposures is difficult because of the need to study a large number of exposed individuals for a long period of time26; instead, risks typically are estimated by extrapolating results from studies of individuals with higher exposures (e.g., Japanese atomic bomb survivors, nuclear workers, and patients exposed to multiple diagnostic X-rays). Nevertheless, comprehensive review of all currently available data supports a linear dose-response relationship between ionizing radiation and cancer risk, suggesting that even very low doses are associated with increased cancer risk.4,5 Indeed, a study of children who received CT scans during 1985–2008 demonstrated an increased risk of subsequent brain cancer and leukemia with increasing radiation dose, with the risk primarily observed at dose levels that would be typical after multiple scans.27

**Focus on Survivors of Cancer**

Survivors of most cancers have a higher risk for subsequent malignancy than the general population28 likely because of prior cancer treatments, other medical history factors, lifestyle and environmental exposures, and genetic susceptibility. Although fewer than 10% of subsequent nonhematologic malignancies among adult survivors of cancer are thought to be related to radiotherapy,29 risks are higher for the development of malignancies in tissues in or near the original radiotherapy treatment fields (which received the highest doses), particularly for patients exposed at younger ages. Indeed, malignancies arising from highly radiosensitive tissues account for approximately 75% of subsequent malignancies occurring within several decades of a childhood cancer.30–32 Individuals with certain, rare hereditary disorders such as ataxia telangiectasia also are particularly susceptible to the effects of radiation, but less is known about genetic susceptibility to radiation-related carcinogenesis beyond the context of these rare disorders.33,34 Most studies are consistent with a multiplicative effect of radiation and other cancer risk factors (e.g., cigarette smoking).

Many survivors of cancer also have a history of chemotherapy treatment, alone or in combination with radiotherapy. Chemotherapy has long been recognized as leukemogenic and increasingly is recognized as affecting risk of nonhematologic malignancies as well (e.g., lung, stomach, bladder, breast, thyroid, bone sarcoma).13–16,18,31,36–38

**Role of Primary Care Clinicians**

For survivors of cancer, primary care clinicians should carefully document all prior cancer treatments, including information on which body regions were irradiated and the age of exposure for radiotherapy and information on the types and doses of chemotherapeutic agents. Consultation of current guidelines for surveillance for certain subsequent malignancies (e.g., from the National Comprehensive Cancer Network [www.nccn.org] or the Children’s Oncology Group [http://www.survivorshipguidelines.org]) can inform decisions about needed follow-up care and monitoring based on a patient’s treatment history, with particular attention paid to childhood cancer survivors because of their increased susceptibility.39 For example, annual chest imaging (X-ray or CT) is recommended for survivors of Hodgkin lymphoma treated with chest radiotherapy, beginning 5 years following treatment (www.nccn.org).

CT scans are typically the greatest source of ionizing radiation exposure other than radiotherapy because of repeated CT scans for cancer diagnosis and follow-up. Increased cancer risks associated even with low doses of ionizing radiation57 suggest that tracking of radiation exposures from nontherapeutic sources and the use of comprehensive risk-benefit analyses to guide decision making for appropriate use of CT scans are warranted.60 Finally, because patients who received radiotherapy have increased risk of nonmelanoma skin cancer (also caused by ultraviolet [nonionizing] radiation), counsel regarding sun protection measures and consideration of skin cancer screening may be particularly warranted.

**CHEMICALS**

Approximately 5% to 10% of cancers diagnosed in the general population are believed to be associated with exposure to workplace chemicals.31,42 This low figure mainly reflects the rarity of exposure to these agents in the general population rather than their carcinogenic potency; indeed, the relative risks associated with some chemical exposures are very large, making them important causes of cancer among exposed subpopulations such as workers in specific occupations and industries. For this review, we define “chemical” as a nonmedicinal substance with a distinct molecular composition that has been artificially formed or concentrated, focusing our discussion on chemicals typically encountered in occupational settings.

For most chemical carcinogens, the strongest epidemiologic evidence of carcinogenicity to humans has come from studies of workers who are exposed to chemical carcinogens at much higher levels than the general population and for longer periods of time. Occupational chemicals also can pose a threat to the general population, however, through releases into the physical environment via industrial air and wastewater emissions, renovation or demolition of buildings, and groundwater leaching from hazardous waste sites.

Table 7-1 lists all workplace chemicals and complex (multichemical) exposures that have been established as...
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Some Exposed Occupations/Industries</th>
<th>Tumor Site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metals and Metalloids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic and inorganic arsenic compounds</td>
<td>Nonferrous smelting, wood preservation, glass manufacturing</td>
<td>Skin, lung, urinary bladder</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Asbestos mining/milling, manufacture of asbestos products, construction, shipbuilding</td>
<td>Lung, mesothelioma, larynx, ovary</td>
</tr>
<tr>
<td>Beryllium and beryllium compounds</td>
<td>Beryllium miners, beryllium alloy makers and fabricators</td>
<td>Lung</td>
</tr>
<tr>
<td>Cadmium and cadmium compounds</td>
<td>Zinc/lead smelting, welding/remelting cadmium-containing steel or solders, producing/processing/handling cadmium powders</td>
<td>Lung</td>
</tr>
<tr>
<td>Chromium (VI) compounds</td>
<td>Chromate production and chromate pigment workers, chrome platers, stainless steel welders, leather tanning</td>
<td>Lung</td>
</tr>
<tr>
<td>Nickel compounds</td>
<td>Nickel mining, smelting, welding, casting, electroplating, production/use of nickel compounds</td>
<td>Lung, nasal cavity, paranasal sinuses</td>
</tr>
<tr>
<td>Silica dust (crystalline, quartz, or crystobalite)</td>
<td>Metal and nonmetal mining, nonmetallic (sandstone/clay/shale) milling, granite and stone industry, construction</td>
<td>Lung</td>
</tr>
<tr>
<td><strong>Other Chemicals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aflatoxins</td>
<td>Handling and processing of contaminated crops and feeds</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>4-Aminobiphenyl</td>
<td>Production, pigment manufacture, use of dyes</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>Auramine</td>
<td>Production/use of auramine dye, coloration of paper</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>Benzene</td>
<td>Production/use of benzene and benzene-containing substances (e.g., glues, rubber, paint, gasoline, detergents, some plastics)</td>
<td>Acute nonlymphocytic leukemia</td>
</tr>
<tr>
<td>Benzidine</td>
<td>Production, pigment manufacture, use of dyes</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>Benzo(a)pyrene</td>
<td>Industrial processes involving pyrolysis/combustion of coal, production and use of coal-derived products (including coal tar)</td>
<td>None</td>
</tr>
<tr>
<td>Bis(chloromethyl) ether and chloromethyl methyl ether</td>
<td>Chemical plant and laboratory workers, ion exchange resin and polymer markers</td>
<td>Lung</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>Petroleum refining, lead smelting, automobile exhaust</td>
<td>Hematolymphatic organs</td>
</tr>
<tr>
<td>Dioxin (2,3,7,8-TCDD)</td>
<td>Occupations where TCDD may be present as a contaminant (e.g., waste incineration, firefighting, chemical research, paper bleaching)</td>
<td>All cancers combined</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>Ethylene oxide production, sterilization of medical equipment</td>
<td>None</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Manufacture of formaldehyde and formaldehyde-based resins, manufacture of wood composite and furniture production, embalming</td>
<td>Nasopharynx, myeloid leukemia</td>
</tr>
<tr>
<td>Magenta</td>
<td>Laboratory workers using magenta dye</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>4,4’-Methylenebis(2-chloroaniline)</td>
<td>Manufacture of polyurethane/plastic products where chemical is used as a curing agent</td>
<td>None</td>
</tr>
<tr>
<td>2-Naphthylamine</td>
<td>Production, pigment manufacture, use of dyes</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>Ortho-toluidine</td>
<td>Rubber vulcanization</td>
<td>Urinary bladder</td>
</tr>
<tr>
<td>2,3,4,7,8-Pentachlorobenzofuran</td>
<td>Occupations where chemical may be present as a contaminant (e.g., waste incineration, firefighting, chemical research, paper bleaching)</td>
<td>None</td>
</tr>
<tr>
<td>3,3’, 4,4’, 5-Pentachlorobiphenyl (PCB 126)</td>
<td>Production/servicing/disposal of PCB-containing transformers and capacitors</td>
<td>None</td>
</tr>
<tr>
<td>Sulfur mustard</td>
<td>Military mustard gas disposal site</td>
<td>Lung</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Production of vinyl chloride resins and products</td>
<td>Hepatic angiosarcoma, hepatocellular carcinoma</td>
</tr>
</tbody>
</table>
human carcinogens as part of the International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans (http://monographs.iarc.fr/). Also listed are examples of occupations and industries where workers have potential exposure and the tumor sites for which a causal relationship has been established. In addition, occupations and industries that have been classified by IARC as causally associated with cancer, but for which the specific carcinogenic exposures are not yet known, are listed in Table 7-2. Chemicals evaluated by IARC as probable or possible human carcinogens are not addressed in this chapter.

Workers in mining and smelting operations, chemical production industries, and selected manufacturing industries are exposed to many of the identified carcinogenic chemicals. Cancers of the lung and urinary bladder have been most commonly linked to occupational exposures. For some chemicals, the implicated cancer is exceedingly rare in unexposed populations, such as mesothelioma following exposure to asbestos, hepatic angiosarcoma following exposure to vinyl chloride, and nasal/sinonasal cancer following exposure to wood dust.

Role of Primary Care Clinicians

Primary care clinicians play an important role in diagnosing cancers with an occupational etiology. Physicians can improve their recognition of such malignancies by increasing their level of suspicion for occupational disease, incorporating occupational screening questions into a patient history, and administering a comprehensive occupational history to patients when an occupational link is suspected. Referral to an occupational medicine specialist may be appropriate for patients who need additional follow-up or assistance.
References


CHAPTER 8 Obesity and Physical Activity

Peter Greenwald, MD, DrPH • Sasha Nunes • Elaine B. Trujillo, MS, RD

KEY POINTS

- Obesity accounts for approximately 20% of all cancer cases and has been identified as a cause of cancer in about 14% of cancer deaths in men and 20% of cancer deaths in women.
- Obesity is associated with increased risk of cancers of the esophagus, breast (postmenopausal), endometrium, colon and rectum, kidney, pancreas, thyroid, gallbladder, and possibly others.
- There is convincing evidence that physical activity (PA) is protective against colon cancer and probable evidence for PA and prevention of postmenopausal breast and endometrial cancer.
- Sedentary behavior is associated with increased colorectal, endometrial, ovarian, and prostate cancer risk.

"Maintenance of a healthy weight throughout life may be one of the most important ways to protect against cancer. This will also protect against a number of other common diseases.” American Institute for Cancer Research.

As the nation ages, the primary care clinician (PCC) can play an important role in encouraging patients who are overweight and obese to become healthier through weight reduction and increasing physical activity (PA). Obesity accounts for approximately 20% of all cancer cases and has been identified as a cause of cancer in about 14% of cancer deaths in men and 20% of cancer deaths in women. Obesity is associated with increased risk of cancers of the esophagus, breast (postmenopausal), endometrium, colon and rectum, kidney, pancreas, thyroid, gallbladder, and possibly others.

Regular PA of all types, including occupational, household, transport, and recreational, has been found to decrease cancer risk of the colon, breast (postmenopausal and possibly premenopausal), endometrium, lung, and pancreas. Sedentary behavior, defined as the absence of whole-body movement and lack of PA beyond normal daily activities are behavioral risk factors for cancer of the colon, endometrium, ovary, and possibly prostate.

OBESITY AND CANCER

Obesity is a complex condition associated with a plethora of comorbidities. Strong evidence indicates that body fatness, obesity, and overweight increase the risk of several cancers (Fig. 8-1). Unlike postmenopausal breast cancer, in which there is convincing evidence for an increased risk, body fatness decreases premenopausal breast cancer risk. Additionally, higher weight or body mass index (BMI) during teenage and young adulthood (18 to 20 years of age) is associated with a 10% to 30% decrease in breast cancer risk for both premenopausal and postmenopausal breast cancer. Furthermore, achieving and maintaining normal body weight by postmenopausal women can also lower risk and improve prognosis. See formulas for calculating BMI in Box 8-1.

The causal relationship of body fatness to cancer risk is unclear. Obesity is a state of chronic low-grade inflammation and accompanying inflammatory cytokines and mediators. The search for tumor-promoting agents such as insulin and insulin-like growth factor-1 and mechanisms to explain the cancer/obesity connection is ongoing.

ENERGY BALANCE AND OBESITY

According to data from the National Health and Nutrition Examination Survey (NHANES) 2003–2006 and 2007–2008, more than two-thirds of adults in the United States are overweight or obese, and more than one-third are obese. Overweight and obesity are pandemic. The causes are multifactorial and include genetic, environmental, behavioral, and socioeconomic factors. It has been estimated that 30% to 40% of the variance in BMI can be attributed to genetics and 60% to 70% to the environment. Single-gene defects, which are rare, are associated with Prader–Willi syndrome, Bardet–Biedl syndrome, and congenital leptin deficiency.

Overweight refers to an excessive amount of body weight that may come from muscles, bone, adipose tissue, and water. Obesity is a condition of excess body fat accumulation in relation to lean body mass. The increase in body fat may be evenly distributed over the body, or concentrated in specific regions, and body fat distribution is gender specific.
For patients who are morbidly obese and those at high risk because of comorbidities, bariatric surgery often is indicated. Recent studies have shown that bariatric surgery is associated with decreased gastric cancer risk in patients who are obese who had the surgery compared to patients who are obese who had not.¹³

The most commonly used measurement to define overweight and obesity is the BMI (Table 8-1). There are limitations to the usefulness of BMI. Body fat in athletes and those who have a muscular build may be overestimated. Conversely, body fat in older persons or those who have muscle loss or wasting may be underestimated. New imaging techniques have been developed to measure body fatness.⁸,¹¹

**OBESITY TREATMENTS**

Independent of the method used to determine overweight or obese status, achieving a weight loss to maintain a healthy weight is an important factor in cancer prevention.¹² If lifestyle modifications and/or behavioral interventions are not able to achieve realistic weight loss goals for a patient,⁹ additional treatment may be required, especially in patients who are obese, at increased medical risk, or have comorbidities. See http://win.niddk.nih.gov/publications/prescription.htm for more information for approved medications for obesity treatment.

For patients who are morbibly obese and those at high risk because of comorbidities, bariatric surgery often is indicated. Recent studies have shown that bariatric surgery is associated with decreased gastric cancer risk in patients who are obese who had the surgery compared to patients who are obese who had not.¹³

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**TABLE 8-1**

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Principal Cutoff Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.50</td>
<td></td>
</tr>
<tr>
<td>• Severe thinness</td>
<td>&lt;16.00</td>
<td></td>
</tr>
<tr>
<td>• Moderate thinness</td>
<td>16.00–16.99</td>
<td></td>
</tr>
<tr>
<td>• Mild thinness</td>
<td>17.00–18.49</td>
<td></td>
</tr>
<tr>
<td>Normal range</td>
<td>18.50–24.90</td>
<td></td>
</tr>
<tr>
<td>Overweight⁴</td>
<td>≥25.00</td>
<td></td>
</tr>
<tr>
<td>• Obese class 1</td>
<td>30.00–34.99</td>
<td></td>
</tr>
<tr>
<td>• Obese class 2</td>
<td>35.00–39.99</td>
<td></td>
</tr>
<tr>
<td>• Obese class 3</td>
<td>≥40.00</td>
<td></td>
</tr>
</tbody>
</table>

⁴ Asians can have higher percentage of body fat at a lower body mass index (BMI); therefore, overweight for Asians is a BMI between 23 and 29.9 kg/m². Adapted from World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: American Institute for Cancer Research; 2007. To learn more about the work of World Cancer Research Fund/American Institute for Cancer Research, please visit www.wcrf.org.
PHYSICAL ACTIVITY AND EXERCISE AND CANCER RISK

Research suggests that PA interventions may reduce the risk of developing some cancers, improve long-term health of cancer survivors, and possibly reduce the risk of recurrence of cancer.\textsuperscript{14,15} There is convincing evidence that PA is protective against colon cancer and probable evidence for PA and prevention of postmenopausal breast and endometrial cancer. PA also may prevent lung and pancreatic cancer (Fig. 8-2).\textsuperscript{1}

A systematic review of 18 studies on sedentary behavior and cancer risk found associations with increased colorectal, endometrial, ovarian, and prostate cancer risk as well as increased cancer mortality in women.\textsuperscript{16}

Prolonged television viewing time, which is how sedentary behavior is often measured, is associated with the presence of the metabolic syndrome (abdominal obesity, abnormal glucose levels, and lipid regulation)\textsuperscript{17} and with likely markers of systemic inflammation.\textsuperscript{19} A review of the literature on sedentary behavior and biologic pathways supports the association of adiposity and metabolic dysfunction as mechanisms responsible for the association between sedentary behavior and cancer.\textsuperscript{16}

WHAT THE PRIMARY CARE CLINICIAN CAN DO

Current PA guidelines for adults have been released by various groups, including the U.S. Department of Health and Human Services and the American College of Sports Medicine; these guidelines include PA specifically for reducing cancer risk.\textsuperscript{19,20} It is important for the PCC to work with the patients to develop a program of PA that meets their physical needs for moderate or vigorous activity based on an assessment of their current health. A list of moderate and vigorous activities including the measurement of their metabolic profiles can be found at www.cdc.gov/nccdphp/dnpa/physical/pdf/PA_Intensity_table_2_1.pdf. There are numerous tools available for the PCC to help patients choose PA activities that meet their needs (Table 8-2).

![Figure 8-2. Effects of physical activity on decreasing the risk of cancer. This figure shows the effect of physical activity on decreasing the risk of cancer by the strength of evidence. There was no evidence identified that linked physical activity with increased cancer risk. “Much of the evidence reviewed by AICR grouped colon and rectal cancer together as “colorectal” cancer. The AICR Panel judged that the evidence is stronger for colon than for rectum.” (Data from World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: American Institute for Cancer Research; 2007. To learn more about the work of World Cancer Research Fund/American Institute for Cancer Research, please visit www.wcrf.org.)](image-url)

<table>
<thead>
<tr>
<th>TABLE 8-2</th>
<th>Tools to Incorporate Physical Activity into Daily Life</th>
</tr>
</thead>
</table>
| **Desktop Helpers** from the American Cancer Society | • Downloaded to a computer desktop, this helper gives daily tips about increasing physical activity, nutritious eating habits, quitting smoking, and more.  
  • www.cancer.org/Healthy/EatHealthyGetActive/GetActive/desktop-helper |
| **Exercise Counts** from the American Cancer Society | • This tool gives the approximate calories burned for different activities.  
  • www.cancer.org/healthy/toolsandcalculators/calculators/app/exercise-counts-calculator |
| **Are you getting enough exercise quiz** from the American Institute for Cancer Research | • This is an easy-to-use quiz that gives a score based on a person’s exercise level and describes what the score means.  
  • www.aicr.org/reduce-your-cancer-risk/physical-activity/reduce_physical_quiz.html |
| **Be Active Your Way: A Guide for Adults** | • Based on the 2008 Physical Activity Guidelines for Americans, this tool helps create a plan, which includes how and when to fit physical activity into a schedule; intended for adults aged 18–64 y; available in Spanish.  
  • www.health.gov/paguidelines/ |
| **Target Heart Rate Calculator** from the American Cancer Society | • This tool asks a few questions and gives the range for a person’s target heart rate; easy to use but does not include detailed information about target heart rate.  
  • www.cancer.org/healthy/toolsandcalculators/calculators/app/target-heart-rate-calculator |
| **Simple Steps for Physical Activity (1, 2, & 3) pamphlets** from the American Institute for Cancer Research | • These pamphlets walk people through getting started with physical activity; additional information is provided as fitness levels increase.  
  • www.aicr.org/publications/brochures/simple-steps/start-where-you-are.html |

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References


The connection between diet and disease is one of the most compelling health stories of the past century and is likely to remain so for the current century. The primary care clinician (PCC) can play a significant role in promoting healthier food choices based on the evidence from epidemiologic and clinical studies which shows that specific bioactive food components (BFCs) can reduce the risk of cancers, cardiovascular disease, diabetes, and other diseases. A substantial number of cancers are related to environmental and lifestyle factors, with many of those associated with diet, although the diet and cancer relationship is not always clear. How diet affects cancer risk depends on the type of diet, a person’s genetic makeup, and the cancer type.

We consume thousands of BFCs daily. Many of these compounds might modify cancer risk and numerous cancer-related cellular processes. These BFCs include essential and nonessential nutrients from plants (phytochemicals), animals (zoochemicals), fungochemicals from mushrooms, and bacteriochemicals from bacteria in the gastrointestinal tract.

The most comprehensive evidence-based report on the role of food, nutrition, and cancer prevention was compiled in 2007 by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR). The WCRF/AICR provides an ongoing update through the Continuous Update Project (http://www.wcrf.org/cancer_research/cup/index.php).

Public health guidelines for cancer prevention emphasize that people should eat a plant-based diet with plenty of vegetables and fruits, limit red and processed meats, choose whole grains instead of refined grains, limit alcohol, and achieve and maintain a healthy weight (Table 9-1). The use of dietary supplements has not been found to reduce cancer risk, and in the case of some supplements, such as folic acid (colon cancer) and genistein from soy (breast cancer), they may increase risk.

**FOODS AND FOOD COMPONENTS**

Since the early 1980s, a systematic approach for identifying BFCs that might prevent cancer has been undertaken to improve the public’s health. The rise of nutritional sciences in the past three decades has focused on clues provided by epidemiologic dietary studies in populations with increased or decreased risk of various cancers. This information is weighed against preclinical and clinical studies to determine mechanisms of action to account for the level of cancer risk. The following food groups, foods, and food components listed focus on those that have shown promise through rigorous nutritional research; in this fast-evolving field, new findings will add to these in the next few years. The following reviews of evidence are for foods or food groups rather than dietary supplements; evidence for cancer prevention regarding foods or food groups is much stronger than that for dietary supplements. The basic message, however, should stress that one food choice will not prevent cancer; but a combination of foods that make up an individual’s total diet can reduce cancer risk, especially when part of a healthier lifestyle includes moderate exercise, avoiding tobacco, and maintaining a healthy weight.

**Vegetables and Fruits**

Vegetables and fruits might decrease the risk of mouth, pharynx, larynx, esophageal, and stomach cancers, but evidence is limited that vegetables and fruits protect against colorectal cancer. The BFCs found in vegetables and fruits, such as folate, vitamin C, fiber, and carotenoids, have been associated with a decreased risk of several cancers.

Recent studies have shown that cancer risk is influenced by genetic differences; for example, a glutathione S-transferase genotype has been found to influence the relationship between cruciferous vegetable intake and lung and colorectal cancer risk.

**Whole Grains**

Common whole grains include wheat, oat, barley, brown rice, and rye, each of which is a good source of dietary fiber. Public...
TABLE 9-1  Dietary Recommendations for Cancer Prevention

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consume a healthy diet with an emphasis on plant foods.</td>
<td>Choose foods and beverages in the portions that help achieve and maintain a healthy weight.</td>
</tr>
<tr>
<td>Limit consumption of processed meats and red meat.</td>
<td>Choose whole grains instead of refined grain products.</td>
</tr>
<tr>
<td>Eat at least 2.5 cups of vegetables and fruits each day.</td>
<td>If you drink alcoholic beverages, limit consumption to no more than one alcoholic drink per day for women or two per day for men.</td>
</tr>
</tbody>
</table>


health guidelines recommend choosing whole grains instead of refined grains. The public health message to increase whole grains in the diet originates from the benefits of dietary fiber contained in whole grains and the connection of dietary fiber to cancer risk. The preponderance of evidence is convincing that eating foods containing dietary fiber protects against colorectal cancer.3,4,6

Milk and Dairy
Milk and other dairy products are a good source of calcium, an essential mineral that is a major component of bones and teeth. Consumption of milk and calcium potentially protects against colorectal cancer; however, diets high in calcium potentially increase prostate cancer risk.3,4 Vitamin D fortification in milk and dairy foods improves normal calcium absorption and immune function and is essential for the formation, growth, and repair of bones.

Meat
In the United States, red meat accounts for 58% of meat consumption despite a continued shift toward poultry consumption. Processed meats, such as bacon, sausage, lunch meats, and hot dogs, account for 22% of the meat consumed.3 Meat intake may be an important factor in cancer etiology and risk. Higher intake of red and processed meats is associated with an increase in the risk of total cancer and cardiovascular disease mortality, whereas white meat intake appears to be protective. Specifically, red meat intake increased the risk of prostate, pancreatic, liver, and colorectal cancers but not breast cancer.8,9

Dietary Fats
The association between the intake of dietary fats and an increase or decrease in the risk of cancer has been investigated throughout the past four decades with little success. Because these studies involved a variety of fats, were not designed the same, were conducted in preclinical or animal studies, and with the knowledge that people may respond to different fats depending on their genetic makeup or other factors, no clear and convincing evidence has been found to confirm this association.10,11 An exception may be polyunsaturated fatty acids (PUFAs) of the omega-3 class found in fatty fish. These dietary fats have been associated with the prevention of cardiovascular disease, arthritis, asthma, and some cancers, although insufficient evidence is available for clear recommendations regarding cancers.3,4,12,13

Tea
Tea is one of the most ancient and popular beverages consumed worldwide. Tea, whether black, green, oolong, or white, contains a varied amount of polyphenolic compounds depending on the type of tea and the processing.

Tea intake from beverages, extracts, and polyphenol supplements has been studied for potential anticarcinogenic properties. Although the results have been inconsistent, there is some evidence from animal and human studies for a reduction in the risk of colon, stomach, breast, ovary, and prostate cancers.14

Soy
Asians have been eating soy, a member of the legume family, as a staple food for thousands of years. Soy foods contain various compounds that may have anticancer effects including protease inhibitors, saponins, phenolic acids, and isoflavones (genistein and daidzein).15

Soy’s isoflavones (genistein and daidzein) resemble weak forms of natural hormones; these isoflavones have been studied for their potential in preventing breast and prostate cancers, although the evidence is inconclusive. Because genistein has been shown to stimulate the growth of estrogen-dependent human tumor cells that were injected into animals, women should be cautious about taking soy supplements.16 Recent evidence suggests that soy consumed in childhood may be protective against breast cancer in adulthood.17,18

Garlic
Garlic is a vegetable, Allium sativum, and belongs to the Allium class of bulb-shaped plants that also includes onions, chives, and leeks. For centuries, garlic has been known for its medicinal properties, including antimicrobial, anticarcinogenic, and cardioprotective benefits.19 Epidemiologic studies have found that garlic intake might reduce the risk of cancers of the gastrointestinal tract, such as the stomach, esophagus, and colon.3

Folate
Eating foods rich in folate, such as vegetables, legumes, and fruits, is part of a healthy diet. Folate is an essential B vitamin that might be protective against cancers of the breast, pancreas, esophagus, uterus, and cervix.20 Folate above the recommended level of dietary intake (including increasing levels through the use of a folic acid supplement) has been associated with an increase in colorectal cancer risk.20

Carotenoids
Carotenoids, such as phytoene, phytofluene, α-carotene, β-carotene, γ-carotene, and lycopene, might protect against cancer of the mouth, pharynx, larynx, prostate, lung, and stomach.3,21–24 The bioavailability of the carotenoid lycopene, an antioxidant responsible for the red coloring in tomatoes, is influenced by food processing, cooking, and other components in the meal, including lipids and fiber. Lycopene is

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absorbed more efficiently when heated and when cooked with fats. The Mediterranean style of eating tomatoes cooked in olive oil increases lycopene absorption.21

WHAT THE PRIMARY CARE CLINICIAN CAN DO

Changing an individual’s eating habits is difficult because they are enmeshed in cultural, sociologic, and economic factors. Recommending healthy dietary choices as part of an overall emphasis on creating a healthier lifestyle for patients should be the goal. There are compelling reasons to talk to patients about healthy food choices that improve cardiovascular health, assist in maintaining a healthy weight, and prevent cancer. Various public health recommendations for individuals may be found that are based on the best available evidence from epidemiologic and clinical studies. Examples are those from the U.S. Department of Agriculture (http://www.cnpp.usda.gov/DGAs2010-PolicyDocument.htm) and the WCRF/AICR (http://www.dietandcancerreport.org/expert_report/recommendations/index.php). New reports are constantly emerging that will produce a clearer picture of how diet and BFCs reduce cancer burden.

References


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Cancer Screening
CHAPTER 10
Principles of Cancer Screening

Robert A. Smith, PhD • Jack S. Mandel, PhD, MPH

KEY POINTS

- Death from cancer is the leading cause of death before the age of 85 years and the leading cause of premature mortality.
- Cancer screening is an important preventive health service in the primary care setting.
- Most adults rely on their primary care clinicians to refer them to cancer screening, and thus two critical roles for the primary care clinician are insuring adherence to regular screening and advising patients on the benefits and limitations of cancer screening.
- The benefits of cancer screening should be understood in the context of the protection regular cancer screening provides against the odds of being diagnosed with an advanced cancer.
- Empirical studies of cancer screening require long-term follow-up, generally 20 years or more, to observe the fullest benefit of screening.

Cancer screening should be a core preventive health activity in the primary care setting. Just as measuring vital signs to monitor chronic conditions or identifying new problems is routine, cancer risk assessment, counseling, and referral to appropriate screening should be routine because these preventive services can prevent disability and premature death associated with advanced cancer. The challenge to the primary care clinician is to recognize and respond to this opportunity among an otherwise healthy group of patients and include these services in a demanding setting.

The burden of cancer is high (Table 10-1). Men and women have a 45% and 38%, respectively, lifetime risk of developing cancer.1 Cancer is the leading cause of death before the age of 85 years and the leading cause of premature mortality from all causes of death; meaning cancer is commonly diagnosed at a time in a person’s life when he or she is healthy and leading a productive life.

A person dying from cancer on average loses 15.5 years of life—25% more than the average number of years of life lost from heart disease mortality (11.7 years).1 More than half of the cancers diagnosed each year are cancers of the breast, cervix, colon and rectum, lung, and prostate.2 These cancers account for 47% and 40% of the cancer deaths in men and women, respectively.2

Primary care clinicians should care about cancer screening because they, more than any other health professional, have the greatest influence on adherence to recommendations for cancer prevention and early detection.3 In this chapter, we describe the basic principles of cancer screening and address key issues of relevance to primary care clinicians.

BASIC PRINCIPLES OF CANCER SCREENING

Cancer screening, a form of secondary prevention, is applied to an asymptomatic population to identify individuals with early stage cancer or precursor lesions when treatment is more likely to be beneficial compared with treatment of symptomatic disease.4 Thus, screening is different than case detection or case finding, which occurs when a patient presents to a physician with symptoms.

Screening the population can be recommended if there is solid evidence that early diagnosis and treatment of asymptomatic disease will reduce mortality and/or disease severity. Screening can contribute to primary prevention, for example, when colorectal cancer screening leads to removal of adenomas, subsequently reducing the incidence of colorectal cancer.5,6 When there is evidence suggesting reduced mortality or disease severity associated with screening but insufficient evidence to recommend that all individuals undergo screening, informed and shared decision making may be endorsed. Screening for prostate cancer is the most notable example of a cancer for which the balance of benefits and harms is generally regarded as uncertain.7

The Decision to Screen for Cancer

The observation that most cancers have better survival if diagnosed earlier in their natural history is not in itself sufficient to justify screening the population. Rather, several well-established criteria must be met before policymakers can justify the expense of screening the many to find the few (Table 10-2).
Burden of Disease

The burden of specific cancers should be considered within the context of two measures of absolute risk: lifetime risk and age-specific risk. The lifetime risk of being diagnosed and dying from cancer are good measures of disease severity as is the magnitude of the associated premature mortality (see Table 10-1). The age-specific risk is an indication of both individual risk and the underlying prevalence of disease. Thus, screening programs are designed to ensure that screening all adults within a particular age range will be productive in terms of cancers detected and premature deaths avoided.

An issue in cancer screening pertains to how both the effectiveness and yield from screening can be improved by targeting the population offered screening. At the most basic level, these debates focus on the age to begin and end screening, but better targeting with individual risk factors also is endorsed as a way to make screening more effective. However, from a programmatic standpoint, four points are important:

1. **Risk estimation programs may be good at estimating risk in groups with a common risk profile, but they are poor at estimating individual risk.** Thus, although most adults in any age group will not develop a cancer within a 10-year period or in a lifetime, there is no way to accurately predict who will and who won’t. Therefore, age-specific recommendations for screening commonly begin at an age when the incidence of disease begins to increase rapidly, or there is a sizable prevalence of occult precursor lesions. Stopping screening tends to occur when average longevity is less than 10 years or when life-limiting comorbidity renders preventive care of little value. Failure to consider general health status in the context of age leads to considerable overscreening as well as underscreening. For risk-based screening, the challenge is to use risk factors to identify most cases while screening a smaller subset of the population. To date, risk-based strategies have not been shown to be effective insofar because most individuals who develop cancer are at average risk.

2. **The mortality that occurs within an age interval generally does not account for most deaths that ultimately will be...**

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**TABLE 10-1**

<table>
<thead>
<tr>
<th></th>
<th>Breast</th>
<th>Cervix</th>
<th>Colon and Rectum</th>
<th>Lung</th>
<th>Prostate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime risk⁴</td>
<td>12.40%</td>
<td>0.68%</td>
<td>4.96%</td>
<td>6.90%</td>
<td>16.15%</td>
</tr>
<tr>
<td>Median age at diagnosis</td>
<td>61</td>
<td>48</td>
<td>69</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Incidence rate⁵</td>
<td>124.3</td>
<td>8.1</td>
<td>46.3</td>
<td>62.6</td>
<td>154.8</td>
</tr>
<tr>
<td>Number of new cases⁶</td>
<td>226,870</td>
<td>12,170</td>
<td>143,460</td>
<td>226,160</td>
<td>241,740</td>
</tr>
<tr>
<td>Median age at death</td>
<td>68</td>
<td>57</td>
<td>74</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>Mortality rate⁷</td>
<td>23.0</td>
<td>2.4</td>
<td>16.7</td>
<td>50.6</td>
<td>23.6</td>
</tr>
<tr>
<td>Number of deaths⁸</td>
<td>39,510</td>
<td>4,220</td>
<td>51,690</td>
<td>160,340</td>
<td>28,170</td>
</tr>
<tr>
<td>5-y survival (all)⁹</td>
<td>89.00%</td>
<td>67.90%</td>
<td>64.30%</td>
<td>15.90%</td>
<td>99.20%</td>
</tr>
<tr>
<td>Localized</td>
<td>98.40%</td>
<td>90.70%</td>
<td>89.90%</td>
<td>52.20%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Regional</td>
<td>83.90%</td>
<td>56.70%</td>
<td>69.60%</td>
<td>25.10%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Distant</td>
<td>23.80%</td>
<td>16.20%</td>
<td>11.90%</td>
<td>3.70%</td>
<td>27.80%</td>
</tr>
<tr>
<td>Average years of life lost (AYLL) ³</td>
<td>18.9</td>
<td>26.5</td>
<td>14.8</td>
<td>15.0</td>
<td>9.4</td>
</tr>
<tr>
<td>Person years of life lost (PYLL) ³</td>
<td>770,700</td>
<td>103,600</td>
<td>765,300</td>
<td>2,373,200</td>
<td>264,300</td>
</tr>
<tr>
<td>Prevalence ³</td>
<td>2.747,459</td>
<td>247,711</td>
<td>1,140,161</td>
<td>387,762</td>
<td>2,496,784</td>
</tr>
</tbody>
</table>

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**TABLE 10-2**

- The disease should be an important public health problem in terms of its frequency and/or severity.
- The natural history of the disease presents a window of opportunity for early detection before symptoms develop, that is, a detectable preclinical phase (DPCCP).
- There should be an appropriate screening strategy for the target population, that is, an age to begin screening and a screening interval.
- The screening test should be accurate, acceptable to the population, fairly easy to administer, safe, and relatively inexpensive.
- The treatment should be available and should be more effective if initiated during the presymptomatic (or earlier) stage than during the symptomatic (or later) stage.
- The screening guidelines should be based on good scientific evidence (usually and preferably based on results from a randomized controlled clinical trial).
attributable to a diagnosis within that age interval because they may occur many years in the future. This is the difference between age-specific mortality and incidence-based mortality. Whereas age-specific mortality measures the death rate within an age interval, incidence-based mortality measures the death rate attributable to a diagnosis within that age interval. For example, for the period 2005–2008, 10.1% of breast cancer deaths were among women ages 40 to 49 years, whereas after 10 years of follow-up, 16.5% of breast cancer deaths were attributable to a diagnosis between ages 40 and 49 years.10

3. Although the death rate may appear to be low for a particular age group, the rate of premature mortality may be high. Although cancer screening may avert fewer avoidable deaths in a younger cohort compared with an older cohort, the years of potential life lost (YPLL) associated with a diagnosis during a younger age interval may be significantly greater than the YPLL in an older age group of adults with a higher cancer mortality rate. The Health Insurance Plan (HIP) of Greater New York randomized controlled trial of breast cancer screening included women ages 39 to 49 years, because breast cancer deaths associated with a diagnosis during the 40s accounted for approximately one-third of all premature mortality associated with breast cancer.11 Although the goal of cancer screening is described as preventing deaths from cancer, more appropriately, it is to avoid “premature” deaths from cancer.

4. For individuals, screening is best understood as an ongoing course of preventive care rather than in the context of the results of each screening test. In any given year, most adults undergoing cancer screening in the primary care setting will not be diagnosed with cancer. In most adults’ lifetime, they will not be diagnosed with the cancers for which periodic testing is recommended. In contrast, they have a higher probability of false-positive results. This observation has led some to endorse a consumerist approach to screening, where adults are advised that the benefit in their case is lower than the likelihood of the continuum of harms.12 However, apart from the reassurance that an adult with normal test results does not have cancer, the greater potential benefit of screening is obtained if an adult develops cancer at some point in his or her lifetime. Thus, regular cancer screening should be thought of as a type of insurance that offers protection against the lower but significant lifetime odds of being diagnosed with an advanced cancer in the absence of screening.13

### The Screening Test

The ability of a screening test to distinguish diseased from non-diseased is measured by sensitivity and specificity. **Sensitivity** measures the test’s performance at correctly identifying individuals with the disease among the screened population and is defined as the number of true positives divided by the number of people with the disease (Table 10-3).

**Specificity** refers to the test’s performance at correctly identifying individuals without the disease among the screened population and is defined as the number of true negatives divided by the number of people who do not have the disease. Although most screened individuals will have accurate test results, no cancer screening test performs perfectly. Some with a positive test will be determined not to have the disease following the workup, that is, *false positives*; and some with a negative test will eventually be determined to be missed cases, that is, *false negatives*. Measures of screening performance typically are defined within the boundaries of the screening interval; that is, test sensitivity is determined by the incidence of cancer within 1 year of screening if an annual screening interval is recommended. Thus, true positives and false positives are measured close to the time of screening, whereas false negatives typically are identified at some future time within the screening interval when the patient presents with symptoms.

**Sensitivity** and **specificity** are generally inversely related; that is, an increase in sensitivity results in a decrease in specificity or vice versa. This is not strictly true because it is possible to improve performance in both measures simultaneously, although at higher levels of accuracy, further gains in one measure will diminish the other. Higher sensitivity results in fewer missed cases, whereas higher specificity results in fewer individuals unnecessarily subjected to costly and sometimes risky diagnostic procedures. Thus, balancing sensitivity and specificity (when possible) is important in determining the outcome of a screening program.

### The Evaluation of Screening

The most informative method to evaluate the efficacy of a screening test is a randomized controlled clinical trial (RCT) comparing cause-specific mortality in a group screened with a group not screened. An RCT overcomes biases that can give

| TABLE 10-3 | Measures of Screening Performance |
|---|---|---|
| **Screening test results** | **Yes** | **No** | **Total** |
| Positive | a | b | a + b |
| Negative | c | d | c + d |
| Total | a + c | b + d | |
| True-positive results | a | | |
| True-negative results | d | | |
| False-negative results | c | | |
| False-positive results | b | | |

Test sensitivity = true positives / true positives + false negatives, or a / (a + c)  
Test specificity = true negatives / false positives + true negatives, or d / (b + d)  
Positive predictive value (PPV) = true positives / true positives + false positives, or a / (a + b)  
Negative predictive value (NPV) = false negatives / false negatives + true negatives, or c / (c + d)
the appearance of better survival in a group screened, when, in fact, the screening test is not effective. Although screening for cervical cancer with the Pap smear has never been evaluated in an RCT, evidence of effectiveness of the Pap smear was judged to be sufficiently high that screening was established before the value of an RCT was fully appreciated. Today, most recommended cancer screening has been evaluated with an RCT; although once the efficacy of screening for a particular cancer is established, newer screening technologies for that cancer are not usually evaluated with an RCT because of ethical concerns and costs. More commonly, one technology is compared with another using a matched-pairs design where results of both tests are obtained for all study subjects and compared as if only one test versus the other had been done.

**Randomized Controlled Trials**

The appearance of improved survival associated with earlier cancer detection can be deceiving because the improved survival may be caused by several biases including lead-time bias, selection bias, and length bias. RCTs overcome these biases because the two randomized groups are equivalent, and cause-specific mortality rates in the two groups are compared from the study start date.

The goal of screening is to advance the time of diagnosis, that is, to gain lead time, which is the duration of time between when a cancer is detected by screening and when it would have been detected because of symptoms. The lead time gained is usually less than the duration of the MST because the lead time gained is a function of the interplay between the onset and duration of the MST and the timing of screening (Fig. 10-1). The only way to ensure the maximum potential lead time gained is adherence to regular screening.

It is important to distinguish lead time from lead-time bias. The crude survival rate is based on the percentage of individuals diagnosed with a particular cancer who are alive after a specific duration of time. If screening advances the time of diagnosis (compared with diagnosis after symptoms develop), but death occurs at the same time as it would in the absence of screening, then there will appear to be an increase in survival associated with screening when in fact there is not (Fig. 10-2).

Length bias is a function of the variability in cancer progression rates and refers to the tendency for screening to be more successful at detecting slow growing, less aggressive disease and to be less successful at detecting faster growing, more aggressive disease (Fig. 10-3). When evaluating survival data, better survival among the screen-detected cases may simply be the result of the predominance of cancer cases that are not life threatening regardless of how they are detected.

Length bias refers to the greater likelihood of screen-detected cancers having a longer sojourn time and hence a greater likelihood of being detected. In Figure 10-3, where the sojourn time intersects the screening time, the assumption is that the cancer was or could have been detected, although nonattendance to screening and human and technical factors can result in a missed opportunity to detect the cancer. The presence of some length bias is expected, although it is often invoked as a reason to question the value of screening. This criticism neglects the fact that there is no way a priori to identify who will or will not develop a fast or slow growing cancer nor are slow growing cancers inherently nonlethal or not associated with worse outcomes when detected late.

Selection bias influences survival rates because healthier individuals with a lower risk of dying are more likely to attend screening. Although selection bias has the theoretical potential to exert significant influence on survival rates, in RCTs to date, the estimates of the influence of selection bias are modest.

**Observational Studies**

Observational studies generally are not sufficient to support offering screening to the public. They can provide evidence
to invest in RCTs and afterward are useful for answering new questions about screening and for program monitoring. Because the evaluation of an RCT is based on intention to treat, observational designs provide the opportunity to measure the direct effect of exposure to screening versus invitation to screening.

Case-control studies tend to measure the actual effect of exposure to screening, whereas cohort studies may measure the effect of attending screening, an invitation to screening, or both. In the case of mammography screening, numerous studies demonstrated that long-term results typically were as good as or better than those in RCTs that showed the greatest breast cancer mortality reductions.\textsuperscript{14–16}

Cohort studies face several methodologic challenges. To properly evaluate the effectiveness of screening, it is important to determine the extent to which an analysis adhered to fundamental epidemiologic concepts, such as the rate of screening uptake in the population, exposure to screening, contemporaneous trends in incidence and mortality, and isolation of screened and unscreened cohorts. Other factors, often not measured, include the quality of screening, adequacy of follow-up of positive test results, and the quality of treatment. Most important is the requirement for very long-term follow-up. A recent 29-year follow-up of the Swedish Two-County Trial demonstrated a stable, statistically significant 31% reduction in the relative risk of dying from breast cancer in the group invited to screening compared with the control group but a steadily improving reduction in the absolute risk of dying from breast cancer over the entire follow-up period.\textsuperscript{17}

When cohort studies have too little follow-up\textsuperscript{18} and also fail to isolate screened and unscreened cohorts,\textsuperscript{19,20} they tend to demonstrate little benefit from screening. Similarly, although it seems intuitive to evaluate trends in mortality within a population to measure the influence of screening, drawing conclusions with measurable confidence also faces similar methodologic challenges.\textsuperscript{21}

**BENEFITS, LIMITATIONS, AND HARMS OF SCREENING**

Historically, more attention focused on the benefits of screening, but recently, there has been growing emphasis on the limitations and harms of screening. No cancer screening test or screening program is perfect. Although most adults undergoing screening will have accurate test results, several factors result in missed cancers or false-positive results. False-positive results can lead to anxiety, although the effects do not appear to be long lasting. However, actual harm could occur when false-positive test results are not resolved with additional noninvasive testing and an invasive procedure is required to determine the presence or absence of cancer.

A potential harm associated with screening is overdiagnosis, defined as the diagnosis of a cancer by screening that would never have been diagnosed in the patient’s lifetime if screening had not taken place. The harm associated with overdiagnosis is overtreatment; that is, the patient undergoes therapy, which has side effects for a cancer that did not require treatment. An overdiagnosed cancer is by definition nonprogressive but also pathologically indistinguishable from a cancer that is progressive and potentially life threatening. Thus, overdiagnosis must be thought of as a statistical concept rather than a pathologic concept because tumor features provide no insights into its frequency. Rather, estimates are derived by evaluation of incidence trends in groups exposed and unexposed to screening; and to properly estimate overdiagnosis, compensation for preexisting incidence trends, the effect of screening on lead time, and long-term follow-up are necessary.\textsuperscript{22}

**CONCLUSION**

Screening for breast, cervical, colorectal, and lung cancer can significantly reduce morbidity and mortality and are recommended based on an assessment that the benefits exceed the harms. Primary care clinicians can play a key role in reducing deaths from these cancers by encouraging and supporting cancer screening among their patients and by using systems to ensure regular adherence to recommended cancer screening intervals. With respect to prostate cancer screening, insofar as there is uncertainty about the balance of benefits and harms, men should have an opportunity to make a shared decision about whether or not to be screened.

**References**


KEY POINTS

• Biennial screening is likely to have the greatest benefits. This would harmonize with European guidelines.

• Breast cancer is not a single disease. We treat based on the likelihood and timing of recurrence and can use receptor subtypes and molecular tools to tailor systemic therapy. Use of these tools can avoid overtreatment of the screen-detected tumors, which may have a more indolent behavior.

• Screening is most likely to be of benefit in slower growing disease, which is why screening every other year is effective.

• Rapidly growing aggressive cancers most often present as interval cancers. Systemic therapy is what makes the difference in mortality for these women. A negative mammogram should not deter the performance of full evaluation in a patient with a new lump.

• The benefit of early diagnosis of premalignant lesions is unclear, less aggressive approaches to these entities need to be studied, and participation in relevant clinical trials should be encouraged.

Even though breast cancer surveillance is considered to be a central tenant of high-quality “preventive care,” there remains a great deal of controversy about the topic. Mammography screening is not prevention, it is early detection. After more than two decades of routine screening, what have we learned about the impact of breast cancer screening, and how do recent advances in scientific knowledge help us to understand and optimize that impact? To improve the impact screening has on mortality, we need to bring our understanding of this biologic heterogeneity of the disease into the screening and prevention realms.

SCREENING AND MORTALITY REDUCTION

Over the course of their lifetime, it is estimated that one in eight women will be diagnosed with breast cancer. Data show that cancers caught while still confined to the breast tend to have better outcomes (5-year survival rate of 98.1%, 83.8%, and 27.1% for localized, regionally advanced, and metastatic disease, respectively). The early randomized controlled trials, which showed a reduction in mortality from mammographic screening, sparked the introduction of mammographic screening programs first across northern Europe and then North America. The original trials took place prior to the advent of adjuvant systemic therapy, particularly the use of tamoxifen, and so when data is shown about the drop in breast cancer mortality over the last few years, there is likely a significant component because of therapy effect as well as screening itself. In the setting of standard adjuvant treatment for breast cancer, the impact that screening has on lowering mortality from breast cancer will not be as high as in the original trials. A recent study suggests that only one-third of the drop in mortality is because of screening, whereas two-thirds can be attributed to modern adjuvant treatment. Efforts to model the relative contributions of screening and systemic therapy to mortality reduction arrive at a similar proportion. So it is important to recognize that although screening is a tool contributing to reducing breast cancer mortality, that contribution is modest.

Breast cancer is heterogeneous and varies from high-grade, rapidly progressing cancers to low-grade, slow growing lesions with very low risk for early recurrence and variable risk for late recurrence. There appears to be a significant number of cancers that may have little or no risk for progression, a behavior that does not fit what we have come to think of as “cancer.” Such lesions have increased over the past two decades and may represent up to 30% of screen-detected cancers. Every breast cancer detected is not one that is necessarily life threatening. A significant proportion of screen-detected tumors are low-risk lesions, which includes in situ disease that varies from low to high grade. Importantly, just because a cancer is detected with screening does not mean that a woman’s life is saved because of that early detection.

Before we had molecular markers, a larger invasive cancer was treated differently from a smaller one regardless of grade. Nowadays, a 1.1-cm tumor that is low risk based on a molecular test would be treated the same and have a similar outcome as a tumor that is 2.2 cm and molecularly low risk. Tumors do not change biologic profiles over time, so even...
though there might have been tumor growth in the interim, the risk is similar, which is why screening every 2 years is effective. In fact, screening likely has maximal impact on slow and moderately growing tumors.

INTERVAL CANCERS

At the other end of the spectrum are the so-called “interval cancers,” which are cancers found between screening rounds. Although these tumors are often mammographically visible when clinically detected, they are usually not present on the prior mammograms, even viewing retrospectively. These tumors are usually higher grade, and they occur more frequently in younger women.16

The biology of screen-detected cancers appears to differ from that of tumors that present as masses.10,11 This is likely tied to growth rates that underlie these cancers. A recent report that evaluated the frequency of interval cancers among women who presented with large tumors (at least 3 cm, median of 6 cm) in a neoadjuvant trial—the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and molecular Analysis)—demonstrated that most, 91%, of such tumors had poor risk biology as measured by the 70-gene profile.12-14 In women older than the age of 40 years who were undergoing routine screening, a larger fraction of this population presented with interval cancers (84% vs. 32% expected).15 This contrasts with 30% to 40% of tumors presenting as high risk in the screen-detected population.

For these high-risk cancers, the most important interventions will be those that reduce the development of metastases. All of these women will get adjuvant or neoadjuvant therapy. For these women, finding the most effective treatments—optimizing systemic therapy and rapidly identifying new targeted agents—is what will likely reduce mortality. This is the goal of I-SPY 2 TRIAL and other neoadjuvant chemotherapy trials looking to identify promising new agents in women with aggressive cancers.16 The I-SPY 2 TRIAL is using the 70-gene prognosis assay as well as several emerging biomarker assays to help researchers rapidly understand which women should receive aggressive chemotherapy and targeted agents.16

The only way to pick up some of these cancers would be to screen more frequently, but the frequency required to pick up this type of aggressive cancer early is unknown, especially because some of these when found are subcentimeter and are node positive. This is where stratification of screening strategies to allow for more frequent screening in the younger age range makes sense.

HARMS OF SCREENING

Harms refer to the detection of tumors that might never have come to clinical attention or would not have been lethal if left alone (overdiagnosis) and also false-positive lesions (eventually proven to be nonmalignant). Over the two decades since screening has been introduced, there has been an increase in the rates of early-stage cancers—ostensibly indicating earlier detection—without a concomitant drop in the rates of regional cancer detection.17 Breast cancer incidence rates have risen, and the fraction of early-stage cancers detected has increased over time6—a statistic that we have used in the past to measure the effectiveness of screening. The total number of cancers is higher largely because of an increase in early-stage cancers without a big change in the number of regional or higher stage cancers5,6; this seems to suggest that screening may not be as effective as we had hoped in preventing aggressive cancers from presenting at more advanced stages and demonstrates that screening likely contributes to overdiagnosis. One way to mitigate against this is to use molecular tools to better classify tumors based on their metastatic potential. The tools to classify these lesions with more certainty are emerging; and once validated, we can classify these lesions and give them a different name, such as “IDLE” tumors (indolent lesions of epithelial origin)9 that better fits their biologic phenotype, and potentially avoid the problem of overtreatment that is the real problem associated with overdiagnosis.

CHALLENGES OF SCREENING

DCIS: Have We Found the Right Precursor?

If a substantial fraction of invasive tumors are extremely low risk and are not destined to become life threatening, we do not want to find the precursors of such cancers. Ductal carcinoma in situ (DCIS)—which in and of itself is not life threatening because it is a process of cellular proliferation that is contained within the ducts—has increased at least sevenfold18 since the advent of mammographic screening. DCIS, like invasive cancer, ranges in biologic risk from low grade, which only poses a 25% to 30% risk of progression to invasive cancer over 10 to 20 years; to high grade, which poses a 30% to 60%19 risk for progression over the first 5 years of diagnosis. The standard of care for all types of DCIS is nearly identical to that of invasive cancer, with lumpectomy and radiation or mastectomy intending to eliminate what is believed to be a precursor lesion for invasive ductal carcinoma (IDC).

Yet the incidence of IDC has not fallen over the past 20 years. This stands in contrast to the colon and cervical cancer screening settings in which screening has resulted in an incidence drop of 17% and 52%, respectively, between 1975 and 2003 versus an 18% increase in breast cancer incidence in the same period.2 For cervical and colon cancer, removal of cervical intraepithelial neoplasia (CIN) and polyps, respectively, have had a direct result on driving down incidence rates. From these observations, we have concluded that polyps and CIN are precursor lesions worth ablating. It is not clear that we can conclude the same for the DCIS we detect.19

We should consider high-grade DCIS as a precursor of higher grade cancers and thus a target of surgical intervention because of the 5-year progression trajectory. For the other 60% to 80% of DCIS,2 which are low to intermediate grade, we could consider more of a nonsurgical prevention strategy. We need to explore and test some new approaches. Active surveillance is used in low-potential prostate cancer, and we could apply the same criteria to lower risk breast lesions such as DCIS. Atypia—which is notoriously difficult to differentiate from low-grade DCIS and confers a similar risk—is only looked at as a risk factor for invasive cancer, and we thus do not recommend invasive intervention. In fact, the risk of progression to invasive cancer was shown to be reduced to 85% by the use of tamoxifen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-01 trial.20

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We could start to look at low-grade DCIS as well as atypia as particularly good candidates for chemoprevention. Hopefully, emerging molecular tools will enable clinicians to think about the risk of developing invasive cancer and enable more preventive approaches rather than surgical approaches.21

**How Do Current Guidelines Fit with Our “Biologic” Understanding of Screening?**

The 2009 U.S. Preventive Services Task Force (USPSTF) updated their screening guidelines, which adjusted the age and frequency recommendations for mammography. Data analysis of several randomized screening trials found insufficient evidence to recommend routine screening mammography for women older than the age of 75 years given competing risks from comorbidities, and they recommended that women younger than the age of 50 years only begin screening on an individual basis after consideration of personal and family history as well as the risks and benefits of screening. They were attempting to balance benefit with harms reducing false-positive examinations and overdiagnosis.22 There is increasing recognition of the problem of overdiagnosis.23,24 However, this puts a large burden onto primary care clinicians who do not have the appropriate tools to inform their patients. Therefore, we need to provide tools for primary care clinicians to assess a woman’s personal risk of breast cancer. As part of the Athena Breast Health Network, the authors have been developing online tools to allow patients to obtain their own personalized breast cancer risk, and these could be used by the primary care physician to inform discussion regarding the age to begin and the frequency of screening.

**What You Can Do to Improve the Quality of Screening Today**

Data suggests that screening every other year may be a cost-effective approach because biennial screening does not result in a higher fraction of locally advanced cancers. In a study of 169,456 women from the Breast Cancer Surveillance Consortium (BCSC), there was only a 3% increase in the percentage of locally advanced cancers with biennial screening, and this number was not statistically significant.25 However, the chance of having a biopsy decreased from 61% with annual screening to 42% with biennial screening over 10 years.25

Refer your patients to fellowship-trained mammographers who review their results. Just because a facility has a Mammography Quality Standards Act (MQSA) accreditation does not mean that there are trained mammographers who review the images. Trained mammographers maximize the diagnosis of cancer with the fewest false positives.24,26 In fact, in the United Kingdom and Sweden, it is required that you read a minimum of 5,000 images a year (most read between 12,000 and 20,000) to interpret screening mammograms, and you have to participate in quality improvement activities such as the PERFORMS test given to all radiologists every 6 months. Finally, there is an issue of resources. In the United States, there is a very small number of fellowship-trained mammographers who can evaluate mammograms on the target population of 85% of women aged 40 years and older. By adopting the USPSTF guidelines, we would more likely have the appropriate capacity.

**Future Trends**

Given that microcalcifications represent most of the mammographic abnormalities that result in either false positives or DCIS, rather than biopsy these initially, a decision could be made after following them for a period to determine if they change into a more suspicious lesion. There is no emergency to the diagnosis of either benign or DCIS lesions, and, therefore, waiting could provide an opportunity to be more judicious. We suggest that a criterion based on at least a 50% chance of DCIS and at least a 10% chance of invasive cancer would likely reduce the biopsy rates substantially (maybe by as much as 40%) and not likely make a material difference in outcome. To institute such a policy, it will be necessary to evaluate the new thresholds in large reader studies both to establish rules for calibration as well as to test various new proposed thresholds that may safely reduce biopsy rates, some of which are underway.27

Perhaps the best way forward is to consider risk-based screening,28 including the assessment of breast density at the first screening to refine risk estimates and appropriate screening frequency.29–31 What might be optimal is to develop risk-based screening much as is done in colorectal cancer. For those at very low risk, or at risk for low-risk slow growing tumors, screening might be very infrequent. For those at higher risk, with more dense breast tissue, the frequency might be higher and the techniques might vary.28

**Opportunity for Prevention**

Although the increase in complexity surrounding screening for breast cancer may at first seem daunting, it also allows us to provide options for women to decrease their risk of breast cancer. A focus on prevention would reduce both morbidity and mortality.

Level 1 evidence from randomized trials32–37 has been published, showing a 50% reduction in risk from drugs such as tamoxifen and raloxifene.37 Millions of women are estimated to be eligible for chemoprevention,35 yet risk assessment is not routinely offered and prevention interventions are rarely discussed. There is evidence that lifestyle interventions can also reduce risk (exercising,38 maintaining a healthy body weight,39 and avoiding excess alcohol40,41 and combination hormone replacement therapy42).

Extremely high-risk women (BRCA1 and BRCA2 mutation carriers), who have a 50% to 85% lifetime risk of developing invasive cancer, should be routinely identified as part of a routine in primary care or gynecology visits. Models such as breast cancer probability (BRCAPRO) or the American Society of Clinical Oncology (ASCO) or National Comprehensive Cancer Network (NCCN) guidelines can also be used to identify women at risk that merits BRCA1 and BRCA2 testing.43,44 There are real opportunities to prevent breast cancer in families with strong family history across several generations and to pinpoint whether or not the unaffected individual has a mutation that is found to be in affected persons in the family. We have strong evidence for the effectiveness of surgical prophylaxis43 in reducing genetic risk conferred by BRCA mutations.

Some groups, such as the Athena Breast Health Network, have initiated a demonstration project to evaluate the impact of routine risk assessment and prevention counseling and targeted intervention.25 Using both genetic and sporadic risk models, they are testing the impact of identifying the top 5%
of risk by age and providing special counseling to inform women of their risk and the potential options for prevention.

CONCLUSIONS

As we continue to refine our ability to treat breast cancer and prevent metastatic spread by identifying which treatments are optimal for which cancers, we can bring that knowledge back to the screening and prevention. Setting our goal should be able to identify populations who are at risk for specific tumor types and base future screens on the types of tumors for which women are at risk. Importantly, we should be able to reduce morbidity by also improving our tools to discriminate indolent from lethal cancers. Over time, we will be able to develop and tailor our prevention strategies.

The conversation about screening should not be about whether screening is “good or bad” but rather about how we can improve the process and how we can best use it to decrease mortality from breast cancer. We must understand the limitations of screening practices given breast cancer’s heterogeneous biology and identify which risk factors correspond to different tumor types so that we can most effectively improve our practices and optimize patient outcomes.

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CHAPTER 12

Screening for Gynecologic Malignancies

Diane M. Harper, MD, MPH, MS • Mack T. Ruffin IV, MD

KEY POINTS

• Of the gynecologic malignancies, only cervical cancer has an evidence-based early detection screening program that has reduced the incidence of cervical cancer.

• Liquid cytology and conventional cytology have the same sensitivity for detecting cervical intraepithelial neoplasia grade 3 (CIN 3) lesions.

• Screening recommendations include starting at 21 years of age and stopping at 65 years, extending the interval to every 3 years if cytology alone is used and every 5 years if cytology and oncogenic HPV cotesting is used.

• HPV vaccination may reduce the incidence of abnormal cytology screens, of colposcopy exams, and of excisional procedures.

• Cervarix offers protection from seven oncogenic HPV types at the cervix for at least 9.4 years, is 100% effective in one dose, and offers protection against five oncogenic HPV types at the vulva/vagina.

• Gardasil offers protection from two oncogenic HPV types at the cervix, vulva, and vagina for at least 5 years and from HPV-6 and -11, the major cause of genital warts.

Gynecologic malignancies occur at the cervix, uterus, fallopian tubes, ovaries, vulva, and vagina. Cervix cancer has the only evidence-based successful secondary screening process for early detection and treatment.

CERVIX

In 1928, George Papanicolaou showed that vaginal cytology could detect cervical cancer, but physician organizations in the United States were reluctant to adopt this screening method until the 1950s. Over the past 60 years, organized programs of repeated Pap smears have reduced the incidence of cervical cancer by 75%.

Human Papillomavirus Causation

At least 13 types of human papillomavirus (HPV) are considered human carcinogens, and at least one of these oncogenic types is necessary but not sufficient for oncogenesis. More than 90% of oncogenic HPV infections never progress to a precancerous state. Once a cervical intraepithelial neoplasia grade 3 (CIN 3) does develop, only 20% will progress to invasive carcinoma within 5 years, and only 40% will have progressed to invasive carcinoma within 30 years. It is the inability to predict which of the women with CIN 3 will progress to invasive cancer that guides the clinical algorithms of treating all women with CIN 3.

Cytology Screening Programs: The Target

The incidence of cervical cancer in the United States is 8.3/100,000 and varies according to ethnicity: American Indian/Alaskan Natives at 6.4/100,000, Asian/Pacific Islanders at 7.5/100,000, Blacks at 11.1/100,000, and Hispanics at 12.8/100,000.

The CIN 2/3 lesions, those clinically considered precancerous, occur hundreds of times more frequently than cervical cancers and have become the focus of the U.S. Cervical Cancer Screening guidelines. Their incidence peaks at 800/100,000 among women 25 to 29 years old, with an average incidence of 150/100,000 per year over all ages. Because CIN 2 has little true prognostic significance and has not been validated as a true cancer precursor, the overall incidence of CIN 3, also called carcinoma in situ (CIS), of 70/100,000 reflects more accurately the risk of cervical cancer in the United States (Fig. 12-1).

Cytology Screening Programs: The Method

Both conventional cytology and liquid-based cytology are equivalent methods for the detection of precancerous lesions (Table 12-1). Ancillary to CIN 2/3 detection, liquid-based cytology allows for concomitant laboratory-directed testing of
other sexually transmitted infections (STIs), including HPV, chlamydia, and gonorrhea.\textsuperscript{16} Testing for these STIs does not have to be linked to cytology screening, although, as the recommendations for routine chlamydia and gonorrhea screening end at the age of 25 years.\textsuperscript{17}

**Cytology Screening Programs: The Limitations**

There are five limitations to the current cytology screening programs. The first is lack of screening initiation.\textsuperscript{18} Without at least 70% of the population initiating and continuing participation, only individual health benefits will accrue, not population decreases in cancer incidence.\textsuperscript{19}

The second limitation is the inherent limits of technologic precision. The false-negative rate does not allow cytology screening to reduce the incidence of cervical cancer below 2–3/100,000.\textsuperscript{20} Adding aggregate oncogenic HPV testing for women 30 years and older allows near complete identification of women with CIN 3 and the ability to extend the screening interval to every 5 years but at a cost of tripling the

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**TABLE 12-1**

Cervical Cancer Screening Guidelines for the United States for Women with or without Human Papillomavirus (HPV) Vaccination\textsuperscript{10,11}

| Age to start | 21 y | Screening is not effective at identifying cervical cancer in women younger than 21 y.\textsuperscript{23} |
| Interval to screen | Every 3 y | Cytology for all ages 21–65 y\textsuperscript{22} |
| | Every 5 y | Cytology and HPV cotesting in women 30–65 y\textsuperscript{22} |
| Technology to use | Cytology as primary screen | Conventional or liquid-based cytology in all women 21–65 y; if negative for intraepithelial lesion or malignancy (NILM), repeat the screening every 3 y.\textsuperscript{15} |
| | HPV cotesting with cytology as a primary screen | Test for aggregate high-risk HPV types for women 30–65 y used in conjunction with cytology for primary screening. Hybrid Capture II and Cervista are the only FDA-approved tests.\textsuperscript{22} Negative high-risk HPV testing with NILM cytology requires repeating screening every 5 y.\textsuperscript{22} |
| Age to stop | 65 y | If three consecutive NILM cytologies within 10 y, with the most recent NILM cytology within past 5 y |
| | | If two consecutive NILM cytology/negative HR HPV within 10 y, with the most recent NILM/ negative cotesting within past 5 y |
| | For women who have treatment for a CIN 2/3 lesion at 45 y or older | Continue to screen for at least 20 y after return to NILM cytology after CIN 2/3 treatment.\textsuperscript{27} |
| | At hysterectomy | Only if the cervix is removed and past cervical screening history has no evidence of or treatment for CIN 2/3 or cervical cancer. |

**FIGURE 12-1.** Annual incidence of cervical intraepithelial neoplasia grades 2 (CIN 2) and 3 (CIN 3) lesions by age group. (From Insinga RP, Glass AG, Rush BB. Diagnoses and outcomes in cervical cancer screening: a population-based study. Am J Obstet Gynecol. 2004;191[1]:105–113, with permission.)
cost of the testing and quadrupling the false-positive rate.\textsuperscript{21} Physicians who adopt the cytology/HPV cotesting screening method must not screen normal women any more frequently than every 5 years because of its prohibitive cost to the health care system with no increase in health care benefit.\textsuperscript{22}

The third limitation is the decreased quality of life associated with the vulnerability of the speculum examination to obtain cytology specimens and the follow-up colposcopy examination. The high false-positive rate for CIN 3 from any abnormal cytology report\textsuperscript{14,23} should be guiding revisions in our clinical recommendations for referral to colposcopy because the effects of this false-positive rate include anxiety, depression, and lifetime changes in body perception,\textsuperscript{24,25} causing a substantial proportion of women not to seek colposcopic follow-up.\textsuperscript{26}

The fourth limitation is the potential reproductive morbidity of premature births associated with treatment by electrosurgical excision procedures of diagnosed CIN 3 lesions.\textsuperscript{27,28}

The fifth limitation is the lack of compliance with continuing screening, especially after the completion of childbearing. In addition, women who have had a past CIN lesion remain at high risk for recurrence of HPV-associated anogenital cancers. Within 10 years of treatment for any CIN lesion, there is a 3- to 12-fold increase in the development of cervical, vaginal, anal, and vulvar cancers\textsuperscript{29} and a threefold increased risk of death from any HPV-associated anogenital cancer excluding cervical cancer.\textsuperscript{30} From initial CIN treatment, the risk of cervical and vaginal cancer development over the subsequent 25 years continues to be double the general population incidence.\textsuperscript{31}

### Cytology Screening Programs: Current US Recommendations

The U.S. Preventive Services Task Force and the American Cancer Society, in conjunction with others, have raised the age to start screening to 21 years regardless of prior sexual experience and recommend no further screening in women with a normal history after the age of 65 years (see Table 12-1). Both groups recommend screening every 3 years with cytology alone or every 5 years in women older than age 30 years with cytology and HPV cotesting. This reduces the lifetime number of screens to 10–17 from the 40 per lifetime in past annual recommendations.\textsuperscript{10,11}

Only testing for aggregate oncogenic HPV types, such as in the Hybrid Capture II or the Cervista test, is the U.S. Food and Drug Administration (FDA) approved for screening in conjunction with cytology.\textsuperscript{32} Screening for specific HPV types has insufficient evidence to show any cost-effectiveness for population screening. The combination of cytology and HPV testing allows an extended screening interval of 5 years before the risk of CIN 2/3 development exceeds the 5/1,000 threshold considered acceptable for cervical screening tests.\textsuperscript{22,33}

#### Primary Prevention: Human Papillomavirus Vaccination

Two prophylactic vaccines are FDA approved for the prevention of persistent type-specific HPV infections and their disease sequelae. Trial data from randomized controlled trials provides a more robust understanding of the two vaccines.

Cervarix contains virus-like particles (VLPs) to HPV-16 and HPV-18 yet has efficacy for at least 9.4 years against seven oncogenic HPV types because of cross protection: HPV 16/18/31/33/45/51/52 in both the α7 and α9 species.\textsuperscript{34} Cervarix is 100% effective for at least 4 years with one dose for HPV 16/18 infections\textsuperscript{35}; and no trial participant has lost vaccine-induced immunity after 9.4 years after three doses.\textsuperscript{36}

Gardasil contains VLPs to HPV-16 and -18 as well as to HPV-6 and -11, the cause of most genital warts, and has efficacy for at least 5 years to only these types.\textsuperscript{37} There is no cross protection and no efficacy documented for less than three doses. Figure 12-2 shows the large loss of detectable antibody titers for all four vaccine-related HPV types in women within 8.5 years.\textsuperscript{38,39} Figure 12-3 shows that more men lose detectable antibodies to the vaccine-relevant HPV types than women, and men lose them 1 to 3 years earlier than women, often within the first 2 years.\textsuperscript{39–42} Other vaccines have shown similar gender differences in immunogenicity and longevity of duration.\textsuperscript{43–45}
The two vaccines are proven effective at reducing the incidence of abnormal Pap tests, of colposcopic exams, and of excisional treatment procedures (Table 12-2). Primary prevention is targeted to 11- to 12-year-old girls with permissible vaccination of women up to the age of 26 years. Unless the vaccines have efficacy beyond 15 years, the incidence of cervical cancer will be unaffected.

Various modeling exercises have indicated a very small reduction in cervical cancers with the use of both cytology and vaccination after 60 years if there has been near complete population compliance with vaccination, complete three-dose implementation, and lifetime efficacy of the vaccine. Current Centers for Disease Control and Prevention (CDC) data indicates that 60% of the Gardasil doses administered are not effective because of inappropriate timing of the three doses or less than three doses being received.

**VULVA, VAGINA**

There are no secondary screening programs for vulvar or vaginal cancers. Most are detected because of symptoms or incidentally during pelvic exams for cytology screening or STI testing.
Half of vulvar and 90% of vaginal cancers are HPV associated. The HPV-associated cancers occur in younger women and are less morbid than non–HPV-associated cancers.

Both vaccines were effective against HPV-16–associated vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) lesions during the 3.7 years of trial follow-up, but Cervarix was also protective against HPV-18–, HPV-31–, and HPV-45–associated VIN and VaIN lesions.

Any protection from HPV vaccination against vulvar or vaginal cancers is incidental to the purpose of prevention of cervical HPV infections and subsequent cervical disease.

**OVARY**

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial has not shown any screening modality, including CA-125 and transvaginal ultrasound, to decrease the incidence of ovarian cancer. The use of oral contraceptives is protective in most studies.

High-risk groups include those with a family history of ovarian cancer, with Lynch syndrome or breast cancer suspected because of BRCA 1/2 mutations.

### ENDOMETRIUM AND FALLOPIAN TUBES

Vaginal bleeding is often the symptom heralding endometrial cancer even early in the disease process. Women older than the age of 35 years may have atypical glandular cells or atypical glandular cells of endometrial origin on screening Pap test, from which up to 20% are true endometrial cancers.

Transvaginal ultrasound and endometrial sampling are not appropriate screening tests for either fallopian tube cancers or endometrial cancers in asymptomatic women but may be useful in the diagnostic workup of a symptomatic woman or one whose Pap test coincidentally shows abnormal glandular cells.

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CHAPTER 13 Colorectal Cancer Screening

Richard C. Wender, MD

KEY POINTS

- Have an office screening policy that has at least two options for patients—colonoscopy and a sensitive fecal occult blood test/fecal immunochemical test (FOBT/FIT).
- Clearly recommend screening for all eligible patients.
- Use office systems and technology to track screening results, identify care gaps, and issue reminders.
- Develop an "open access" colonoscopy system with your colonoscopist partners.
- Monitor practice-wide screening rates and strive for 80%.

The value of colorectal cancer (CRC) screening is proven. Although colon cancer remains the second leading cause of cancer-related death in the United States and will kill an estimated 51,690 people in the United States in 2012, age-adjusted mortality rates are falling every year, and much of this decline is attributable to improving screening rates.1,2 Screening for CRC and for precancerous polyps (CRC screening) represents a vitally important public health opportunity and a fundamental responsibility for all primary care practices. The chief determinant of whether or not an individual is up to date with screening is a recommendation from their primary care clinician.3

The highest performing systems and practices are now achieving CRC screening rates of close to 80%. But we have a long way to go as a nation to reach the 80% goal, and it will demand the dedicated effort of all primary care practices, and the systems that support those practices, to achieve that goal.

Screening guidelines for average-risk men and women aged 50 years and older—authored by the American Cancer Society (ACS), U.S. Multi-Society Task Force, and the American College of Radiology as well as the U.S. Preventive Services Task Force—have a high degree of concordance and, operationally, are identical.4,5 Although both organizations include flexible sigmoidoscopy as a screening option and the ACS guideline includes stool DNA, barium enema, and computed tomographic (CT) colonography, (“virtual” colonoscopy) on their menu of acceptable tests, almost everyone in the United States is being screened with one of two modalities: high sensitivity fecal occult blood testing, performed using a guaiac fecal occult blood test (gFOBT), or fecal immunochemical test (FIT), performed on spontaneously passed bowel movements, or colonoscopy. Offering all patients either a colonoscopy every 10 years or a sensitive stool blood test every year defines a national screening strategy for all patients. Of interest, a recent study demonstrated a 50% reduction in CRC mortality using a screening strategy based on flexible sigmoidoscopy.6 Given the overwhelming shift toward colonoscopy, it seems unlikely that flexible sigmoidoscopy screening will undergo a resurgence. Table 13-1 summarizes five key points to maintaining a high-quality screening program.

RECTAL EXAMINATIONS ARE NOT PART OF SCREENING

Many clinicians continue to perform a one-time stool blood test on samples obtained during a rectal examination.7 Based on high-quality evidence, guidelines conclusively state that the one-time FOBT obtained during rectal examination is insensitive for polyps and cancers.8 The test does not qualify as a screening option. Even if a clinician chooses to continue to perform this examination, the patients still require one of the evidence-based screening tests, either colonoscopy or at home FIT/gFOBT obtained on spontaneously passed bowel movements.

ALL POSITIVE GFOBT AND FIT MUST BE FOLLOWED BY COLONOSCOPY

The benefit of a stool blood–based screening strategy can only be realized if every patient who tests positive on any one specimen receives a follow-up colonoscopy. For that matter, every patient with an abnormal flexible sigmoidoscopy, barium enema, or CT colonography must undergo a colonoscopy. Abnormal stool tests should not be repeated even if a patient did not adhere to the prescribed diet.
for gFOBT or did not stop medications that can produce false positives.

**COLON CANCER SCREENING WORKS**

Screening by any method substantially reduces the risk of dying of colon cancer. A large trial of offering annual gFOBT testing demonstrated a 33% reduction in mortality with annual screening.9 Another study of colonoscopy screening of a group of individuals with a history of colonic polyps demonstrated a 53% reduction in death.10 In fact, high-quality health outcome modeling has demonstrated that any of the recommended approaches to screening, assuming 100% adherence to the testing strategy, can result in a similar number of life-years saved.11

**HIGH-RISK GROUPS**

Obtaining a personal medical history and a family history that includes age of diagnosis of cancer or polyps is the key clinical tool used to assign risk. Individuals with a family history of polyps or cancer in a first-degree relative are at increased risk for CRC. Individuals with a hereditary syndrome such as hereditary nonpolyposis colorectal cancer syndrome or familial adenomatous polyposis and individuals with a personal history of inflammatory bowel disease, even if it is clinically dormant, are at high risk and should be referred to a specialist for close surveillance.12-14 Individuals at higher than average risk must be screened with colonoscopy and may need to start screening at age younger than 50 years old and/or be screened more frequently.

**RISKS OF SCREENING**

Virtually all of the risk of screening is associated with colonoscopy—the final common pathway for all screening methods. Adverse effects of colonoscopy without polypectomy are estimated to occur in about 0.1% to 0.3% of all individuals, with a substantial higher risk of bleeding and other complications if polypectomy is performed, with complication rates of about 0.5% to 2.8%. Cardiovascular complications occur infrequently in individuals younger than age 70 years; about 0.13% suffer a complication in the 30 days following colonoscopy, but these rates increase with advancing age and are twice as high in individuals older than age 80 years.15

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**WHEN TO STOP SCREENING**

There is no absolute age to stop screening that is appropriate for all people. Stopping depends on life expectancy, patient preference, the likelihood of benefit, and the risk of screening, which does increase with age. Removing a precancerous polyp has the potential to prevent a colon cancer death in about 10 years, so an aggressive approach to remove all polyps in an individual with a limited life expectancy is not sensible. It’s reasonable to stop all screening by age 85 years and to consider the health of the patient between ages 75 and 85 years. Screening older patients with annual gFOBT or FIT as opposed to colonoscopy is also worth considering.

**REACHING 80% SCREENING RATES**

The Centers for Disease Control and Prevention (CDC) has set a national goal to achieve an 80% screening rate for the population. Although this rate is being approached in several large integrated delivery systems, few independent primary care practices are achieving this milestone. And most practices don’t actually know their practice-wide screening rates. To reach this screening rate, practices must be able to identify their population of eligible patients, determine and record the screening status of each of these eligible individuals, establish systems to reach individuals due for screening, use a team-based approach in the office to ensure that every opportunity is used to recommend and implement screening, and develop a partnership with colonoscopists that clearly delineates responsibilities for screening and facilitates patient hand-offs. Implementing a system of “open access” colonoscopy for healthy individuals that allows patients to go directly for colonoscopy without a previsit is a key strategy to increasing screening rates.16-18

**SPECIAL CONSIDERATIONS**

Practices Must Be Able to Offer a Stool Blood Testing Screening Option

Many practices now recommend colonoscopy every 10 years as their preferred approach to screening, a policy that is completely consistent with screening guidelines. Some patients cannot afford or will not accept screening colonoscopy. Therefore,

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**TABLE 13-2**

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achieving the 80% threshold is not possible in most practice settings unless an alternative to colonoscopy is available. For patients who hesitate when offered colonoscopy, giving them a stool testing kit makes sense.

FITs Should Replace gFOBTs

FITs are specific for colon blood and are unaffected by diet or medications. Some FITs can be performed on only one or two specimens instead of the three tests required for gFOBT testing. As a result, return rates are higher for FITs than for gFOBT. FITs have very good performance characteristics, with equal or greater sensitivity with preserved or even better specificity when compared to gFOBT. Table 13-2 lists commercially available FITs. Medicare and other insurers do pay for FITs.

CONCLUSION

Colon cancer screening will prevent premature cancer deaths. Primary care clinicians will ultimately determine whether the nation can achieve the 80% screening goals. A systematic approach to screening and taking advantage of fecal immunochemical testing and colonoscopy confers the best opportunity to realize this national goal.

References

KEY POINTS

- Hepatocellular Carcinoma (HCC) is the fastest rising cancer in the United States.
- All patients with cirrhosis should be screened for HCC.
- Ultrasound every 6 months is the most widely accepted screening and surveillance regimen.

Patients with chronic hepatitis B virus (HBV) infection (regardless of degree of fibrosis) and all patients with cirrhosis (no matter the cause) are at risk of developing hepatocellular carcinoma (HCC). The evidence for screening is based on one randomized controlled trial of 18,000 people infected with HBV in China. The study showed a 37% reduction in HCC-related mortality in patients who received twice yearly ultrasound and measurement of serum α-fetoprotein (AFP) level.1 There are no similar trials in patients with hepatitis C virus (HCV) or in patients with cirrhosis. However, several studies (nonrandomized trials and observational studies) have also shown a survival benefit of screening.2,3

The American Association for the Study of Liver Diseases (AASLD) Practice Guidelines and the National Comprehensive Cancer Network (NCCN) Guidelines recommend screening and surveillance for patients at high risk for HCC (cirrhosis and chronic HBV infection)4,5 (Table 14-1). The AASLD guidelines are most comprehensive and call for ultrasound every 6 months in patients with cirrhosis and in HBV carriers with or without cirrhosis if they are Africans older than 20 years of age, Asian males older than 40 years of age, or Asian females older than 50 years of age. If a patient infected with HBV has a family history of HCC, it is recommended to screen that patient 10 years earlier than the age at diagnosis of the affected first-degree relative. Serum AFP is very helpful when it is significantly elevated or rises substantially from a previous level, but the low sensitivity of this test and the lack of an elevated AFP in 30% to 50% of cases make it inadequate and misleading because AFP may also be elevated in the ongoing process of liver injury and repair that underlies the pathogenesis of fibrosis. Ultrasoundography has a sensitivity of approximately 65% and a specificity of more than 90% for early detection.6 However, ultrasound is operator dependent, and there are significant geographical variations in the level of training of the operator and time spent on the exam.

Contrast-enhanced, multiphase imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), are not generally recommended for HCC screening because of their high cost and potential harm. However, in patients in whom ultrasound is insensitive (e.g., obesity or significant heterogeneity), a yearly dynamic image (MRI if tolerated) alternating with ultrasound may be considered. However, the sensitivity, specificity, and positive and negative predictive values of dynamic imaging for the purpose of screening and surveillance are unknown.

| Table 14-1: Recommended Populations for Screening/Surveillance |
|-----------------------------|-----------------------------|
| **Cirrhosis**               | **Noncirrhotic HBV Carriers** |
| All causes                  |                             |
| - Viral                     | Asian males >40 y           |
| - Autoimmune                | Asian females >50 y         |
| - Hereditary                | African blacks >20 y        |
| - Metabolic                 | Family history of HCC       |

HBV, hepatitis B virus; HCC, hepatocellular carcinoma.
References


Barrett’s Esophagus

Anil B. Nagar, MD

CHAPTER
KEY POINTS

- Barrett’s esophagus is common, affecting about 3 million Americans.
- Screening of general population is not recommended.
- Screening may be considered in elderly, white male patients with chronic GERD and additional risk factors such as hiatal hernia and obesity.
- Patients with known Barrett’s esophagus should be surveyed with upper endoscopy and biopsy every 3 to 5 years and treated with proton pump inhibitors.
- Endoscopic therapy is recommended as first-line therapy for high-grade dysplasia.

RISK FACTORS AND CLINICAL PRESENTATION

The risk factors for Barrett’s esophagus include a chronic history of GERD; older age; male sex; white ethnicity; large hiatal hernia and obesity, especially intra-abdominal fat; smoking; and alcohol use. Adenocarcinoma of the distal esophagus shares similar risk factors as Barrett’s esophagus. Most patients are diagnosed in the sixth decade because of complaint of heartburn; importantly, approximately 50% of patients with Barrett’s will not complain of heartburn.

DIAGNOSIS

The diagnosis of Barrett’s esophagus rests on endoscopic appearance and tissue histology. Barrett’s (columnar) epithelium appears as reddish pink or salmon colored, as compared to the pale grayish white normal squamous epithelium. This “columnar” epithelium should be observed above the esophagogastric (EG) junction and thus in the distal esophagus and biopsies must document metaplasia with specialized intestinal epithelium as defined by the presence of goblet cells in the epithelial lining.

Clinical Implications of Barrett’s Esophagus and Dysplasia

Esophageal adenocarcinoma is increasing in incidence, and Barrett’s esophagus is recognized as the most important risk factor. Currently, the method to predict and demonstrate progression to malignant transformation is by observing microscopic changes in cellular architecture on routine histology examination, defined as dysplasia. Dysplasia is classified as low-grade dysplasia (LGD) and high-grade dysplasia (HGD) based on histology. The annual risk of esophageal adenocarcinoma in an adult patient with Barrett’s esophagus is very low and is estimated to be approximately 0.12% to 0.5% per patient year. The presence of HGD increases the risk of adenocarcinoma more than 20 times to about 5.6% per year.

Screening for Barrett’s Esophagus

Because of lack of evidence demonstrating a benefit from endoscopic screening of adult patients for Barrett’s esophagus, professional organizations are divided on the routine practice of screening. Primary care clinicians may consider...
screening upper endoscopy in a patient with a long history of GERD, particularly if they are elderly white males with additional risk factors such as a large hiatal hernia, smoking, obesity, or increased intra-abdominal distribution of fat.

**Endoscopic Surveillance**

Once a patient has been diagnosed with Barrett’s esophagus, medical societies recommend endoscopic surveillance for dysplasia, with the assumption that regular surveillance endoscopy will diagnose dysplasia and early cancer and result in reduction of deaths from esophageal adenocarcinoma. No randomized controlled trials exist, although clinical evidence suggests benefit in surveillance. The optimal surveillance interval is unclear, but a 3- to 5-year interval is suggested for nondysplastic Barrett’s esophagus with shorter intervals in the presence of dysplasia (Table 15-1).

**Management of Dysplasia**

There is no consensus on immediate use of endoscopic therapy when LGD is initially diagnosed. If persistent LGD is found on follow-up, endoscopic therapy may be considered, especially in a young patient with a long segment of Barrett’s esophagus. Several decision models have demonstrated cost-effectiveness of endoscopic ablation therapies over just endoscopic surveillance strategies in dysplastic Barrett’s esophagus. The presence of HGD requires therapy, either endoscopic treatment or surgical esophagectomy. Watchful waiting is not recommended because of the high risk of progression to cancer. Endoscopic therapy is generally accepted as a first-line therapy in HGD. There is a zero chance of lymph node metastasis in HGD and approximately 1.9% chance in intramucosal cancer. Endoscopic therapy include (1) endoscopic mucosal resection (EMR), where a part of the mucosa and submucosa is removed by endoscopic snare cautery; and (2) endoscopic ablation therapy, where the entire segment of Barrett’s epithelium is destroyed using a thermal energy or photodynamic energy.

EMR is most useful for limited resections of visible lesions such as a nodule and provides histology information on depth of invasion (mucosa or submucosa) to differentiate intramucosal carcinoma from invasive cancer. EMR is usually combined with ablative therapy to treat the residual Barrett’s tissue that remains after limited EMR resections, and this strategy results in 5-year survival rates compared to surgical resection.

**Ablative Therapy**

Destruction of the mucosal layer by radiofrequency thermal energy (BARRX, Covidien California), argon plasma coagulation (APC), or photodynamic therapy (PDT) causes injury that results in necrosis of the mucosal layer followed by regrowth of normal squamous epithelium in the distal esophagus. PDT involves a systemic light-activating photosensitizer (chemical); this is then activated by performing upper endoscopy and shining a laser in the esophagus resulting in destruction of the abnormal epithelium. Side effects include bleeding, pain, and stricture formation. Although PDT compares favorably to surgical esophagectomy for HGD, it is not available in most centers. Radiofrequency ablation (RFA) with the HALO system is the most frequently used ablation system. A balloon with an array of electrodes is used to endoscopically deliver RFA energy to the Barrett’s tissue, resulting in a circumferential thermal injury and necrosis. Multiple studies have demonstrated that there is a high rate (>90%) of complete reversion to neosquamous epithelium. A recent 3-year follow-up of 106 patients with dysplasia treated with RFA demonstrated an eradication of dysplasia in 98% and eradication of Barrett’s esophagus in 91% of patients.

**Endoscopic Surveillance for Dysplasia**

It is recommended that patients be enrolled in an endoscopic surveillance program with regular upper endoscopy every 3 to 5 years to look for dysplasia.

**TABLE 15-1 Endoscopy Surveillance Intervals for Barrett’s Esophagus Based on Histology Findings**

<table>
<thead>
<tr>
<th>Endoscopy Findings</th>
<th>Surveillance Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett’s without dysplasia</td>
<td>3–5 y</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>6–12 mo</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>3 mo if not removed/treated</td>
</tr>
</tbody>
</table>
therapy with esophagectomy for HGD, but cohort studies have demonstrated that at 5 years, cancer-specific mortality and all-cause mortality are similar between surgical and endoscopic management. Esophagectomy should be offered to patients whose HGD is upstaged to invasive cancer based on EMR histology and in patients who have failed or progressed on endoscopic therapy.

**Patient Follow-up**

Patients undergoing endoscopic therapy should continue to have endoscopic surveillance initially 3 months after complete ablative therapy and then surveillance biopsies at regular intervals. It is not currently known if surveillance can be discontinued after complete neosquamous replacement of the distal esophagus following ablation.

**References**

KEY POINTS

- Skin cancer is the most common malignancy in the world.
- Prevention through targeted education, public awareness campaigns, and regular sunscreen use are critical primary steps.
- Several risk factors for skin cancer are well known.
- Although US screening guidelines promulgated by the USPSTF do not recommend for or against total body skin exams, there has been an increase in screening campaigns globally. These appear to have become popular as well as effective.
- Although large prospective studies are required to evaluate the true costs and benefits of skin cancer screening, it is likely that nondermatologists have an important role in primary and secondary prevention of skin cancer.

Each year, more than 3 million skin cancers are diagnosed in the United States, and it is now estimated that one in five Americans will develop skin cancer in the course of their lifetime.1,2 Regarding the overall cancer burden, there are more new cases of skin cancer than the combined incidence of cancers of the breast, prostate, lung, and colon.3 Basal cell and squamous cell cancers of the skin (the nonmelanoma skin cancers [NMSCs]) make up the majority of skin cancers but are rarely fatal (Figs. 16-1 and 16-2). Although melanoma accounted for only 123,590 new cases in the United States last year (53,360 in situ and 70,230 invasive), 8,790 deaths from melanoma occurred (Fig. 16-3).4 Unlike other cancers, a growing body of research has demonstrated that melanoma incidence is increasing over time.5–8

The Centers for Disease Control and Prevention estimates that morbidity and mortality costs attributable to melanoma and NMSC range from $28.9 to $39.2 million and $1.0 to $3.0 billion, respectively.9 Often, melanoma strikes people in the prime of their life, and the cost in terms of years lost is high. The National Cancer Institute approximated the value of life lost from melanoma to increase to 21.6 billion by 2020; sex- and age-specific average earnings are combined with expected productivity trends and years of life lost to estimate unrealized lifetime earnings.10 Americans lose 20.4 years of potential life during the course of their lifetime secondary to melanoma mortality compared with 16.6 years of potential life for all other malignancies; the estimated annual productivity loss attributed to melanoma mortality is estimated at $3.5 billion, with an average loss of $413,370 in foregone lifetime earnings in an individual who dies of melanoma.11

PRIMARY PREVENTION

Primary prevention is defined by the U.S. Preventive Services Task Force (USPSTF) as measures provided to individuals to prevent the onset of a targeted condition and include activities that help avoid a given health problem; and for skin cancer, these include patient education on risk factors for skin cancers, public awareness campaigns, and sunscreen use—all of which are measures of primary prevention for skin cancer.12 For example, the USPSTF recently recommended primary care counseling on the hazardous effects of ultraviolet (UV) radiation to persons aged 10 to 24 years.13

Risk Factors

Risk factors for skin cancer include severe blistering sunburns, lifetime sun exposure, personal and family history, skin that burns easily (fair skin, blue or gray eyes, blond or red
country encouraging multiple sun protection modalities. The 14% increase in consults to treat NMSC between 1998–2000 and 2005–2007 (836,500 vs. 950,000) may partly be attributed to this effort. Public awareness campaigns in the United States have taken a different direction over the past few years, with fashion designers and skin care companies partnering with academia to educate the masses, although mass media coverage in the United States is limited in scope.

Yet, the number of NMSC diagnosed as well as the number of procedures (an increase of 77% from 1992 to 2006) in US Medicare beneficiaries has increased dramatically since the early 1990s. The rate of Mohs micrographic surgery for the treatment of NMSC doubled from 2002 to 2006 (0.75 vs. 1.5 of 100 Medicare beneficiaries), which may indicate higher patient education levels on optimal treatment practices.

Sunscreen use reduces the deleterious effects of UV radiation and may prevent NMSC. A recent randomized controlled study in Australia, for the first time, reported that a 10-year follow-up of those patients randomized to daily sunscreen as opposed to ad lib sunscreen usage developed fewer melanomas. Routine use of sunscreen is associated with decreased melanoma risk. Recently, the U.S. Food and Drug Administration (FDA) made a rule on labeling and effectiveness of sunscreen products for consumers: an acknowledgement of sunscreen benefit by this governmental organization (Fig. 16-4). Yet sunscreen use is declining; the proportion of white high school students in the United States who never or rarely wore sunscreen when outside on a sunny day increased from 57.5% to 69.4% (1999–2009), and only 30% of adults routinely practice sun protection behaviors. In addition, widespread misconceptions regarding sunscreen use and increased vitamin D deficiency or risk of skin cancer have created greater confusion, although regular sunscreen use is not linked to vitamin D deficiency or cutaneous malignancy.

Sunscreen has changed over the past few decades to attract all consumer types from children to the elderly. Both physical (titanium dioxide and zinc oxide) and chemical (oxybenzone, avobenzone, etc.) blockers provide protection against UVA and UVB radiation and are readily available. With more than 1,700 products containing photoprotection ingredients currently on the market as well as technological advancements in delivery and strategic marketing.

Public Awareness Campaigns
The effects of UV radiation and sun awareness have become an international concern; educational programs, such as INTERSUN through the World Health Organization, have encouraged countries to reduce UV-induced health risks through continued research and education. Public awareness campaigns to teach healthy sun behavior and prevent skin cancer have been identified throughout the globe. Australia has one of the highest incidences of skin cancer globally because of high UV radiation levels and a fair-skinned population. In Australia, skin cancers account for 80% of all newly diagnosed malignancies, and educational efforts have been underway since the 1980s. In 2006, the Australian federal government launched a successful “scare tactic” public awareness campaign throughout the country encouraging multiple sun protection modalities. The 14% increase in consults to treat NMSC between 1998–2000 and 2005–2007 (836,500 vs. 950,000) may partly be attributed to this effort. Public awareness campaigns in the United States have taken a different direction over the past few years, with fashion designers and skin care companies partnering with academia to educate the masses, although mass media coverage in the United States is limited in scope.

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campaigns, sunscreen is no longer solely targeted to the lifeguard.\textsuperscript{34,35}

Chemoprevention

The use of retinoids in chemoprevention has been effective in patients at high risk for NMSCs, including xeroderma pigmentosum and transplant recipients.\textsuperscript{36-38} However, a recent multicenter study demonstrated that topical retinoids were ineffective in preventing skin cancer in patients with a history of NMSC.\textsuperscript{39} Photodynamic therapy has also shown efficacy in patients with premalignant actinic keratoses.\textsuperscript{40} A recent randomized controlled trial found that a cyclooxygenase 2 inhibitor reduced both basal and squamous cell carcinoma development in patients with previous NMSC.\textsuperscript{41} Chemopreventive agents that are currently being explored include nonsteroidal anti-inflammatory drugs, difluoromethylornithine, T4 endonuclease V, polyphenols, and perillyl alcohol.\textsuperscript{32}

SECONDARY PREVENTION

Secondary prevention measures as defined by the USPSTF identify and treat asymptomatic persons who have already developed risk factors or preclinical disease but in whom the condition is not clinically apparent and have significant risk for negative outcome without treatment.\textsuperscript{13} Screening tests are examples of secondary prevention activities and are useful in prevalent, well-understood disease entities in which cost-effective strategies are crucial.

Screening Guidelines

In 2009, the USPSTF concluded that there was insufficient evidence to recommend for or against routine screening in primary care for skin cancer using a total body skin exam (TBSE).\textsuperscript{43} The American Cancer Society does recommend that persons older than 20 years of age have a TBSE as well as perform monthly self-exams. Other organizations including the American College of Preventive Medicine and the American Academy of Dermatology promote TBSEs, particularly in high-risk individuals. The paucity of randomized studies with optimal long-term follow-up has led to a lack of substantial evidence on the role of TBSEs because the logistics are complex and require more than half a million participants as well as substantial funding.\textsuperscript{34,45}

Factors Associated with Screening, Detection, and Prognosis

A greater body of research has been published regarding factors associated with screening, detection, and prognosis. Increased dermatologist density (as well as family physicians) and access to dermatologic care has been associated with early detection and better prognosis of skin cancers.\textsuperscript{35-40} Thinner melanomas with a better prognosis are more likely to be detected by physicians, whereas increased tumor thickness was associated with patients living alone and with a lower socioeconomic status.\textsuperscript{49-51} Middle-aged and older patients are more likely to have a physician detect their skin cancers; younger persons often present to the physician with lesions of concern.\textsuperscript{52,53} Older, unmarried, or widowed patients are more likely to present with a later stage of melanoma than married persons; married men are more likely to present with a later stage of melanoma as compared to their female counterparts.\textsuperscript{54,55} Although the USPSTF does not incorporate risk factors into screening guidelines, these studies play an important role in the design and implementation of optimal, targeted surveillance, and screening efforts.

Screening Campaigns

Skin cancer screening campaigns should be differentiated from public awareness campaigns; health care practitioners are actively performing TBSEs, whereas education on prevention is the key component to public awareness. Extensive literature has been published on the success of a growing trend in screening campaigns throughout the world. Euromelanoma, a 29-country organization, sponsors annual screening campaigns with a focus on early detection and treatment. Almost 60,000 persons were screened through Euromelanoma from 2009–2010, of which high rates of clinically suspected melanoma were diagnosed.\textsuperscript{56} Published outcomes from Euromelanoma campaigns throughout Europe have shown great success as well as lessons learned and methods to attract participants.\textsuperscript{57-59} To attract “men older than the age of 50 years,” the former prime minister of Belgium participated in a 2007 service announcement, which resulted in a substantial increase in screening (37% to 64%) that year (Fig. 16-5).\textsuperscript{60} In addition, the recent SCREEN (Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany) project in Germany demonstrated the impact of effective screening on melanoma incidence as well as the feasibility in performing large-scale screening campaigns to reduce cancer burden.\textsuperscript{61,62} The American Academy of Dermatology skin cancer screening program has conducted more than 2.1 million screenings since 1985 and has detected more than 200,000 suspicious lesions, all performed by volunteer dermatologists.\textsuperscript{63}
The Role of Nondermatologists

Nondermatologists play a significant role in education and screening for skin cancer. Research has demonstrated that only 60% of family practitioners and 56% of internists perform TBSEs; additional research in the primary care setting has shown similar findings. However, a recent international study found that the TBSE is crucial in patients with focused skin symptoms and increases cancer detection with low rate of false-positive results. Although nondermatologist health care providers throughout the world diagnose and treat cutaneous neoplasms, there has been an inadequate attempt to educate the nondermatologist in TBSEs and skin cancer diagnosis in the United States, and educational initiatives for the primary care clinician are essential.

Telemedicine can be defined as health care delivery that uses telecommunication technology to transfer medical information; when used by dermatologists to render care to patients at a distance, it is commonly known as “teledermatology.” Teledermatology may have a role for evaluation of some skin lesions to patients in areas without access to dermatologists. However, a recent study suggested that the use of teledermatology to assess a specific lesion of concern may lead to the underdiagnosis of clinically significant lesions not appreciated by the referring nondermatologist.

CONCLUSION

Patient education and screening through TBSEs are important measures in prevention and early diagnosis of skin cancer. Although the USPSTF believes that there is inconclusive evidence for skin cancer screening, recent studies throughout the world demonstrate otherwise. Novel technologies may potentially assist researchers in performing large, prospective studies to thoroughly evaluate the benefit of skin cancer screening on patient diagnosis, treatment, and prognosis.

References


KEY POINTS

- Whether prostate cancer screening saves lives remains uncertain.
- Men should be apprised of the potential benefits and known risks of prostate cancer screening and decide with their doctor whether or not to screen.
- The PSA with or without the digital rectal exam remains the screening test of choice.
- The screening interval can be extended to every 2 years for men whose PSA levels are low (≤2.5 ng per dL).
- The conventional PSA threshold for biopsy has been 4.0 ng per mL; this can be modified based on other prostate cancer risk factors, including age, race, and family history.

Few questions in clinical medicine are as controversial as the question of whether or not to screen asymptomatic men for prostate cancer. Soon after the advent and dissemination of the prostate-specific antigen (PSA) blood test in the late 1980s, controversy erupted whether the PSA was contributing to a reduction in mortality and morbidity from prostate cancer or was simply detecting prostate cancer at an earlier stage without affecting mortality (lead-time bias) and subjecting men to potentially serious complications of prostate cancer treatment without offering any true benefit. More than two decades later, the answer to this critical question remains elusive. As the most commonly diagnosed cancer in men and the second leading cause of cancer death, prostate cancer certainly would warrant universal screening if its efficacy could be definitively established. This chapter will review the available screening tests, summarize the state of the evidence related to screening outcomes and harms, present the core information that men should have to decide whether to screen, and distill current prostate cancer screening guidelines.

THE SCREENING TESTS

The PSA is presently the primary tool for the early detection of prostate cancer. The advantages of the PSA relate to its acceptability to patients and providers in terms of cost, convenience, and safety. However, its limitations as a screening test are numerous. First, estimates of its sensitivity vary widely, ranging from as low as 21% to as high as 87%, depending on the PSA threshold and the reference standard used. Despite uncertainty regarding the “true” sensitivity of the PSA, it is clear that many men with “normal” PSA values harbor undiagnosed prostate cancer. The specificity of the PSA is reported to be in the range of 90%, indicating that approximately 10% of men without prostate cancer will have an elevated level. The most common benign cause of an elevated PSA is prostatic hypertrophy. Another common cause of PSA elevation is chronic prostatitis, which is often asymptomatic and diagnosed only by biopsy. This has led some physicians to treat men whose screening PSA levels are elevated with antibiotics prior to retesting—a practice that has been determined to be ineffective for discriminating cancer from noncancer. Whether digital rectal exam (DRE) leads to clinically important elevation of the PSA remains controversial, but there is consensus not to defer DRE prior to PSA testing if it is used as part of the screening strategy.

The value of the old mainstay of prostate cancer screening—the DRE—has been increasingly questioned in recent years. Accuracy of the DRE is highly variable, and interobserver reliability is generally poor in terms of detecting abnormalities warranting biopsy. Only 17% of prostate cancers are detected through DRE screening alone (i.e., when PSA levels are under 4.0 ng per mL), and these tend to be smaller and less aggressive tumors. More important, the only randomized trial of screening to include the DRE as part of its protocol showed no benefit for the combination of annual DRE and PSA in reducing prostate cancer mortality. Although DRE may not be useful as an initial screen for prostate cancer, it has been demonstrated to help refine patient-specific estimates of prostate cancer risk. In particular, the DRE can help determine whether to further evaluate men whose PSA levels are at the high end of normal (e.g., 2.5 to 4.0 ng per mL).

OTHER TESTS

The PSA velocity, or rate of rise of PSA over time, has been proffered as one means of screening for cancer because the proliferation of malignant prostate cells can lead to acceleration...
of the PSA increase. However, the rate of PSA rise offers no greater predictive value than the absolute level of PSA and, accordingly, has not taken hold as a useful tool. Another screening tool, the percent-free PSA, is premised on the observation that a greater proportion of PSA produced by malignant cells is complexed with a glycoprotein than the PSA produced by benign cells. Although men with a percent-free PSA below 10% (calculated by dividing the free PSA by the total PSA) are more likely to harbor cancer than men with a high percent-free PSA (above 25%), the test lacks sufficient discriminatory value in most men with borderline PSA levels to guide the decision of whether or not to proceed to prostate biopsy. There are several novel markers under investigation, which have not been sufficiently studied for general use. The urine PCA3 test, for example, has been demonstrated to predict prostate biopsy positivity in men who have had previously negative biopsies, but its use in general populations has not been sufficiently validated.

### Screening Interval

The optimal interval for prostate cancer screening is uncertain. The European Randomized Study of Prostate Cancer (ERSPC) generally used a 4-year screening interval and demonstrated a reduction in prostate cancer mortality. Modeling studies have uniformly indicated that for men with initially low PSA values, the likelihood of progressing to a level above 4.0 ng per mL is very low (under 3%) over the ensuing 2 years. Moreover, extending the screening interval from annually to every 2 years can reduce biopsy rates by half while preserving more than 90% of years of life saved. The American Cancer Society guideline (the only one to specify intervals) currently recommends every 2-year screening for men whose initial PSA level is under 2.5 ng per mL and annual screening if the level is 2.5 ng per mL or higher.

### When to Refer for Biopsy

In that there is no PSA threshold that accurately discriminates between cancer and noncancer, the decision regarding when to refer for prostate biopsy is, accordingly, somewhat arbitrary. In the United States, a PSA level of 4.0 ng per mL or higher has conventionally been considered an indication for biopsy. However, using this threshold, the prostate arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial did not demonstrate a prostate cancer mortality reduction, whereas the ERSPC, using a PSA cutoff of 3.0 ng per mL, did demonstrate a mortality benefit. The American Urological Association does not specify a threshold PSA level to prompt a biopsy but instead recommends individualized decision making based on risk factors in addition to the PSA level, such as DRE result, age, family history, race, and prior biopsy results. The American Cancer Society recommends using the cutoff of 4.0 ng per mL as an indication for referral, reserving individualized decision making for levels between 2.5 and 4.0 ng per mL. Risk calculators have been developed to integrate PSA level with these other risk factors to predict the probability of cancer on biopsy, particularly the probability of high-grade cancer.

### What Men Can Expect from Screening

Should a man decide to undergo PSA testing, the probability of an abnormal result (PSA >4.0 ng per mL) is 12% after three screenings. The likelihood that the abnormal result represents cancer is only 24%; that is, three of every four elevated readings represent false-positive results. The likelihood of being referred for biopsy is about 5% after serial screenings. Biopsy has about a 1% risk of serious complications (urinary retention and hospitalization for prostatectomy), although bleeding, fever, and pain are more common.

### Screening Benefit

Whether routine prostate cancer screening reduces the risk of dying from prostate cancer remains in doubt. The two largest trials of prostate cancer screening have yielded conflicting results. The US PLCO screening trial examined the impact of four annual PSA tests and DREs compared with usual care and found no benefit in terms of reduced prostate cancer mortality after 13 years of follow-up. On the other hand, the European trial (ERSPC) did find a mortality benefit to screening with the PSA only: Roughly 1,400 men needed to be screened to save one life over about a decade of follow-up, comparable to the effectiveness of screening mammography in 50-year-old women. A third randomized trial, the Göteborg trial, which was partially incorporated into the ERSPC, demonstrated a mortality benefit to screening men aged 50 to 69 years with a PSA every 2 years. After 14 years of follow-up, the number needed to screen to save one life was about 300, although these men were, on average, younger than in other studies, and the PSA threshold for biopsy was lower than in the US study. Case control and observational studies have had mixed results in terms of mortality benefit conferred by screening.

### Screening Harm

Beyond the risks of false-positive results and biopsy complications noted previously are the harms incurred by treating screen-detected prostate cancer. The principal risks of radical prostatectomy are urinary incontinence and erectile dysfunction. Incontinence rates range from 18% to 28%, and erectile dysfunction occurs in 26% to 36% of men. The risk of death because of surgery is approximately 0.5%. Radiation therapy also appears to increase the risk of both urinary incontinence and erectile dysfunction, but reported rates vary widely depending on the type of radiation and study design. Bowel injury occurs in between 3% and 8% of men undergoing radiation therapy.

Another important risk often overlooked in discussions of screening harm is the risk of overdiagnosis and overtreatment, that is, the risk of detecting and treating early-stage prostate cancers that would never have become clinically apparent during the life of the patient. The overdiagnosis rate has been estimated to be between 23% and 42%. Overtreatment in the ERSPC was substantial: 49 men needed to be treated to save one life over a decade. In the Göteborg trial, 12 men needed to be treated over 13 years to save one life. Although these numbers would be expected to improve with longer follow-up, it is clear that both overdiagnosis and overtreatment are significant risks of screening.

### Informed and Shared Decision Making

Given the uncertain benefits and known harms of prostate cancer screening, it is incumbent on primary care clinicians to apprise their patients of these risks and benefits prior to
deciding whether to screen. Primary care clinicians should also assist their patients in arriving at a screening decision commensurate with their values. Essential elements of informed decision making for prostate cancer screening are included in Table 17-1. To assist patients in the screening decision, many decision aids are available that can facilitate this process and relieve physicians of the time burden involved.3

CURRENT RECOMMENDATIONS

There are significant discrepancies among the current guidelines for prostate cancer screening. The American Cancer Society recommends that beginning at the age of 50 years, average-risk men should be offered the opportunity to make an informed decision whether to screen, and that higher risk men (African American and/or a family history of prostate cancer in a first-degree relative) begin this discussion at the age of 45 years.3 The American Urological Association also recommends informed decision making but recommends that men who opt for screening begin at the age of 40 years with subsequent screening based on their initial PSA value.12 The U.S. Preventive Services Task Force (USPSTF) determined that there was insufficient evidence to issue a recommendation in 2008 but in 2012 issued an updated recommendation against screening at any age.16 All authorities recommend against screening men whose life expectancy is under 10 years; the USPSTF explicitly recommends against screening men aged 75 years and older.17

References


TABLE 17-1

Core Elements for Informed Decision Making in Prostate Cancer Screening

- Screening with the PSA blood test with or without the DRE detects cancer at an earlier stage than if no screening is performed.
- It is presently unclear whether screening reduces the risk of dying from prostate cancer.
- Some men whose prostate cancer is detected through screening would have died from unrelated causes before their cancer became serious enough to affect their health or shorten their lives.
- Treatment for screen-detected prostate cancer can lead to urinary, bowel, sexual, and other health problems.
- The PSA and DRE often result in false-positive or false-negative results, meaning that men without cancer may have abnormal results and get unnecessary additional testing, and significant cancers may be missed. False-positive results can cause prolonged anxiety about prostate cancer risk.
- An abnormal PSA or DRE result requires a prostate biopsy to determine whether or not the abnormal findings are cancer. Biopsies can be painful and may cause complications such as infection or bleeding.
- Not all men with screen-detected cancer require treatment, but they may need periodic blood tests and prostate biopsies to determine the need for future treatment.

PSA, prostate-specific antigen; DRE, digital rectal exam.
CHAPTER 18

Lung Cancer Screening

Lauren G. Collins, MD • Richard C. Wender, MD

KEY POINTS
• Although there is still no justification for lung cancer screening with chest radiography, there is now good evidence based on the National Lung Screening Trial (NLST) that annual low-dose computed tomography screening reduces mortality from lung cancer by 20%.
• Based on new data from the NLST, primary care clinicians should focus on informing patients eligible for lung cancer screening of the benefits, limitations, and potential harms before screening is initiated.
• All screening discussions should be accompanied by a discussion of smoking cessation.
• Adults who choose to be screened should follow the NLST screening protocol and ideally receive care from an experienced multidisciplinary team.

The search for an effective screening tool has been a major focus for lung cancer research for several decades. As of 2011, no major organizations recommended lung cancer screening with any modality. However, in June of 2011, the landscape of lung cancer research was drastically changed with the publication of a landmark study—the National Lung Screening Trial (NLST); this randomized trial compared annual chest radiography to annual low-dose computed tomography (LDCT) in high-risk men and women and became the first trial to show a significant reduction in lung cancer mortality.1

NATIONAL LUNG SCREENING TRIAL

Methods
The NLST trial enrolled more than 53,000 persons at high risk for lung cancer. Trial participants were asymptomatic current and former heavy smokers (with a $\geq30$ pack-year history) aged 55 to 74 years with no prior lung cancer diagnosis and no evidence of other cancers. If participants were former smokers, they must have quit less than 15 years ago. After enrollment, participants were randomized to three rounds of LDCT screening or chest radiography (at baseline, year 1, and year 2) and were then followed for an average of 6.5 years without additional screening.1

Benefits
The major benefit from the NLST, and the reason the study was stopped early, was that researchers found a 20% reduction in lung cancer–related mortality in those screened with LDCT relative to those screened with chest radiography. The rates of death from lung cancer were 247 and 309 per 100,000 person-years, respectively, with LDCT versus chest radiographic screening.1 Based on the study’s findings, the number needed to screen with LDCT to prevent one death from lung cancer is 320, which compares favorably to the number needed to screen for widely accepted screening tests such as colonoscopy and mammography.

In addition to reducing lung cancer–specific mortality, the LDCT screening arm also experienced a 6.9% lower all-cause mortality, with most (60.3%) of the excess deaths in the chest radiography group caused by lung cancer. Cancers discovered through LDCT screening were also more likely to be early stage (stage IA and stage IB), and therefore more treatable, than those in the chest radiography screening arm.

After careful evaluation of the study, many experts believe that the full mortality benefit of LDCT screening may actually be underestimated because LDCT screening was compared to chest radiography rather than “usual care” and because NLST participants were generally younger, had a higher level of education, and were more likely to be former smokers than a US census survey of patients who met NLST eligibility criteria.1–3

Limitations/Harms
Although the mortality benefit of the NLST cannot be understated, no cancer screening modality, including LDCT for lung cancer, is perfect; evaluating LDCT therefore requires a careful evaluation of benefits and limitations or risks associated with screening.
False-Positive Results
In the NLST study, the false-positivity rate was approximately 95%. Nearly one-quarter of all computed tomography (CT) scans were screen positive (i.e., detecting a nodule with a diameter of 4 mm or larger), and 40% of individuals in the LDCT arm had at least one abnormal CT during the three rounds of screening. Most screen-positive results were resolved with follow-up CT only, but some required invasive diagnostic procedures with associated anxiety, cost, radiation exposure, and risk of adverse events.1

Invasive Procedures
The NLST study sites were more likely to be large academic centers with experienced clinicians and a high level of quality control. A fairly strict protocol for evaluating abnormal scans was followed with a goal of limiting the number of individuals who required an invasive procedure to arrive at a definitive diagnosis. Overall, the rate of minor complications from the screening examinations was low, with a 1.4% complication rate in the LDCT arm and 1.6% rate in the chest radiography group. The complication rate was higher in those who were ultimately found to have lung cancer. Although the minor complication rate was low, 16 deaths occurred because of medical interventions from an abnormal CT: 10 of these deaths were occurred in patients who were eventually found to have lung cancer and 6 without lung cancer. Whether these deaths resulted from elevated risk or other comorbid conditions is not clear. Overall, the risk of death associated with LDCT screening in a patient who did not have cancer was 0.024%.1

Radiation Risk
One concern from repeat LDCT screening and higher dose diagnostic evaluations is radiation exposure.10 Studies evaluating LDCT have concluded that the dose is generally considered safe; however, there remains variation in radiation dose across CT scanners. As new generations of scanners replace old ones and as quality standards for lung cancer screening are adopted, the radiation risk of screening CT may become less concerning.2,3

Overdiagnosis
Overdiagnosis, the detection of a cancer through screening that is not life threatening, is another concern with all cancer screening tools. In the NLST, there was a 13% difference in number of cases diagnosed in the LDCT arm versus the chest radiographic arm, but it is still too early to determine if this higher rate of diagnosis represents individuals who would have developed a life-threatening cancer at a later point. A longer follow-up period is needed to figure out the true rate of overdiagnosis. Given the high case mortality for lung cancer, it is likely that the rate of overdiagnosis will be low, and, in fact, previous studies have not found a high percentage of overdiagnosed cancers.1

SPECIAL CONSIDERATIONS

Payment
At this point, very few insurers and no governmental insurers cover the cost of screening LDCT. A reasonable charge for the test is $200 to $300, but cost is likely to vary from market to market. Patients who wish to be screened must be prepared to cover this initial cost. If an abnormality is found on the initial test, most insurance products will cover the cost of additional testing.

Estimating Risk
Some patients who do not meet the specific criteria used in the NLST (i.e., a 63-year-old current smoker with a 29 pack-year history) will be at comparable or higher risk for developing lung cancer as individuals who meet the criteria. Several online risk calculators can help estimate risk for lung cancer.4,5 Discussing lung cancer screening with individuals who are at comparable risk to those who were enrolled in the study is reasonable. Of critical importance, individuals who are at lower risk for lung cancer should not be offered screening and should be discouraged from having LDCT. Ongoing trials will shed additional light on the benefits and risks of screening individuals who do not match the NLST criteria.6,7

Underlying Health
Offering lung cancer screening to individuals who are not healthy enough to undergo treatment for early lung cancer is not sensible and should be avoided.

Smoking Cessation
Without question, the safest, most cost-effective, and vital intervention for current smokers is to help them to stop smoking. Any provider or entity involved in a lung cancer screening program must have a way to implement evidence-based smoking cessation efforts.

RECOMMENDATIONS FOR PRIMARY CARE CLINICIANS

As researchers and expert panels work to issue revised lung cancer screening guidelines, informed by the NLST results, interim recommendations are now available from the American Cancer Society (ACS) and the International Association for the Study of Lung Cancer (IALSC).8,9 Based on these recommendations, primary care clinicians (PCCs) should ascertain a patient’s risk and determine if the patient is at similar risk for lung cancer as individuals who meet NLST criteria and is healthy enough to undergo screening and treatment. If yes, providers should initiate a discussion about the benefits and risks of LDCT screening. Patients who place high value on the opportunity to prevent a lung cancer death and are willing to accept the cost and risk associated with screening may choose to have an LDCT every year. Patients who place high value on avoiding the cost and risk of screening and are willing to accept a higher risk of dying of lung cancer may opt to not be screened. All smokers should receive help to quit smoking. Adults who choose to be screened should follow the NLST screening protocol and ideally receive care from a multidisciplinary team with expertise in diagnosis and management of abnormal lung lesions. Finally, data about lung cancer screening are still emerging, and specific recommendations are likely to evolve.
References


Clinical Presentations of Cancer
Does My Patient Have Cancer? Presenting Symptoms

Kimberly S. Peairs, MD • Larissa Nekhlyudov, MD, MPH

KEY POINTS

- Most common symptoms evaluated by primary care clinicians are not reflective of an underlying malignancy.
- Age, gender, environmental, or familial cancer risks of the individual patient should be considered when assessing a cancer “alarm symptom.”
- The positive predictive value (PPV) of a symptom is the proportion of individuals who have that symptom and are found to have a related cancer.
- There are several common symptoms that may have a higher PPV for malignancy: rectal bleeding or change in bowel habits (colorectal), hematuria (genitourinary), hemoptysis (lung), dysphagia (esophageal), breast lump (breast), and postmenopausal bleeding (gynecologic).
- Presenting symptoms, regardless of the likelihood of an underlying malignancy, should be evaluated and followed to resolution or until definitive diagnosis is established.

CHALLENGES OF DIAGNOSIS OF CANCER IN PRIMARY CARE

There were 12.7 million new cases of cancer diagnosed in the United States in 2011. Primary care clinicians are often the first to evaluate and diagnose patients with cancer, often on the basis of their presenting symptoms. However, an even greater number of patients present with similar symptoms, which are not reflective of underlying cancers. Primary care clinicians, using clinical judgment, must therefore determine when the symptoms are more likely of a benign origin or when they represent an underlying malignancy (“alarm symptoms”) while assimilating the specific symptoms with the likelihood of cancer in the individual. The positive predictive value (PPV) of a presenting symptom (the chance that the patient has the cancer when they note the symptom) is higher when the patient reports it to a primary care clinician rather than having the symptom and not seeking medical care, and it increases further if the patient is referred for secondary evaluation. This makes the interpretation of the literature difficult because the predictive values of certain symptoms are obtained from patients in specialty clinics where the pretest probability of the cancer is greater. Still, most “alarm” symptoms are not indicative of an underlying malignancy. Jones et al. demonstrated that for common symptoms evaluated by primary care clinicians, such as hematuria, hemoptysis, dysphagia, and rectal bleeding, more than 90% of the patients did not have cancer. Age, gender, and comorbidities also significantly affect the PPV of the symptoms, as do the presence and number of additional alarm symptoms. Furthermore, the incidence of a particular cancer in the general population and/or in a specific population will also affect the PPV and should influence a primary care clinician’s evaluation of associated symptoms. In general, the PPV of common symptoms seen in a primary care practice is low. Patients may present with nonspecific or localizing symptoms, and recognition of their relative risk may aid in the practitioner’s assessment. Although certain cancers may be uncommon in select patients (e.g., younger patients), a primary care clinician must be astute in taking a careful and detailed history, performing a physical examination, and considering the relative possibility of a malignancy in the evaluation. Unfortunately, delays in diagnosis do occur because of several factors, including lack of detailed evaluation by the primary care clinician. It is critical that symptoms are closely monitored until resolution or alternative diagnosis is achieved.

In this chapter, we describe common presenting symptoms in primary care, how often these symptoms are associated with underlying malignancy, and which malignancies must be considered. We also describe malignancies that are more commonly diagnosed in primary care settings and their respective presenting symptoms.
Fatigue is a common presenting symptom for several cancers, including, but not limited to, lung, ovarian, colorectal, and leukemia. Because fatigue is common in the general population and associated with numerous benign conditions, it has low PPV for cancer.\(^5\) When related to a cancer diagnosis, the etiology of fatigue is often because of symptomatic anemia, which should be evaluated appropriately.

### PAIN SYNDROMES

Pain can be highly variable among individuals when it is one of the presenting features of cancer. When evaluating a patient with pain, it is important to assess the features in the context of the individual and his or her risk for an underlying malignancy as well as accompanying signs and symptoms. The history should include the location, quality, severity, onset, duration, persistence, and exacerbating or modifying factors of the pain. Acute pain presentations are less common than chronic, evolving processes but are often more dramatic and necessitate immediate evaluation.\(^2^1\) Persistent pain among adolescents and young adults is rare and may be attributed to sports injuries; however, ongoing symptoms warrant further evaluation.

When malignancies first present as acute pain, the most common etiologies include tumor hemorrhage, pathologic bone fracture, or mass effect of the tumor leading to obstruction or perforation of surrounding tissues. Larger tumors, such as hepatocellular carcinoma, may rupture and create unstable hemodynamic conditions in addition to severe pain. Acute bone fracture with or without antecedent trauma may be secondary to weakening of the area from a primary or metastatic lesion; the vertebral and axial skeleton are common sites. Intestinal, biliary duct, or ureteral obstructions may result from any pelvic malignancy. The location of the abdominal pain may direct the evaluation.

Chronic, insidious pain is a more frequent presentation of cancer, although most patients presenting to their primary care clinic with 1 to 2 months of pain will have a benign etiology. Etiologies of pain related to cancer may be related to a direct effect from tissue invasion or compression from the tumor. Diffuse pain may also result from paraneoplastic syndromes arising from specific cancer types.\(^2^2\) Chronic tumor-related bone pain may be multifocal or localized, with the spine and pelvis being common sites of spread, particularly for lung, breast, and prostate cancer. Lymphoma, multiple myeloma, certain sarcomas, and leukemia may have bone marrow involvement, which manifests as nonspecific arthralgias. Skull metastases are less common and may also be related to direct spread of head and neck tumors. Most patients with metastatic bone disease experience pain; however, a minority of tumor sites may be symptomatic and areas of pain may not always correlate with the site of metastases.\(^2^3\)

#### Back Pain

Back pain is one of the most common reasons for physician visits in the United States, with more than 85% of the patients presenting to primary care having no obvious underlying disease or spinal abnormality.\(^2^4,2^5\) However, in selected patients presenting with certain symptoms, the possibility of back pain from a more ominous etiology should be entertained. In a prospective study of 1,975 outpatients with a chief complaint of back pain, only 0.66% had an underlying malignancy. Patient
characteristics and laboratory findings that were significantly associated with a cancer included a prior history of cancer, age 50 years or older, duration of pain more than 1 month, failure to improve with conservative therapy, unexplained weight loss, elevated erythrocyte sedimentation rate, and anemia (Table 19-2). The presence of multiple signs or symptoms increase the likelihood of a patient having a malignancy; and if there is no history of cancer but a strong clinical suspicion, then further assessment is warranted. Patients with these symptoms may be initially evaluated with plain radiography, although magnetic resonance imaging (MRI) may be indicated if clinical suspicion is high and initial imaging is negative.27

If back pain presents with progressive neurologic deficits, evaluation for spinal cord compression or cauda equina should be undertaken. Symptoms may include a progressive radiculopathy with weakness, fecal incontinence, or bladder dysfunction or retention. In a study of patients hospitalized for malignant spinal cord compression, the most common cancers were lung, breast, and multiple myeloma; but the tumors with the highest incidence rates were multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma, and prostate cancer.28

**Headache**

Most headache presentations to a physician are related to primary headache syndromes (migraine or tension type), with only a small minority of patients having a defined underlying etiology (secondary headache) such as cancer. Brain tumors account for less than 0.1% of lifetime prevalence of headaches in the general population.29,30 The most frequent metastatic brain tumors are from lung, breast, renal, and GI tumors/cancers and melanoma. Primary brain tumors (gliomas, meningiomas, and pituitary adenomas) are less common. Of patients with primary or metastatic brain tumors, 48% to 60% reported a headache, with 40% to 77% meeting criteria for tension-type headache; however, headache was the sole symptom in only 2% of the patients.31-33 Symptoms varied with size, location, tumor type, and previous headache; and the headaches were mostly bifrontal (often worse on one side), associated with nausea and vomiting in 40% of cases and worse with bending over (32%).33 More recent studies have not confirmed earlier findings suggesting that early morning headaches were common among patients with cancer; however, such headaches may be related to increased cerebral pressure. Leptomeningeal spread from metastatic disease may also present with a headache pattern but often presents with other neurologic abnormalities.

For a patient presenting to his or her primary care clinician for a headache evaluation, a detailed history and physical examination will aid in the identification of “red flags” that would warrant further investigation for an underlying malignancy. These would include (1) sudden-onset headache; (2) progression or change in headache pattern; (3) headache triggered by cough, bending over, or Valsalva (increased intracranial pressure); (4) presence of other focal neurologic signs or symptoms; (5) papilledema; or (6) new headache in a patient with prior cancer or immunosuppression.34 If malignancy is strongly suspected, evaluation with MRI is indicated; otherwise, a referral to neurology is recommended.34

**Paraneoplastic Pain**

Paraneoplastic syndromes are caused by remote effects of substances made directly by a tumor or produced by the body in response to the tumor. They can present in various ways. Several manifest as abnormalities in the nervous system, most commonly related to small cell lung cancer.22 Muscle cramps and joint pain may also be paraneoplastic manifestations. Hypertrophic osteoarthropathy presents with subperiosteal new bone formation typically in the shaft of the digits and may be associated with lung cancer. Clinical findings include digital clubbing, periosteal thickening seen on X-ray, and joint effusions (which may occur in larger joints). The bone changes are painful, and synovitis or joint swelling may be present.35

Musculoskeletal paraneoplastic syndromes can present as painful rheumatologic processes, distinct from pain caused by direct tumor involvement in the muscles, joints, or bones. Dermatomyositis–polymyositis (discussed in the following text) is the most common and well-described entity.36 Dermatomyositis has distinct dermatologic manifestations and is associated with proximal muscle weakness and discomfort. Certain characteristics are more suggestive of underlying malignancy and include increasing age, rapid onset of disease, presence of constitutional symptoms, and cutaneous vasculitis. Associated cancers are most commonly adenocarcinomas. Typically, the presence of a paraneoplastic syndrome is entertained after the standard evaluation for the underlying symptoms. Abnormalities in blood work, including blood counts and electrolytes (syndrome of inappropriate secretion of antidiuretic hormone [SIADH]), may be found. Additional testing for paraneoplastic syndromes may be further directed by the appropriate specialist, that is, neurology, pulmonary, rheumatology, etc.

**LOCALIZED SYMPTOMS**

**Head and Neck Symptoms**

Symptoms that arise from head and neck malignancies will vary based on the anatomical location of the lesions and the surrounding structures they invade or compress. Most head and neck cancers are squamous cell, except for those in the sinus, which are typically salivary gland in origin. The strongest risk factors for squamous cell lesions in the head and neck have been previously reported as older age, tobacco, and alcohol; however, there is a growing number of younger non-smokers presenting with the risk factor of human papillomavirus (HPV) infection.37 HPV-related tumors usually arise in the posterior pharyngeal area (including base of the tongue) and are often asymptomatic until later stages, then present as a neck mass, lymphadenopathy, pain, or oral bleeding. Oral cavity tumors are often noted by patients and present as non-healing ulcers on lips, tongue, and other mucosal surfaces. If advanced, patients may have dysphagia, odynophagia, or

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**TABLE 19-2  Alarm Symptoms of Back Pain**

<table>
<thead>
<tr>
<th>Symptom</th>
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<tbody>
<tr>
<td>Prior history of cancer</td>
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<tr>
<td>Age 50 y or older</td>
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<tr>
<td>Duration of pain more than 1 mo</td>
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<tr>
<td>Failure to improve with conservative therapy</td>
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<tr>
<td>Unexplained weight loss</td>
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<tr>
<td>Elevated erythrocyte sedimentation rate (ESR)</td>
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<td>Anemia</td>
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referred ear pain. Tumors that directly invade the vocal cords often present early with symptoms of hoarseness, but if they are supraglottic or subglottic, they may be asymptomatic until spread occurs. Later in their course, dysphagia, cough, referred otalgia, and possibly stridor may occur if there is airway obstruction. Given that invasive thyroid malignancies would typically present in this manner, a thorough neck and thyroid examination is warranted for new or persistent hoarseness.

Sinus and nasopharyngeal tumors may present with epistaxis, persistent sinus congestion, facial pain, or protracted otitis media. Neurologic symptoms of hearing loss, tinnitus, or other cranial nerve changes may result if there is local spread. Tinnitus may occur from any tumor that will compress the cochlear nerve, including schwannomas. With advanced nasopharyngeal tumors, patients may present with a neck mass, consistent with the spread of the cancer.

In assessing a neck mass, the rapidity of growth of the lesion, a history of smoking, the presence or absence of symptoms suggestive of infection, and the characteristic of the mass will aid the clinician in determining if further evaluation is necessary. Firm, fixed lesions are suspicious for malignancy, whereas rubbery, nontender nodules may be suggestive of pathologic lymph nodes and should be evaluated expeditiously. Imaging with computed tomography (CT) scan (and, less commonly, MRI or ultrasound) may be helpful in the initial assessment; but for a tissue diagnosis, fine-needle aspiration or open biopsy is necessary. Referral of the patient to a head and neck or general surgeon is appropriate. Tender, warm, nodules may be reactive lymph nodes and should be closely followed for resolution.

**Respiratory Symptoms**

Chronic respiratory symptoms, chest pain, dyspnea, and hemoptysis are common respiratory symptoms evaluated in a general medical clinic. Other than hemoptysis, the others have an extensive differential, with noncancer etiologies predominating. If present, the etiology of dyspnea, or shortness of breath, related to an underlying malignancy may be multifactorial. Tumor infiltration of the lung parenchyma, lymphatic system, or pleural space (effusions) may alter oxygen transfer or, less commonly, ventilation. Obstruction of the airways (either extrinsic or intrinsic) may occur at the small or large branches of the bronchial tree. Anemia from an underlying malignancy may contribute to poor oxygenation, and phrenic nerve damage may cause diaphragmatic weakness or paralysis.

Cough is a common presenting symptom in a primary care practice, and lung cancer is the etiology in less than 2% of the cases.

A new-onset cough in a smoker, persistent cough of greater than 1 month, or a cough in the presence of hemoptysis without an infection warrants further evaluation for malignancy. If cough is related to lung malignancy, it is most commonly observed with squamous cell and small cell carcinomas.

Chest pain is a nonspecific symptom and, if related to an underlying malignancy, may be related to direct extension into surrounding tissues in the parietal pleura or chest wall. Dyspnea may not only be associated with a pulmonary malignancy but may also result from an underlying hematomatologic abnormality (described in a later section).

Hemoptysis occurs in up to 40% of patients with bronchitis and is seen with nonmalignant upper and lower respiratory tract conditions; however, it is considered an alarm symptom for more serious underlying pathologies. Tumors including primary bronchial carcinoma, metastatic endobronchial lesions, and bronchial carcinoid may present with hemoptysis. Less commonly, hematologic malignancies may present with upper airway bleeding. Although most pulmonary symptoms have a low PPV for lung cancer, PPV for hemoptysis is the highest (7.5% for men and 4.3% for women). The predictive value increases for men aged 75 to 84 years or if hemoptysis presents with other symptoms such as dyspnea, weight loss, and anorexia.

History and physical evaluation of pulmonary symptoms should be followed by imaging, as indicated, including chest radiography, chest CT scan, and referral to a pulmonary specialist for consultation if further evaluation is warranted.

**Upper Gastrointestinal and Abdominal Symptoms**

Symptoms that may represent upper GI pathologic include dysphagia, bloating, epigastric pain, or early satiety and typically present later in the course of disease. Dysphagia has a PPV of greater than 5% for esophageal cancer. When associated with a gastric tumor, the lesion is typically located closer to the gastroesophageal junction. Solid food dysphagia typically presents prior to liquid dysphagia, and weight loss may occur, either from a limitation in caloric intake or from tumor-related cachexia. Diminished appetite and weight loss are also commonly seen in the presentations of pancreatic cancer.

Hoarseness may occur with upper GI tumors if there is involvement of the recurrent laryngeal nerve but is usually seen with more advanced tumors.

Chronic dyspepsia is an uncommon presentation of gastric cancer and has a low sensitivity and specificity. However, if it presents with other alarm features (unintentional weight loss, vomiting, dysphagia, odynophagia, palpable mass, jaundice, hematemeses), particularly in a patient older than 45 years or with significant tobacco history, then evaluation for underlying malignancy is warranted. Clinical judgment is necessary in assessing the constellation of symptoms in individual patients. However, in patients with dyspepsia younger than the age of 45 years with no associated alarm symptoms, the negative predictive value is 99%, meaning the patient is highly unlikely to have a gastric or esophageal malignancy.

Several different malignancies may occur in the abdominal area, and consideration of their presenting features is beneficial. Common tumors include colorectal, hepatocellular, ovarian, pancreatic, renal cell carcinoma, lymphoma, or prostate, but many are not symptomatic until late stage. Gynecologic etiologies such as uterine malignancy should also be considered. Patients may present with various abdominal symptoms; and host factors, acuity, severity, and combination of symptoms will help guide the clinician. Clinical features that may be associated with cancer include pain, change in bowel pattern (either constipation or diarrhea), hematocrit or melena, weight loss, bloating, increased abdominal girth, and, less commonly, nausea, vomiting, or early satiety.

Unfortunately, many of these common presenting abdominal symptoms are nonspecific and have a low PPV for underlying malignancies. In a study evaluating the diagnostic value of nonacute abdominal complaints, only 14% of patients had organic GI disease and no clinical item had a high sensitivity or specificity. Male gender, older age, nonspecific pain character, weight loss, and elevated sedimentation rate were five items helpful in the prediction of malignancy.

Abdominal pain may occur from various visceral syndromes related to capsular distention (i.e., hepatocellular), tumor penetration into soft tissue or adjacent nerves (pancreatic,
prostate), peritoneal inflammation or ascites (ovarian, colorectal, stomach), or obstruction (ureteral or luminal) such as with ovarian or colorectal malignancies. Although common in patients with abdominal malignancies, abdominal pain is nonspecific for an underlying malignancy. In a population-based case-control study evaluating clinical features of colorectal cancer prior to diagnosis, abdominal pain had a PPV of only 1% for colorectal cancer, whereas rectal bleeding was the symptom with the highest PPV at 2.4%. Weight loss and abdominal tenderness had similarly low predictive values.

In a systematic review and meta-analysis to determine the accuracy of alarm features of colorectal cancer, the sensitivity of individual symptoms were low, but the specificity was >95% for dark red rectal bleeding and abdominal mass. A more recent systematic review confirmed the higher PPV of rectal bleeding and colorectal cancer in patients aged 50 years or older, and if it was present with weight loss or change in bowel habits, the risk of a cancer being present was greater (Table 19-3).

The combination of abdominal bloating, increased abdominal size, and urinary symptoms was more frequently reported by women with ovarian cancer (43%) than in noncancer patients presenting to their primary care clinics (8%). Sustained abdominal bloating or belching has been reported as a more common upper GI symptom in patients with pancreatic cancer, and abdominal distension may be present in any tumor causing ascites. Changes in bowel movements, including new constipation and/or diarrhea, warrant additional evaluation for both common and less commonly diagnosed GI malignancies (i.e., carcinoid).

Evaluation for possible malignancy should be expeditious and may include upper tract imaging with swallowing study, ultrasound, CT scan, and/or endoscopy depending on presentation. Worrisome abdominal symptoms should prompt evaluation with imaging (CT scan or ultrasound) and referral to gastroenterology with possible need for colonoscopy.

**Genitourinary Symptoms**

Hematuria, whether microscopic or macroscopic, warrants evaluation to determine its etiology. Concurrent symptoms such as flank pain may help direct the evaluation, but hematuria often presents without pain. Renal cell carcinoma, bladder carcinoma, and, less commonly, prostate cancer may present with painless hematuria. In a prospective study of patients in a hematuria clinic, 12% had bladder cancer and 0.7% had kidney and upper tract malignancies, with most (61%) having no basis for hematuria identified. Bladder cancer was more common in an older population. The likelihood of bladder cancer is increased if there is gross hematuria (10% to 20%), whereas if microscopic hematuria is present, the incidence is less (2% to 5%).

In a general medical practice, the PPV of gross hematuria associated with urinary tract cancers was greater than 5% among men aged 55 years or older and women aged 65 years or older. If the etiology of the hematuria is not readily apparent (i.e., cystitis or stone), further investigation of the upper tract (kidneys and ureters) as well as the lower tract (bladder and urethra) is recommended. Abdominal and pelvic CT scan or intravenous pyelography (IVP) plus renal ultrasound may be used to evaluate the upper tract. Cystourethroscopy and possible urine cytology are used for lower tract evaluation.

Voiding symptoms may be related to intraluminal bladder irritation resulting in frequency, urgency, dysuria, or urge incontinence. Obstructive symptoms (nocturia, hesitancy, decreased force of stream) are more commonly seen with benign prostatic hypertrophy but may also occur in patients with advanced prostate cancer. Erectile dysfunction that is new in onset may be a result of more advanced prostate cancer. Women with ovarian cancer also reported recurring urinary symptoms, which included urgency and frequent urination.

### Breast Symptoms

Breast symptoms are common among women aged 40 to 70 years presenting to primary care clinics, with cancer diagnosis occurring in up to 6% of the women and 4% of the presentations; the remainder result from benign disease. Younger women (younger than 50 years old) present twice as often as older women, and symptoms vary by age. The most common presenting breast complaints include (1) breast pain, (2) mass (single lump or node), (3) nipple changes (inversion and discharge included), (4) skin changes, (5) multiple lumps or “fibrocystic changes,” and (6) change in size. In addition to the clinical presentation, the individual’s risk for breast cancer should be considered. Older age is the strongest risk factor associated with a new diagnosis of breast cancer, although family history, early menarche, late menopause, nulliparity, and prior biopsies with benign findings (i.e., hyperplasia) should also be considered as risk factors.

Pain is the most common breast complaint in women seeking evaluation and most present with unilateral discomfort. The symptom of pain leads to a diagnosis of cancer in a small percentage of patients (estimated 2% to 7%), but the likelihood of a cancer increased if it was concurrent with a breast mass. Etiologies of benign breast pain may be cyclical because of hormonal alterations of the breast tissue or noncyclical such as with cysts, stretching of ligaments, mastitis, or from compressive clothing.

Nipple discharge is a common complaint for women of reproductive age. The risk of nipple discharge as a presenting feature of cancer is elevated if there is an associated breast mass or if the discharge is unilateral, spontaneous, bloody, or occurs in woman older than the age of 40 years. Straw-colored discharge, if unilateral, may also result from an underlying malignancy (although more often from a papilloma) and would also warrant evaluation.

Breast mass is the symptom most commonly associated with cancer. In one study, 40% of the patients presenting with breast complaints were related to a breast mass. The chance of having breast cancer with a mass was 10%, whereas the likelihood of breast cancer with other common symptoms is less (Table 19-4). On physical examination, distinguishing the presence of a single nodule is important because young women frequently present with multinodular benign breast

---

**TABLE 19-3**

<table>
<thead>
<tr>
<th>Symptoms of Colorectal Malignancy with a Positive Predictive Value ≥5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Rectal bleeding</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Change in bowel habits</td>
</tr>
<tr>
<td>Associated iron deficiency anemia</td>
</tr>
</tbody>
</table>

Gynecologic Symptoms

Abnormal vaginal bleeding may be a presentation of vaginal, cervical, endometrial, or ovarian pathology. In premenopausal women, bleeding between menses is often related to structural lesions that are benign and less likely malignant. In postmenopausal women, uterine bleeding is more ominous, and endometrial cancer may be the cause in up to 10%; however, benign conditions such as mucosal atrophy are more common. Adenocarcinoma of the endometrium is the most common genital cancer in women older than the age of 45 years, with endometrial sarcomas much less common (3% to 5%). Patients may be at higher risk for endometrial cancer if they have a family history of ovarian, breast, colon, or endometrial cancer; are obese; have diabetes; or take tamoxifen. Irregular or postcoital vaginal bleeding or vaginal discharge may be a presentation of cervical cancer. Less likely as an etiology of postmenopausal bleeding is fallopian tube or ovarian malignancy. With more advanced presentations, pelvic pain or urinary symptoms may present. Ovarian cancer may also present with nonspecific abdominal symptoms such as bloating, abdominal pain, or early satiety.

Evaluation for these symptoms include imaging, such as pelvic ultrasound, MRI, and/or referral to gynecologist or, if possible, gynecologic oncologist.

SYMPTOMS ASSOCIATED WITH HEMATOLOGIC ABNORMALITIES

Malignancies may present with systemic bleeding disorders and/or as thrombotic abnormalities. The clinical presentation is determined by the mechanism, severity, and duration of the underlying disorder. Direct alterations of the hematologic pathways may be concurrent with tumor involvement that exacerbates the abnormalities (liver or splenic derangements). There may be a direct effect of tumor on nearby structures (compression of vasculature, erosion of visceral or mucosal surfaces) or infiltration of the vasculature (renal tumors invading the inferior vena cava [IVC], hepatocellular tumors invading the hepatic vein). Disseminated intravascular coagulation (DIC) is the most common coagulopathy associated with malignancy.

Hypercoagulable disorders most commonly present with deep venous thrombosis (DVT) of extremities or pulmonary embolism (PE). The relative risk of cancer associated with a venous thromboembolism was approximately three times that of a control group without DVT; however, this risk was primarily associated with patients presenting with idiopathic thrombosis. The incidence of cancer in patients presenting with a secondary DVT (identified underlying risk such as recent surgery, prolonged immobilization, use of oral contraceptives or hormone replacement, history of previous DVT, leg trauma, or known coagulation disorder) was only slightly higher than those without cancer. The risk of associated cancer appears to be highest in the first 6 months after presentation of thrombosis and declines quickly to normal within 1 year. Up to 40% of patients diagnosed with cancer in the year following initial thrombosis had metastases, making screening for occult tumors less beneficial because identification may not alter outcome. The strongest association between a hypercoagulable state and cancer is with cancers of the pancreas, ovary, liver (primary hepatic cancer), and brain (Table 19-5); however, given the prevalence of breast, colon, and lung cancer in the general population, these tumors are more commonly found presenting with idiopathic thromboembolisms. A rare but well known hypercoagulable presentation associated with occult malignancies is migratory superficial thrombophlebitis or Trousseau’s syndrome. This presents as recurrent and migratory superficial venous clots usually in extremities. Systemic embolic events may result from nonbacterial thrombotic endocarditis, also referred to as Libman-Sacks or marantic endocarditis. Vegetations on the heart valve result from degenerating platelets with fibrin strands. They vary in size and morbidity but may embolize to the spleen, kidney, extremities, central nervous system, or coronary arteries. Cancer should be considered in a patient presenting with DVT/PE, particularly if no clear precipitating event (i.e., trauma, prolonged immobilization) is present. In addition to a detailed history and physical examination, evaluation should include age-specific screening (i.e., mammography for women aged 40 years and older, colonoscopy for those aged 50 years and older). Extensive evaluation for malignancy has not been recommended.

Hematologic dysfunction related to a malignancy such as thrombocytopenia, DIC, liver disease, or abnormal platelet function may present with bleeding of the superficial surfaces. Patients may present with petechiae (oral or skin) or ecchymoses that are spontaneous or occur with limited trauma. Mucous membrane bleeding may present most commonly as nasal, periodontal, upper or lower GI, or genitourinary bleeding.
Probably the most common symptomatic hematologic derangement with cancer is anemia. Anemia may result from various mechanisms including loss of red blood cells from bleeding, decreased red blood cell production with marrow infiltration by solid tumor, lymphoma or leukemia, or by red blood cell destruction that may be present in hematologic malignancies. Symptomatic anemia may manifest as fatigue, dyspnea on exertion, shortness of breath, decreased exercise tolerance, or chest pain, particularly in an older patient.

**Lymphadenopathy**

Patients presenting with lymphadenopathy may have symptoms related to the location of the enlarged nodes or may have found them incidentally. When related to a malignancy, there may be other presenting features such as B-type symptoms (fevers, chills, night sweats) or history of recurrent infections to suggest an altered immune status that may be associated with lymphoma. Palpable solid tumors (breast or thyroid) may be identified as primary sources for metastatic disease. Localizing pulmonary or abdominal symptoms may herald underlying primary or metastatic lesions that drain to regional lymph nodes.

The clinical presentation of the lymph node enlargement may aid in diagnosis. Painful lymph nodes are typically reactive and drain nearby structures. Searching for a source of possible localized infection, and if not present, a systemic infectious cause should be considered. Reactive lymph nodes are more typically soft and less than 2 cm. Lymph nodes with a firm and rubbery consistency may be more likely related to lymphomas, whereas metastatic nodes may be hard and firm. Concerning features of a presenting lymph node include significant enlargement of >2 to 2.5 cm, persistence for more than 6 weeks, or progressive increase in size.

The location may also help direct evaluation. More than half of enlarged peripheral lymph nodes are benign, with inguinal lymph nodes having the highest incidence of hyperplasia or lymphadenitis. Of lymph nodes that are biopsy positive for metastatic disease, the supraclavicular site has the highest incidence. Patient characteristics should also be considered when assessing the etiology of enlarged lymph nodes (age, comorbidities including history of cancer or infection, tobacco use, associated systemic symptoms, etc). Older patients are more likely to have a malignant process as an etiology of lymph node enlargement; however, younger patients are at equal risk for lymphomas. Patients younger than 30 years old typically have Hodgkin lymphomas whereas older patients were more likely to have non-Hodgkin lymphoma. If there is no obvious underlying cause of minimally enlarged lymph node (<2 cm) with an otherwise unrevealing physical examination, then a complete blood cell count should be done and, if normal, close follow-up (2 to 6 weeks) should be done to ensure resolution. If the node/nodes enlarge or do not remit, referral to a surgeon for a biopsy is warranted.

**CUTANEOUS MANIFESTATIONS OF MALIGNANCY**

Skin involvement may be related to direct invasion of the dermis by visceral tumors either by contiguous spread or metastases. Indirectly, visceral tumors may present as paraneoplastic dermatoses in which the malignancy and skin disease are concurrent and run a parallel course. There are numerous reported paraneoplastic presentations, involving proliferative, inflammatory, bullous, and hormone-secreting mechanisms; several are discussed in the following texts.

Patients with ectopic adenocorticotrophic hormone (ACTH)—producing tumors may present with intense hyperpigmentation of the skin and mucosa in addition to muscle wasting, proximal muscle weakness, hypokalemic metabolic acidosis, glucose intolerance, hypertension, and weight loss. Small cell carcinoma of the lung is the most commonly associated tumor, but it has also been reported with carcinoid tumors, pheochromocytomas, thymomas, and pancreatic tumors.

Acanthosis nigricans is a common skin disorder presenting with velvety hyperpigmented plaques in flexural areas (neck, groin, and axillae), and although typically a benign presentation, it has been reported with malignancies (Fig. 19-1). Gastric adenocarcinoma is the most frequently associated tumor, but acanthosis nigricans may also be found with other solid tumors, particularly abdominal tumors. Patients with malignancy-associated acanthosis nigricans are older, thinner, and may have recent weight loss compared to benign presentations, which typically occur in patients who are obese. An abrupt onset of diffuse seborrheic keratosis (sign of Leser-Trélat) may be a manifestation of a GI tumor. Tripe palms are excessively wrinkled or ridged areas on the palms or soles, and 75% of patients with this finding will also have acanthosis nigricans. Tripe palm is associated with gastric or bronchogenic cancer; and in one review, 94% of cases were associated with a malignancy.

Dermatomyositis presents clinically with an edematous, violaceous eruption of the upper eyelids (heliotrope rash) and scaly papules over bony prominences of the hands (Gottron papules). There may also be photosensitivity, malar erythema, and periungual telangiectasias, but these are less specific. An associated myopathy can present with progressive proximal muscle weakness and difficulty swallowing and has been observed with tumor types including ovarian, breast, lung, gastric, colorectal, and pancreatic cancers.

**FIGURE 19-1.** Acanthosis nigricans. Acanthosis nigricans. (From Goodheart HP. Goodheart’s Photoguide of Common Skin Disorders. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003, with permission.)
<table>
<thead>
<tr>
<th>Tumor</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| Breast                | - Breast mass—most predictive presentation  
- Skin changes (dimpling, erythema, retraction)  
- Nipple inversion  
- Unilateral bloody or serous discharge  
- Less commonly, breast pain |
| Lung                  | - Hemoptysis, dyspnea, cough, weight loss, pain, fatigue, anorexia  
- Sites of metastases may be symptomatic (bone, liver, adrenal glands, and brain) |
| Colorectal            | - Abdominal pain, change in bowel habits, hematochezia or melena |
| Esophageal/gastric    | - Dysphagia (typically to solids then liquids)  
- Anorexia, weight loss, chest or abdominal pain, nausea  
- Hoarseness late in disease if recurrent laryngeal nerve is involved |
| Prostate              | - Asymptomatic until in advanced stage  
- Urinary urgency, frequency, hesitancy, and nocturia  
- Less commonly, impotence and hematuria  
- Metastatic disease, often with weight loss and bone pain |
| Renal cell            | - Hematuria, palpable abdominal mass, and pain  
- Early disease is nonspecific (weight loss, anorexia, malaise)  
- Metastatic disease commonly involving lung, lymph nodes, bone, liver, and brain  
- Paraneoplastic syndromes may include hypercalcemia, erythrocytosis, anemia, neuropathy, myopathy, etc. |
| Pancreas              | - Abdominal pain, weight loss, and jaundice (often painless)  
- Less commonly, bloating, eructation, change in stool, fatigue, dyspepsia |
| Ovarian               | - Often asymptomatic until advanced  
- Pelvic or abdominal pain, urinary urgency or frequency, increased abdominal girth or bloating, early satiety |
| Hodgkin lymphoma      | - Fever, night sweats, weight loss, or fatigue  
- 70% present with asymptomatic neck mass  
- Pain associated with alcohol ingestion (rare)  
- Organ-related symptoms (cough, pruritus, bone pain) |
| Non-Hodgkin lymphoma  | - Slowly enlarging lymph nodes, liver, or spleen if indolent  
- More systemic symptoms with aggressive tumors (fever, night sweats, weight loss)  
- 50% will present with extranodal disease (gastrointestinal and neurologic most common) |
| Melanoma              | - Evolving skin lesions (change in color, size), bleeding, pruritus |
| Endometrial           | - 90% diagnosed after abnormal uterine bleeding  
- More commonly, postmenopausal women |
| Liver                 | - Abdominal pain, weight loss, palpable mass  
- Decompensated cirrhosis: (ascites, jaundice, abdominal swelling) |
| Bladder               | - Painless hematuria (more commonly with gross bleeding)  
- Frequency, urgency, dysuria may occur but are nonspecific  
- Pain if locally advanced or metastatic |
| Testicular            | - Enlarging testicular mass (often painless) “scrotal heaviness”  
- 10% may be extragonadal  
- Retroperitoneal: back pain or abdominal mass  
- Mediastinal: shortness of breath, chest pain, vena caval obstruction |
| Leukemia              | - Fatigue, recurrent infections, and fever  
- Bleeding (oral, gastrointestinal, menorrhagia, ecchymoses)  
- Bone pain, headache |
| Sarcoma               | - Soft tissue mass—some with indolent growth  
- Most commonly in lower extremities (46%), trunk (18%), upper extremities (13%), retroperitoneal (12%), head/neck (9%) |
Generalized pruritus is a common symptom and may be a manifestation of numerous systemic illnesses including liver, kidney, and thyroid disease as well as iron deficiency. Although there does not seem to be an increase in cancers in patients with pruritus, it may be associated with an underlying malignancy. Chronic pruritus (lasting more than 6 weeks) has been reported as a precursor symptom for lymphomas and leukemias. Cases have also been reported in multiple myeloma, leukemia, and solid tumors, such as lung, gastric, and laryngeal tumors. Acquired ichthyosis (noninflamed, dry, scaly skin) may also present with pruritus; and although nonspecific, it may be associated with malignancies, most frequently Hodgkin lymphoma.

In patients with malignancies that predispose to altered immunity, mainly the lymphoproliferative disorders, infections may be more prevalent. Oral candidiasis may present early in the presentation, whereas an increased incidence of herpes zoster may be seen in patients with lymphoma or leukemia and occur later in the cancer’s progression.

### SELECTED CANCERS AND THEIR SYMPTOMS

The epidemiology and risk factors for individual cancers are discussed in other chapters. Some cancers present with nonspecific symptoms and may only be diagnosed after significant progression of disease, whereas others may have localizing features or characteristic clinical patterns. The prevalence of certain tumor types should influence the clinician’s suspicion and concern for further investigation of presenting signs and symptoms. Additionally, the patient’s gender and individual risk factors, whether environmental or genetic, will influence the evaluation. In Table 19-6, we review selected cancers more commonly seen in primary care settings and their associated symptoms as well as cancers that may have unique presentations.

### References


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Paraneoplastic syndromes are a group of clinical disorders associated with malignant diseases that are not directly related to the physical effects of the primary or metastatic tumor. The syndromes may be caused by (1) tumor production of substances that directly or indirectly cause distant symptoms, (2) depletion of normal substances that leads to a paraneoplastic manifestation, or (3) host response to the tumor that results in the syndrome.

The paraneoplastic syndrome may be the first sign of a malignancy, and its recognition may be critical for early cancer detection. Proteins secreted in paraneoplastic syndromes may be used as tumor markers. In some situations, the underlying disease cannot be treated, but the symptoms and complications of the paraneoplastic syndrome can be successfully managed.

Paraneoplastic syndromes are a heterogeneous group of disorders caused by mechanisms other than metastases, metabolic, infection, coagulopathy, or side effects of cancer treatment.

The paraneoplastic syndrome may be the first sign of a malignancy, and its recognition may be critical for early cancer detection.

Hypercalcemia is the most frequently reported paraneoplastic syndrome.

Small cell lung cancer is the most common malignancy associated with ectopic hormone production.

Paraneoplastic syndromes are frequently associated with malignancies of the lung, breast, ovary, and lymphatic system.

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Small cell lung cancer is the most common malignancy associated with ectopic hormone production.

Paraneoplastic syndromes are frequently associated with malignancies of the lung, breast, ovary, and lymphatic system.

Cutaneous paraneoplastic syndromes can be categorized according to their clinical presentation (Tables 20-1–20-3): Epidermal proliferation and excess keratinization results in hyperkeratosis, scaling, papulation, and ulceration; pagetoid changes and neutrophilic dermatosis are caused by direct tumor and white blood cell infiltration, respectively; cutaneous discoloration is a result of pigment deposition or lack; and collagen vascular disorders typically cause erythematous lesions, telangiectasia, and periorbital rash.

Endocrinologic paraneoplastic syndromes (Table 20-4) include cortisol excess which causes truncal obesity, hypertension, hirsutism, decreased libido, osteoporosis, and glucose intolerance; adrenocorticotropic hormone (ACTH) overproduction (Cushing disease or ectopic production) with muscle weakness, weight loss, hyperpigmentation, and hypokalemia; and Cushing syndromes (ACTH independent, adrenal tumors) cause muscle weakness and diverse signs of hypercortisolism. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) produces hyponatremia in the absence of volume excess. Oncogenic osteomalacia causes bone weakness and fractures and hypophosphatemia.

Marked hypoglycemia can be severe, leading to seizures, coma, and death.

Hematologic paraneoplastic processes (Table 20-5) are generally less clinically symptomatic than other paraneoplasias: Erythrocytosis usually causes asymptomatic plethora, occasionally patients may have hypertension or hyperviscosity; granulocytosis is almost always of little consequence; granulocytopenia may be associated with increased infection risk; and basophilia does not cause symptoms, a high eosinophil count may result in end-organ damage.

The consequences of the neurologic paraneoplastic syndromes depend on their associated autoantibodies and targeted proteins.
tissues. The most commonly recognized neurologic paraneoplastic is the anti-Hu syndrome, typically characterized by a peripheral sensory neuropathy and/or cerebellar syndrome. Anti-Hu has activity toward neurons located in the peripheral and central nervous systems and is implicated in several neurologic paraneoplastic syndromes. Other autoantibodies and their associated disorders appear in Table 20-6. These are retinal, cerebellar, cerebral, peripheral nerve, and neuromuscular junction disorders which present with visual disruption, ataxia, disorders of consciousness, paresthesias and pain, and muscle weakness.

Comprehensive history and examination remains key for the diagnosis of paraneoplastic disorders. In the case of endocrinologic paraneoplastic syndromes, this often involves detecting excess hormone or hormone stimulating substances. Specifically, in the circumstance of unexplained hypercortisolism, the investigator needs to differentiate between ectopic ACTH production, Cushing disease, or adrenal tumor. Tumor resection or medical control of hypercortisolism may be indicated. When SIADH is suspected, other causes of hyponatremia must be excluded; serum and urine sodium concentrations and osmolalities should be examined; and, if needed, water restriction, hypertonic saline infused, or specific arginine vasopressin receptor modulators administered and the associated tumor controlled. Serum phosphate and 1,25-dihydroxyvitamin D3 should be measured in patients with osteomalacia and replaced where appropriate.

Patients with paraneoplastic cutaneous presentations should be treated symptomatically or by eradication of the underlying malignancy. Patients suffering from excessive red cell mass or thrombocytosis rarely require treatment. Immunoglobulin (IVIG), and immunoadsorption is variably effective. Immunosuppression has been relatively ineffective in treatment of central paraneoplastic neurologic disease, may demonstrate pleocytosis and elevated protein and changes in CSF IgG.

The best evidence to date is that tumor ablation is more effective than immunosuppression in producing clinical neurologic improvement. Recovery after effective tumor therapy is variable and frequently incomplete. Immunosuppression with corticosteroids, plasma exchange, intravenous immunoglobulin (IVIG), and immunoadsorption is variably effective. Humoral immunosuppression has been relatively ineffective in treatment of central paraneoplastic neurologic diseases, although a series of patients with various

### TABLE 20-1
Paraneoplastic Cutaneous Manifestations of Cancer

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Malignancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired ichthyosis</td>
<td>Hyperkeratosis and rhomboidal scales of the extensor surfaces</td>
<td>Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, Kaposi sarcoma</td>
<td>Develops after malignancy is diagnosed; runs a parallel course; should be differentiated from hereditary form which develops before age 20 y</td>
</tr>
<tr>
<td>Palmar hyperkeratosis</td>
<td>Diffuse (tylosis) or punctate</td>
<td>Esophageal, breast, ovary, uterus</td>
<td>Diffuse—high incidence of breast, esophageal, ovary</td>
</tr>
<tr>
<td>Acrokeratosis paraneoplastica</td>
<td>Psoriasiform acral keratosis (hands, feet, ears, nose)</td>
<td>Squamous cell of esophagus, head and neck cancer, lungs</td>
<td>Male predominance</td>
</tr>
<tr>
<td>Pachydermoperiostosis</td>
<td>Subperiosteal bone formation, acromegalic features</td>
<td>Lung</td>
<td>May be seen in lung abscess and benign tumors</td>
</tr>
<tr>
<td>Exfoliative dermatitis</td>
<td>Progressive erythema followed by scaling</td>
<td>T-cell and other non-Hodgkin lymphoma, Hodgkin lymphoma</td>
<td>Accounts for 10%–20% of all exfoliative dermatitis</td>
</tr>
<tr>
<td>Erythema gyratum repens</td>
<td>Advancing erythema and trailing scales (Wood grain pattern)</td>
<td>Lung, breast, GI, uterus</td>
<td>80% associated with malignancy</td>
</tr>
<tr>
<td>Paget disease</td>
<td>Erythematous keratotic patch over nipple/areola, urogenital/perianal region</td>
<td>Breast, ovary, uterine, prostate, anal</td>
<td>Occurs in &lt;3% of breast cancers</td>
</tr>
</tbody>
</table>

**TABLE 20-2**
Paraneoplastic Disorders of Cutaneous Discoloration and Deposition

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Malignancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis nigricans (AN)</td>
<td>Gray-brown symmetric, velvety plaques on neck, axillae, flexor areas, anogenital region</td>
<td>Adenocarcinomas (especially gastric)</td>
<td>Benign form associated with syndrome X</td>
</tr>
<tr>
<td>Tripe palms</td>
<td>Hyperpigmented, velvety, thickened, hyperkeratotic ridges</td>
<td>Gastric, lung</td>
<td>Often associated with AN</td>
</tr>
<tr>
<td>Melanosis</td>
<td>Diffuse gray-brown skin pigmentation</td>
<td>Melanoma, ACTH-producing tumors</td>
<td>Often seen in benign conditions</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone.
### TABLE 20-3 Paraneoplastic Neutrophilic Dermatoses

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
<th>Malignancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet syndrome</td>
<td>Erythematous, painful, raised plaques</td>
<td>Acute myeloid leukemia, myeloproliferative neoplasm, myelodysplastic syndrome, non-Hodgkin lymphoma, various solid tumors</td>
<td>Responds to corticosteroids; 10%–20% associated with cancer</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>Painful papules ulcers, violaceous borders, exudates</td>
<td>Multiple myeloma, squamous cell carcinomas, cutaneous T-cell and other non-Hodgkin lymphoma</td>
<td>Responds to corticosteroids; may be associated with inflammatory bowel disease or rheumatoid arthritis</td>
</tr>
</tbody>
</table>

### TABLE 20-4 Paraneoplastic Endocrinologic Manifestations of Cancer

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Malignancy</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopic ACTH</td>
<td>Small cell lung cancer, thyroid, pancreatic, thymic, pheochromocytoma, carcinoid</td>
<td>Need to rule out pituitary adenoma and adrenal tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resection of tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical control of cortisol levels</td>
</tr>
<tr>
<td>SIADH</td>
<td>Small cell lung cancer, non–small cell lung cancer, head and neck cancer</td>
<td>Exclude benign causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Water restriction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3% Saline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Demecycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AVPR antagonists</td>
</tr>
<tr>
<td>Oncogenic osteomalacia</td>
<td>Lung, myeloma, prostate</td>
<td>Tumor resection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Replace phosphate and 1,25-dihydroxyvitamin D3</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Mesenchymal cell tumors, non-Hodgkin lymphoma, GI stromal tumor, adrenal</td>
<td>Glucose infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor resection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glucagon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High dose corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Somatostatin analogue</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Multiple myeloma, breast, kidney, lung, head and neck</td>
<td>Hydration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loop diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bisphosphonates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcitonin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plicamycin</td>
</tr>
</tbody>
</table>

**ACTH**, adrenocorticotropic hormone; **SIADH**, syndrome of inappropriate antidiuretic hormone; **AVPR**, arginine vasopressin receptor; **GI**, gastrointestinal.

### TABLE 20-5 Paraneoplastic Hematologic Manifestations of Cancer

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Malignancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytosis</td>
<td>Renal, liver, Wilms tumor, cerebellar hemangioblastoma, uterine fibroids, sarcoma, hemangioma, adrenal</td>
<td>Must exclude benign causes including medications</td>
</tr>
<tr>
<td>Granulocytosis</td>
<td>Many tumor types</td>
<td>Mature granulocytes; BCR-ABL negative; exclude infection</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>Many tumor types, Hodgkin lymphoma, large granular lymphocytic leukemia</td>
<td>Suppression of growth factors; antigranulocyte antibodies in Hodgkin lymphoma, T-cell dysregulation in large granular lymphocytic leukemia</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Hodgkin lymphoma, mycosis fungoides, chronic myelocytic leukemia, non-Hodgkin lymphoma, solid tumors</td>
<td>High levels of eosinophils may cause end-organ damage (Löffler syndrome)</td>
</tr>
<tr>
<td>Basophilia</td>
<td>Myeloproliferative neoplasms</td>
<td>Does not cause symptoms; may be seen in chronic myelocytic leukemia</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>Myeloproliferative neoplasms, many tumor types</td>
<td>Caused by excess thrombopoietin production or IL-6 effect; exclude iron deficiency, hemolytic anemia</td>
</tr>
</tbody>
</table>

**IL-6**, interleukin-6.
CNS paraneoplastic syndromes including limbic encephalitis (LE) reported clinical improvement after rituximab therapy. The relative efficacy and safety of rituximab, corticosteroids, cyclophosphamide, cyclosporine, and tacrolimus remain to be established. The ease and safety of IVIG lead to its frequent choice as the first-line therapy for antibody-associated disorders.

**PARANEOPlastic ENdocrinoLOGIC SYNDromes**

Common endocrinologic paraneoplastic syndromes and the malignancies frequently associated with them are listed in Table 20-4. The SIADH production is the most common. Patients have hyponatremia in the presence of euvolesia and, when the syndrome is severe, suffer from headache, confusion, seizures, and coma. The diagnosis is made by excluding benign causes of hyponatremia and detecting excess renal sodium loss and that urine osmolality exceeds serum osmolality. The treatment for asymptomatic and mild serum sodium abnormalities is water restriction. For worsening or symptomatic disease, hypertonic saline, loop diuretics, demecycline, or arginine vasopressin receptor antagonists may be indicated. The most common malignancy associated with SIADH is small cell lung cancer (SCLC). Treatment of the underlying tumor usually results in resolution of SIADH.

Patients with ectopic ACTH require a chest computed tomography (CT) scan to identify either SCLC or bronchial carcinoid tumors. Octreotide (a somatostatin analogue) scans can be used to localize ACTH-producing tumor sites when the tumor is somatostatin receptor positive. Surgical resection is the best treatment for localized ACTH-producing tumors. If the tumor is unresectable, the hypercortisolism

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**TABLE 20-6 Antibodies Associated with Paraneoplastic Neurologic Syndromes and Associated Cancers**

<table>
<thead>
<tr>
<th>Associated Primary Malignancy</th>
<th>Associated Autoantibody</th>
<th>Site of Activity</th>
<th>Paraneoplastic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell lung cancer; sarcoma; neuroblastoma</td>
<td>Anti-Hu (ANNA-1)</td>
<td>Panneuronal</td>
<td>Paraneoplastic encephalitis; paraneoplastic sensory neuropathy; paraneoplastic cerebellar degeneration; dysautonomia</td>
</tr>
<tr>
<td>Breast; gynecologic</td>
<td>Anti-Yo (APCA-1)</td>
<td>Purkinje cells</td>
<td>Paraneoplastic cerebellar degeneration</td>
</tr>
<tr>
<td>Breast; small cell lung cancer; Hodgkin lymphoma; bladder; gynecologic</td>
<td>Anti-Ri (ANNA-2)</td>
<td>Central nervous system neurons</td>
<td>Paraneoplastic cerebellar degeneration; opsoclonus-myoclonus</td>
</tr>
<tr>
<td>Small cell lung cancer; thymoma; non-Hodgkin lymphoma</td>
<td>Anti-Tr</td>
<td>Purkinje cells</td>
<td>Paraneoplastic cerebellar degeneration</td>
</tr>
<tr>
<td>Small cell lung cancer; renal cell cancer; breast; non-Hodgkin lymphoma; testicular</td>
<td>Anti-CV2 (CRMP5)</td>
<td>Oligodendrocytes</td>
<td>Paraneoplastic encephalitis; paraneoplastic cerebellar degeneration; chorea; uveitis, paraneoplastic neuropathy</td>
</tr>
<tr>
<td>Breast; testicular; lung</td>
<td>Anti-Ma (anti-Ta) (Ma1, Ma2)</td>
<td>Upper brain stem; cerebellum</td>
<td>LE; paraneoplastic cerebellar degeneration; Parkinson-like</td>
</tr>
<tr>
<td>Small cell lung cancer; breast</td>
<td>Anti-ampiphysin</td>
<td>Synapse; central nervous system</td>
<td>Stiff-person syndrome; paraneoplastic encephalitis</td>
</tr>
<tr>
<td>Small cell lung cancer; melanoma</td>
<td>Antirecoverin (anti-CAR)</td>
<td>Photoreceptors</td>
<td>Cancer-associated retinopathy (CAR)</td>
</tr>
</tbody>
</table>

**Paraneoplastic antibodies not completely characterized**

| Small cell lung cancer and Hodgkin lymphoma, respectively | Anti-Zic 4 and mGlur1 | Cerebellar tissue and peripheral neurons | Paraneoplastic cerebellar degeneration sensorimotor gait abnormalities |
| Small cell lung cancer | ANNA-3 | Nuclei of cerebellar Purkinje neurons | Paraneoplastic encephalitis; paraneoplastic sensory neuropathy |
| Small cell lung cancer | PCA2 | | Paraneoplastic encephalitis; paraneoplastic cerebellar degeneration |
| Melanoma | Antibipolar cells of retina | Retina bipolar cells | Melanoma-associated retinopathy |

**Antibodies that occur with and without cancer**

| Small cell lung cancer; Hodgkin lymphoma; thyroid | Anti-VGCC | Voltage-gated calcium channels (VGCC) | LEMS; paraneoplastic cerebellar degeneration |
| Thymoma | Anti-AChR | Acetylcholine receptors (AChRs); Nictinic acetylcholine receptors (nAChRs) | Myasthenia gravis |
| Thymoma; others | Anti-VGKC | Voltage-gated potassium channels (VGKC) | Neuromyotonia; Limbic encephalitis |
| Small cell lung cancer; thymoma; others | Anti-nAChR | nAChRs | Dysautonomia |

ANNA, antineuronal nuclear antibody; APCA, anti-Purkinje cell antibody; CRMP, collapsin response mediator protein; mGlur1, metabotropic glutamate receptor 1; LE, limbic encephalitis; PCA2, Purkinje cell antibody 2; LEMS, limbic encephalitis myasthenic syndrome.
can be controlled with ketoconazole, metyrapone, mitotane, etodolac, or adrenalectomy.13–17 Occasionally, if the tumor is somatostatin receptor positive, octreotide therapy is beneficial.48 Prognosis is dictated by the nature of the tumor and severity of hypercalcemia.49

Patients with tumor-induced osteomalacia have bone pain, normocalcemia, increased serum alkaline phosphatase, low serum phosphate and 1,25-dihydroxyvitamin D3, and high urine phosphate concentrations. The tumor should be resected. If resection is not tenable, the syndrome can be controlled with 1,25-dihydroxyvitamin D3 and phosphate replacement.50

Hypoglycemia associated with non–islet cell tumor is unusual. Mesenchymal tumors and hepatic carcinomas are responsible for two-thirds of cases. Patients have signs and symptoms of hypoglycemia, including generalized neurologic abnormalities.51 The causes vary (increased secretion, altered processing, increased bioavailability of insulin-like growth factor [IGF]-II, hypermetabolism of glucose, ectopic insulin production, production of hepatic glucose inhibitor, insulin binding by a monoclonal protein, and insulin receptor proliferation).52–54 Tumor resection or ablation is indicated when possible. Glucose infusion, glucagon, or high-dose steroid or octreotide administration are additional treatment options.

Hypercalcemia is the most commonly reported paraneoplastic syndrome and has been reported to occur in various cancer types. It has been described most frequently in patients with multiple myeloma, breast, kidney, lung, and head and neck cancer. The pathophysiology varies by tumor type and may be a result of direct tumor involvement; the release of osteoclast stimulating factor which encourages bone resorption; or the production of parathyroid hormone–related protein (PTHrP), a protein which shares limited homology with PTH and stimulates bone resorption and calcium reabsorption from the renal tubules. This hypercalcemia can lead to an osmotic diuresis and result in dehydration and worsening hypercalcemia and renal impairment. Treatment consists of rehydration, the use of potent loop diuretics, bisphosphonates, and occasionally either plicamycin or calcitomax.

**PARANEOPlastic HEMATOLOGIC SYNDROMES**

Erythrocytosis may be associated with a variety of malignancies and benign tumors (see Table 20-5). Causes include the production of erythropoietin by the neoplastic cells.14 It is diagnosed by the detection of disproportionally elevated serum erythropoietin concentrations. A rare cause of anemia in patients with cancer is pure red cell aplasia. One well-described paraneoplastic syndrome is that of thymoma and pure red cell aplasia with associated hypogammaglobulinemia.55 Pure red cell aplasia may also be associated with a variety of lymphoid malignancies, including chronic lymphocytic leukemia (CLL) and large granular lymphocytic lymphoma, and leukemia and nonhematologic malignancies.56 Nontherapy-related aplastic anemia is a rare complication seen in patients with malignancy. It has been reported to occur in patients with lung cancer, gastrointestinal cancers, paroxysmal hemoglobinuria, a variety of leukemia types, and squamous cell carcinoma.57–59

Autoimmune hemolytic anemias are typically associated with B-cell malignancies, including CLL and lymphomas, and arise secondary to immunoregulatory abnormalities in these diseases rather than to a direct secretion of tumor-derived substances. Warm antibody hemolytic anemia is most commonly associated with lymphomas, CLL, and mucin-producing adenocarcinomas. Cold agglutinin disease is most common in Waldenström macroglobulinemia and lymphomas.56 Autoimmune hemolytic anemia is rarely associated with solid tumors; however, an association with ovarian, gastrointestinal (GI), lung, breast, and renal cell cancers has been reported.56

Microangiopathic hemolytic anemia is characterized by fragmentation of red cells, and although often observed in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome, it has been reported in association with malignancy.60,61 Disseminated intravascular coagulation (DIC) may contribute to microangiopathic hemolytic anemia in metastatic carcinomas by inducing the red cell fragmentation from fibrin strands. Patients typically have pronounced schistocytosis with microspherocytes—spherocyte-shaped erythrocytes smaller than 5 µm in diameter. The reticulocyte count is typically increased, and a leukoerythroblastic blood picture may predominate. Microangiopathic hemolytic anemia is typically associated with adenocarcinoma of the GI tract, heart, lung, and prostate.

An elevated white blood cell count with a predominance of neutrophils is common in various malignant tumors, exclusive of infection and leukemia, and may be associated with tumor production of growth factors.62 Cancers may suppress granulopoiesis by producing substances that interfere with growth factors and, in the case of Hodgkin lymphoma, with the presence of associated neutrophil antibodies.15 T-cell dysregulation in patients with large granular lymphocytic leukemia and lymphoma can cause severe neutropenia.63 The neutropenia usually responds to treatment of the underlying lymphoproliferative disorder, although, sometimes, therapy with growth factors is needed.64

Extremely high eosinophil counts can cause symptoms similar to those of Löffler syndrome and may require intervention with corticosteroids.65–67 Basophilia is associated with chronic myelogenous leukemia and a variety of other myeloproliferative disorders but does not typically give rise to symptoms.67,68

Thrombocytosis is common in patients with cancer.69,70 It occurs early in the course of myeloproliferative neoplasms. Thrombocytosis secondary to malignancies may be caused by tumor overproduction of thrombopoietin or interleukin 6.69 Inflammatory disorders, hemorrhage, iron deficiency, and hemolytic anemia should be excluded. Thrombosis and hemorrhage rarely occur, and treatment is not generally indicated.

**PARANEOPlastic RENAL SYNDROMES**

Membranous nephropathy (with nephrosis-range proteinuria, hypertension, and hematuria) is associated with and may precede the detection of lung, colon, stomach, and other cancers. The deposition of tumor or nontumor antigens in the glomeruli promotes antibody deposition, complement activation, and proteinuria.71 The nephrotic syndrome may resolve with successful treatment of the associated malignancy. Careful monitoring for the development of thrombosis, especially renal vein thrombosis, is warranted.

Hodgkin lymphoma is most frequently associated with minimal change disease. It also occurs with other lymphoproliferative disorders, pancreatic carcinoma, and mesothelioma.72 Eradication of the active cancer can result in resolution of the proteinuria. Focal and segmental glomerulosclerosis
is seen in patients with CLL, T-cell lymphomas, and acute myelogenous leukemia; IgA nephropathy with lung, head and neck, and pancreatic cancers, mycosis fungoides, and liposarcoma; and membranoproliferative glomerulonephritis with CLL, Burkitt and other lymphomas, hairy cell leukemia, and malignant melanoma. Rapidly progressive glomerulonephritis can occur with lymphoma and monoclonal gammopathies.72

**PARANEOPLASTIC DERMATOLOGIC SYNDROMES**

Various cutaneous syndromes are associated with malignancies. It is critical that, once a potential cutaneous paraneoplastic syndrome has been diagnosed, an appropriate systemic evaluation for a neoplasm be undertaken. Tables 20-1, 20-2, and 20-3 list the various cutaneous syndromes and describe their clinical presentation, associated underlying malignancies, and varied appropriate comments. It is important to note that, with a few exceptions, their causes are poorly understood. Some of these disorders resolve when the associated tumor remits and others do not (paraneoplastic pemphigus). In some cases, the occurrence of the cutaneous abnormality is more commonly seen with underlying benign circumstances rather than in relation to malignant disease. The occurrence of parallelism is sometimes uncertain because the cutaneous event may precede (acrokeratosis neoplastica, erythema gyratum repens, acanthosis nigricans, melanosis, cutaneous ichemias) or follow the detection of the malignancy (Kaposi sarcoma, acanthosis nigricans, melanosis). Consequently, very common conditions frequently associated with various cancers may not represent true associations and are not true paraneoplastic syndromes, as in the case of the sign of Leser-Trélat (a condition of a sudden appearance of seborrheic keratosis incorrectly thought to be secondary to an occult malignancy).73

Icterus is usually caused by intrahepatic or extrahepatic obstruction or infiltration (e.g., amyloid light-chain [AL] amyloidosis). Vitiligo caused by loss of skin pigment is associated with thyroid carcinoma and melanoma and may signify the appearance of developing of metastatic disease. Plane xanthomas are large yellow-orange lipid laden patches and plaques on the trunk most frequently seen with multiple myeloma, leukemias, and lymphomas.74-78

Vasculitis occurs in patients with solid tumors (most commonly non–small cell lung), esophagus, prostate, and hematologic malignancies (haery cell leukemia, lymphomas, and rarely multiple myeloma).75-80 Purpura secondary to underlying malignancy may have various causes such as thrombocytopenia, consumption coagulopathy, vascular injury, vasculitis, and immunoglobulin abnormalities. Cutaneous ischemia can be caused by autoimmune phenomena, leukostasis, and increased blood viscosity.

Systemic nodular panniculitis is characterized by violaceous nodules; is associated with adenocarcinoma of the pancreas; and may be accompanied by polyarthralgia, fever, and eosinophilia.81 Necrolytic migratory erythema is seen only with glucagonoma and is characterized by erythema, papules, vesicles, and pustules that progress to blistering and epidermal necrosis on the central face, lower abdomen, perineum, and buttocks and other areas.82 It often resolves with tumor resection and somatostatin analogue therapy, which suppresses glucagon secretion.75

Addison syndrome can occur with adrenocortical carcinoma and is characterized by generalized hyperpigmentation, especially in scars, pressure points, and points of friction.83-85 Hirsutism is associated with virilism and is caused by increased levels of glucocorticoids and testosterone, typically from adrenal and ovarian tumors.86-88 Carcinoid syndrome may cause telangiectasias and scleroderna- and pellagra-like skin changes.89

Flushing is an episodic reddening of the face and neck, lasting a few minutes, typically associated with the carcinoid syndrome but also seen with leukemia, medullary carcinoma of the thyroid, renal cell carcinoma, and other malignancies.90-92 Harlequin syndrome is unilateral flushing and sweating caused by ciliary ganglion destruction.93-95 Isolated palmar erythema may be observed in liver failure caused by hepatic malignancy.

Paraneoplastic pemphigus is a rare bullous disorder most frequently seen in B-cell lymphoproliferative disorders and spindle cell neoplasms.96 Patients develop painful oral and conjunctival ulcers and erosive skin lesions. Internal organ involvement is common.96-98 The course of the disease is progressive and independent of the underlying malignancy. Thirty percent of patients die from respiratory failure.98 The respiratory failure is thought to be caused by autoantibodies directed against an intracellular protein target called plakin. This antibody-target interaction results in acantholytic changes of the respiratory epithelium.99 Corticosteroids, cyclosporine, and mycophenolate mofetil are beneficial.97,100

Diffuse hair loss may be present in advanced cancers because of numerous factors, including telogen effluvium (characterized by thinning and shedding of hair) and alopecia areata.101 Increased hair growth has been associated with numerous malignancies, including endocrinologic tumors.102 Hypertrichosis lanuginosa acquisita is the sudden appearance of downy hair on the entire body and is most commonly associated with lung cancer, followed by colon, bladder, ovarian, uterine, and pancreatic cancers.103 Resolution of these hair growth disorders is uncertain.

Patients with Muir–Torre syndrome have numerous sebaceous gland neoplasms, including carcinomas that may precede, follow, or coexist with visceral cancers or lymphoma.104 Patients with Cowden syndrome may have polyposis coli and a risk of breast, GI, and thyroid carcinoma.105 Breast exposure to diagnostic irradiation is contraindicated. Bilateral mastectomies may be recommended.

Gardner syndrome typically includes hundreds of adenomatous colorectal polyps, with an inevitable progression to colorectal cancer. Patients can have numerous epidermal cysts and soft tissue tumors, congenital hypertrophy of the retinal pigment epithelium, osteomas, and dental anomalies.106 Multicentric reticulohistiocytosis manifests as violaceous papules overlying joints with associated arthritides, malignant and squamous cell lung cancers, and melanoma. There is no effective therapy.107 Generalized pruritus may be the initial feature of either overt or occult malignancy. It is most frequently associated with Hodgkin and non-Hodgkin lymphoma and polyarthritis vera.108,109 Severe pruritus localized in the nostrils has been reported in some patients with advanced brain tumors.110

**PARANEOPLASTIC NEUROLOGIC SYNDROMES**

Table 20-6 categorizes the various paraneoplastic syndromes by the implicated autoantibody and the associated malignancy types. The multiplicity of presentations by autoantibody type

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and non-Hodgkin lymphoma may target peripheral nerves causing pure sensory peripheral neuropathies or mixed sensory-motor peripheral (resembling chronic inflammatory demyelinating polyneuropathy [CIDP]) and centrally mediated motor disorders (e.g., chorea).5,126-136 Stiff person syndrome (muscle stiffness and rigidity in the paraspinal and abdominal muscles) and dysautonomia (characterized by muscle fiber hyperexcitability) are associated with antibodies, which affect the neuron synapse and neuromuscular junction.5 Rarely, patients with neuroblastoma can develop opsoclonus-myoclonus syndrome, which shares disorderly ocular motility and multifocal myoclonus.137 Patients with dermatomyositis have erythema or telangiectasia of knuckles, chest, and periorbital region and proximal muscle weakness.138 Breast cancer and gynecologic cancer are the most commonly associated cancer in women and lung and GI cancer in men.13 Dysautonomia, associated with anti-Hu or anti-nAChR (antibody directed against nicotinic acetylcholine receptors), may cause severe hypotension, gastroparesis, constipation, and variety of other symptoms.

Paraneoplastic parkinsonian syndromes are rare.139 Rapidly progressive parkinsonism and autonomic failure occur with multiple myeloma. Parkinsonian-like features are associated with anti-Ma2 (antibodies directed against paraneoplastic Ma2 protein) and testicular seminoma.140 Rapidly progressive multisystem degeneration resembling progressive supranuclear palsy, but associated with peripheral neuropathy and fever, occurs with B-cell lymphoma.141

References

4. Valdes-Socin H, Niaourou V, Vandeva S, et al. Paraneoplastic endocrine dysfunction and cerebellar degeneration.111–114 Similarly, patients with varying underlying malignancies (e.g., breast, gynecologic cancers) may develop the same paraneoplastic process, apparently mediated by the same autoantibody, anti-Yo (antibody directed against Purkinje cells).114–125 Patients may develop visual change (night blindness, color blindness) or loss (progressive blindness) from a paraneoplastic retinopathy as a result of autoantibodies with differing target antigens but associated with the same type malignancy (antirecoverin, antibipolar cells of retina, melanoma).126,127 Paraproteins in the form of monoclonal gammopathies of unknown significance, multiple myeloma, POEMS syndrome (polyneuropathy, organomageligy, endocrinopathy, M-protein, skin changes) and non-Hodgkin lymphoma may target peripheral nerves.


Incidentally Found Cancers

Theodore S. Lawrence, MD, PhD, FASTRO • Nirav S. Kapadia, MD • Elon J. Granader, MD, MSc

KEY POINTS

- Incidental pulmonary nodules are very common. Both patient risk stratification and the nodule’s specific imaging profile are important for subsequent clinical management. Fleischner Society recommendations should be followed when possible.
- Mediastinal masses are infrequently incidental, but when encountered, the differential diagnostic considerations can be segregated by location. Further evaluation of mediastinal lymphadenopathy is necessary when enlarged, morphologically abnormal lymph nodes are discovered.
- Most incidental adrenal lesions are benign in patients without a history of primary malignancy. Indeterminate lesions can be further characterized with adrenal-specific protocol CT or MRI.
- Incidental renal masses can be cystic or solid and should be managed according to established guidelines.
- Some incidental cystic lesions of the pancreas have malignant potential. Further evaluation of incidental pancreatic lesions with pancreatic protocol CT, magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasound (EUS) should be performed if warranted.
- Multiphasic CT or MRI are excellent imaging modalities in the assessment of incidentally detected hepatic lesions with suspicious features or those detected in patients of high-risk profiles.
- Pelvic ultrasound is an inexpensive imaging modality that does not expose the patient to ionizing radiation and can be very helpful in the characterization of incidental adnexal masses. Clinical workup should also be dictated by the patient’s menopausal status.

The goal of this chapter is to provide the reader with commonly encountered incidental findings on routine imaging of the chest, abdomen, and pelvis; general differential diagnoses; and what (if any) further workup should be performed. Incidental finding appearances on computed tomography (CT) and ultrasound are presented here because of their frequent use in the primary care setting. The information in this chapter should be used as an adjunct to the radiologist’s report rather than as a replacement for his or her recommendations and considered in the context of the patient’s overall clinical presentation.

PULMONARY NODULES

Pulmonary nodules are extremely common incidental imaging findings (Fig. 21-1A). Large, prospective CT-screening trials of older patients with heavy smoking histories have revealed that half of this population harbors at least a single pulmonary nodule. More than 90% of those nodules, however, were benign.1 When a pulmonary nodule is incidentally encountered, it is essential for the primary care physician to know whether the finding is suspicious and requires further workup and/or surveillance or whether the finding is benign and can be safely ignored.

It is paramount for the radiologist to have access to any prior imaging studies when evaluating an incidental pulmonary nodule. A lesion’s duration and rate of growth are important to note because nodules stable for 2 years are unlikely to be malignant.2,3 Bronchoalveolar carcinoma can be slow growing and a notable exception.3,4

The differential diagnosis of an incidental pulmonary nodule is broad. Pulmonary nodule size is also an important consideration as less than 1% of nodules smaller than 5 mm are malignant.5 In fact, the Fleischner Society recommendations for incidental pulmonary nodule follow-up are guidelines stratified by nodule size and patient risk (i.e., smoking status) (Table 21-1).6

Although only direct tissue sampling, when necessary, can provide a definitive diagnosis, there are several other imaging characteristics which can suggest a malignant or benign diagnosis (Table 21-2). For example, lesions with central or popcorn-like patterns of calcification have very low likelihoods of malignancy1,2,4 and are most consistent with benign hamartomas (Fig. 21-1B) or calcified granulomas. In contrast, more than 80% of masses with spiculated borders (Fig. 21-1C) are malignant.10 Malignant nodules can represent either primary pulmonary carcinoma or metastatic disease. Metastatic disease...
FIGURE 21-1. Incidental pulmonary nodules (arrows). A: Axial CT image of the chest (lung windows). Incidental 5 mm solitary pulmonary nodule in a patient with an extensive smoking history. Initial imaging follow-up was recommended at 6 to 12 months per Fleischner Society guidelines. B: Non–contrast-enhanced axial CT image of the chest (soft tissue windows). Pulmonary hamartoma with a benign pattern of central calcification. C: Axial CT image of the chest (lung windows). Spiculated pulmonary nodule which is concerning for malignancy in this patient with emphysema and an extensive smoking history. D: Contrast-enhanced axial CT image of the chest (soft tissue windows). Multiple pulmonary nodules consistent with metastatic disease in this patient subsequently diagnosed with melanoma.

Follow-up of an indeterminate pulmonary nodule involves subsequent imaging surveillance in accordance with Fleischner Society recommendations to assess for nodule stability. It is important to note that these recommendations do not pertain to patients younger than 35 years, patients with unexplained fever, or patients with known or suspected malignancy. For lesions larger than 8 mm in size, PET/CT or tissue sampling should be considered.

<table>
<thead>
<tr>
<th>TABLE 21-1</th>
<th>Fleischner Society Recommendations for Follow-up and Management of Pulmonary Nodules Detected Incidentally at Nonscreening CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule Size (mm)</td>
<td>Low-Risk Patient (Minimal/Absent Smoking History)</td>
</tr>
<tr>
<td>≤4</td>
<td>No follow-up needed</td>
</tr>
<tr>
<td>&gt;4–6</td>
<td>1-y follow-up CT (if unchanged, then no further follow-up)</td>
</tr>
<tr>
<td>&gt;6–8</td>
<td>Initial follow-up CT at 6–12 mo. If no change, then follow-up at 18–24 mo.</td>
</tr>
<tr>
<td>&gt;8</td>
<td>Follow-up CT at 3, 9, and 24 mo, contrast-enhanced CT, PET/CT, and/or biopsy</td>
</tr>
</tbody>
</table>

CT, computed tomography; PET, positron emission tomography.
ADRENAL

Although incidental adrenal masses can be found on up to 5% of abdominal CTs,14 most of these lesions are benign adenomas (Fig. 21-4A) or, less commonly, benign myelolipomas (Fig. 21-4B). In fact, none of 1,049 incidental adrenal masses in a series of patients without known malignancy turned out to be cancer.15 Fortunately, the CT appearance of an adrenal lesion can be very helpful in making the distinction between a worrisome mass and a benign finding. Masses larger than 4 cm and those demonstrating necrosis or enhancement (Fig. 21-4C) may be adrenocortical carcinomas.15 Most adrenal adenomas and myelolipomas demonstrate low or fat attenuation on CT, respectively.

If an incidental adrenal lesion is difficult to characterize on the initial imaging study (Fig. 21-4D), adrenal protocol CT

TABLE 21-2 Imaging Features Suggestive of Benign and Malignant Pulmonary Nodules

<table>
<thead>
<tr>
<th></th>
<th>Benign Features</th>
<th>Malignant Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;5 mm</td>
<td>&gt;2 cm</td>
</tr>
<tr>
<td>Calcification morphology</td>
<td>Popcorn, diffuse</td>
<td>Stippled, amorphous</td>
</tr>
<tr>
<td>Calcification location</td>
<td>Central</td>
<td>Eccentric</td>
</tr>
<tr>
<td>Borders</td>
<td>Smooth, rounded</td>
<td>Spiculated</td>
</tr>
<tr>
<td>Doubling time</td>
<td>&lt;7 d, &gt;2 y</td>
<td>Weeks/months</td>
</tr>
</tbody>
</table>

MEDIASTINUM

Incidental mediastinal masses are considerably less common than pulmonary nodules. One large study demonstrated that the prevalence of incidental mediastinal masses on screening CT in a population at high risk for lung cancer was less than 1%. Thymic lesions were the most commonly detected incidental findings.12 Other differential diagnostic considerations when encountering an anterior mediastinal mass include lymphoma, teratoma, and thyroid carcinoma. Middle mediastinal masses include bronchogenic cyst, lymphadenopathy, and esophageal-related entities. Neoplasms of the posterior mediastinum most often arise from neurogenic structures and include neurofibroma, schwannoma (Fig. 21-2), and ganglioneuroma.

In contrast to incidental mediastinal masses, incidental mediastinal lymph nodes are frequently detected. Lymph nodes, which demonstrate abnormal size and morphology (Fig. 21-3A), are concerning and prompt further diagnostic workup. Incidental lymph nodes, which measure smaller than 1 cm in short axis13 and have classic nodal architecture, are normal (Fig. 21-3B).

ADRENAL

Although incidental adrenal masses can be found on up to 5% of abdominal CTs,14 most of these lesions are benign adenomas (Fig. 21-4A) or, less commonly, benign myelolipomas (Fig. 21-4B). In fact, none of 1,049 incidental adrenal masses in a series of patients without known malignancy turned out to be cancer.15 Fortunately, the CT appearance of an adrenal lesion can be very helpful in making the distinction between a worrisome mass and a benign finding. Masses larger than 4 cm and those demonstrating necrosis or enhancement (Fig. 21-4C) may be adrenocortical carcinomas.15 Most adrenal adenomas and myelolipomas demonstrate low or fat attenuation on CT, respectively.

If an incidental adrenal lesion is difficult to characterize on the initial imaging study (Fig. 21-4D), adrenal protocol CT
FIGURE 21-4. Incidental adrenal lesions (asterisks). Inferior vena cava (I). A: Non–contrast-enhanced axial CT image of the abdomen. Benign homogeneous, low-attenuation, lipid-rich left adrenal adenoma. Left adrenal gland medial limb (arrow). B: Contrast-enhanced axial CT image of the abdomen. Note the very low attenuation (macroscopic fat) in this benign left adrenal myelolipoma. C: Contrast-enhanced axial CT image of the abdomen. Large, heterogeneously enhancing and necrotic right adrenal mass proved to be adrenocortical carcinoma in this younger patient undergoing workup for gynecomastia. D: Non–contrast-enhanced axial CT image of the abdomen. Indeterminate left adrenal lesion by CT attenuation criteria warranted further characterization with either adrenal mass protocol CT or magnetic resonance imaging (MRI). With contrast washout determination or a magnetic resonance imaging (MRI) are recommended for further evaluation. If desired, the American College of Radiology’s Appropriateness Criteria for the incidentally discovered adrenal mass can be reviewed for further information regarding radiologic and clinical management recommendations.16

RENAL

Up to 41% of patients will have an incidental simple renal cyst on CT.17 Nonetheless, half of all renal malignancies are also incidentally detected.18,19 Therefore, the classification of an incidental renal lesion as benign or suspicious based on its imaging characteristics is of utmost clinical significance. Heuristically, two algorithms are used in the evaluation of an incidental renal mass, depending on whether the lesion is cystic or solid.

The Bosniak classification for renal cystic lesions is presented in Table 21-3. Simple renal cysts require no further intervention or surveillance (Fig. 21-5A), whereas cysts with enhancing septations (Fig. 21-5B) or solid components (Fig. 21-5C) require further characterization or surgical intervention, respectively.20 Solid renal masses include renal cell carcinoma (Fig. 21-5D) and metastatic disease as well as benign entities such as the fat-containing angiomyolipoma (Fig. 21-5E) and oncocytoma. Generally speaking, solid lesions smaller than 1 cm can be followed, whereas masses larger than 3 cm should be removed.21 Intermediate lesions can be further characterized by ultrasound, renal protocol CT, and/or MRI. Although most benign entities can be safely observed, large angiomyolipomas are prone to hemorrhage and should be considered for resection.20,22,23

PANCREAS

Incidental pancreatic cysts were detected in nearly 3% of one outpatient population.24 Solid pancreatic lesions (such as adenocarcinoma) are more likely to be malignant25,26 but rarely present as incidental findings. Even though most cystic lesions (Fig. 21-6A) are benign, malignancy is not always excluded.27,28
Mucinous cystic neoplasms and intraductal papillary mucinous neoplasms (IPMN) are common macrocystic lesions with malignant potential. Mucinous cystic neoplasms can demonstrate peripheral calcification, are located in the pancreatic tail, and are generally found in middle-aged women. IPMN should be suspected if the cyst communicates with the main pancreatic duct (Fig. 21-6B) or one of its side branches.\textsuperscript{21,29,30} Even though these lesions carry a better prognosis than adenocarcinoma, they can be fatal and should be resected if possible.\textsuperscript{31}

If further evaluation of an incidental pancreatic lesion is indicated, a pancreatic protocol CT/MRI, magnetic resonance imaging.
Multiphasic liver CT or MRI. These specific imaging modalities can accurately identify the unique contrast enhancement pattern of most hepatic lesions (Fig. 21-7). For patients without a history of hepatobiliary disease or primary malignancy, the American College of Radiology does not recommend follow-up for any abnormality less than 5 mm in size. Homogenous low attenuation simple cysts (Fig. 21-8A) and asymptomatic hemangiomas (Fig. 21-8B) are common benign incidental hepatic lesions, which similarly do not need to be followed.

**LIVER**

Similar to the pulmonary and renal nodules, incidental hepatic lesions are frequently encountered. Up to one-third of asymptomatic patients may demonstrate a hepatic lesion on contrast-enhanced CT. A comprehensive differential diagnosis for benign and malignant hepatic lesions is beyond the scope of this chapter. Hepatocellular carcinoma (HCC), cholangiocarcinoma, and metastatic disease are a few of the more common malignant hepatic entities. Patients at greatest risk for metastatic disease and HCC include those with a history of primary cancer and those with predisposing liver disease (i.e., alcohol or hepatitis-induced cirrhosis), respectively. Therefore, an incidental hepatic lesion without clear features of benignity in these patients warrants further characterization with dedicated multiphasic liver CT or MRI. These specific imaging modalities can accurately identify the unique contrast enhancement pattern of most hepatic lesions (Fig. 21-7). For patients without a history of hepatobiliary disease or primary malignancy, the American College of Radiology does not recommend follow-up for any abnormality less than 5 mm in size. Homogenous low attenuation simple cysts (Fig. 21-8A) and asymptomatic hemangiomas (Fig. 21-8B) are common benign incidental hepatic lesions, which similarly do not need to be followed.

**ADNEXAL MASSES**

Asymptomatic adnexal masses are common imaging findings on both pelvic ultrasound and CT, with incidental CT detection rates approaching 5% of patients. Although a significant portion of these masses prove to be benign in both the premenopausal and postmenopausal populations, indeterminate or malignant-appearing lesions warrant further evaluation.
Figure 21-9A shows the normal follicular ultrasound appearance of the ovary without the presence of an incidental finding. Incidental adnexal masses can be divided into three categories: benign, indeterminate, and suspicious for malignancy. Benign lesions do not contain solid tissue or demonstrate internal vascularity on pelvic ultrasound. Simple ovarian cysts (Fig. 21-9B) have smooth thin walls and are anechoic, whereas hemorrhagic cysts (Fig. 21-9C) demonstrate internal echogenicity. Dermoid cysts contain both fat and calcification, both of which are easily appreciated on CT (Fig. 21-9D).
In premenopausal women, small (less than 5 cm) benign simple ovarian cysts and hemorrhagic cysts do not require any follow-up. Medium-sized simple cysts (5 to 7 cm) should be followed by ultrasound annually and hemorrhagic cysts should be followed more closely (every 6 to 12 weeks). Lesions larger than 7 cm should be referred for tissue sampling or resection.\textsuperscript{37} The threshold for close follow-up in postmenopausal women is much lower: Any simple cyst larger than 1 cm or any hemorrhagic cyst should be followed.

Indeterminate incidental adnexal masses contain multiple thin septations or solid nodules without detectable internal vascular flow (Fig. 21-10). Follow-up ultrasound at 6 to 12 weeks or MRI is recommended for premenopausal women because less than 2\% of such patients have a negative MRI have ovarian cancer.\textsuperscript{38} Any indeterminate mass in a postmenopausal woman should be further characterized with MRI. Finally, frankly concerning imaging features such as thick, irregular septations or solid components with internal vascularity on ultrasound and large necrotic masses on CT\textsuperscript{36} should be promptly referred for surgical evaluation in both the premenopausal and postmenopausal populations.\textsuperscript{37}

References


CHAPTER 22 Principles of Cancer Diagnosis and Staging

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KEY POINTS
- Each tumor type has a separate stage classification system to categorize the extent of disease.
- A cancer staging workup involves a series of imaging and pathologic studies to assess the extent of disease. However, the accuracy of each study may vary significantly by the specific situation and tumor type.
- Tissue confirmation of a suspected cancer is critical. The biopsy approach is dictated by the location of the suspicious lesion and the amount of tissue required for diagnosis.
- A multidisciplinary tumor board can expedite the diagnosis and staging of patients with cancer and help plan and coordinate treatment.

INTRODUCTION
Few clinicians have the power to affect the oncologic outcome more than the primary care clinician (PCC). The PCC has the enormous responsibility of reacting to the clinical change, physical finding, or incidental laboratory or radiology result that exposes the disease of a patient with cancer. The clinical skill set to recognize subtle indicators of cancer reflects the art of medicine, something most clinicians strive to master throughout their practice. The challenges from a PCC perspective are the potential to “underdiagnose” or “overdiagnose” a cancer and the associated health consequences.

The term underdiagnosis refers to a delay in the diagnosis. This most often results from the following:
1. Failure to appreciate an indicator of malignancy (symptom, physical finding, laboratory, or radiologic abnormality)
2. Misdiagnosis of a cancer as being a benign process
3. Acceptance of a negative cancer test result without considering limitations in the accuracy of the study

The most feared consequence of underdiagnosis is a transition from a curable cancer to one that is terminal. The time line for this transition is unknown, but most would agree that a thoughtful and expeditious evaluation is best.

Overdiagnosis refers to subjecting a patient to invasive procedures and radiation exposure from imaging and anxiety while pursuing a cancer diagnosis for a benign disease. Although it is obviously better to err on the side of caution, the physical and psychological consequences of the workup (even a negative one) are very real to the patients.

Once a patient has been diagnosed with an abnormality that is concerning for malignancy, three important objectives must be pursued in parallel before initiating a treatment plan: A tissue confirmation of cancer must be obtained, the tumor must be staged, and the patient’s overall health must be assessed before an optimal treatment plan can be established. Along the same lines, there are three tenets of the staging and diagnostic evaluation that maximize efficiency and the productivity of the PCC–oncologist collaboration:

Build Evaluation, Study by Study
The use of most radiographic studies is affected by the results of earlier studies. Avoid the knee-jerk “shotgun” ordering of a battery of imaging studies without interpreting the first-line studies. For example, ordering a brain magnetic resonance imaging (MRI) in an asymptomatic patient that has an extremely early appearing lung cancer by chest computed tomography (CT) scan is more likely to give erroneous information than finding a true metastasis.

Maximize Yield of Biopsies
A biopsy is required to confirm that a suspicious lesion is a cancer and, in some scenarios, a second biopsy is used to confirm the patient has metastatic disease by biopsying a suspicious lesion elsewhere in the body. A single biopsy of the presumed metastasis may accomplish both goals. Consider a patient with suspected lung cancer found to have a suspicious liver lesion. A liver biopsy could both confirm the cancer and establish the patient to have a liver metastasis.

Consider Your Fellow Combatants
Specific imaging protocols are often needed by the surgeons and radiation oncologists who will be involved in treating the patient (such as a specific CT scan to visualize the blood vessels around a pancreatic cancer). It is always best to engage
CONFIRMATION OF CANCER DIAGNOSIS

The confirmation of a suspected cancer requires some portion of the lesion to be removed and examined by a pathologist. There are three general types of biopsies: aspiration, incisional, and excisional.

Aspiration involves the insertion of needles of various gauges into the lesion and applying suction to capture tissue from within the lesion. Small needle biopsies are considered “fine needles,” and large needle biopsies are referred to as “cores.” The key features of the aspiration include the following:

- Localization of the lesion for needle placement, which may occur by touch if the lesion is close to the surface of the skin (such as a thyroid nodule), or use of an imaging study to plot the trajectory of the needle into the lesion (ultrasound, CT scanning, etc.).
- Selecting the appropriate needle: The greater the importance for maintaining tumor architecture, the larger the needle diameter that is needed, such as for some lymphomas and epithelial tumors.

The chief advantage of aspiration is the ability to access the broadest range of locations in the body. The needle can be introduced percutaneously (by ultrasound or CT guidance), transbronchially (endobronchial ultrasound), transvisceral (endoscopic ultrasound), or transvascular (endovascular ultrasound). The complications vary by the location such as pneumothorax for lung lesions or bleeding from lesions in the spleen. The chief limitations of aspiration relate to the amount of material collected and the degree to which the material represents the entire lesion. Areas of necrosis and scarring are common in cancers, and if the needle happens to land in these regions, the collected material may fail to capture sufficient tumor cells. This can be reduced by including an on-site cytopathologist to review the specimens as they are collected. It is important to first inform patients of the possibility of the aspiration failing to identify the tumor cells in a lesion, so they are prepared for the possible need to obtain additional tissue if the result is negative for cancer.

Incisional biopsies refer to the process of obtaining a sample of cells or tissue from a suspicious lesion for examination. The advantages of incisional biopsy are that they are less invasive and preferred when removal of the entire intact lesion is not necessary to help determine if the lesion is benign or malignant. This can be done by a scalpel (during a small surgery), a biopsy forceps (during a colonoscopy or a diagnostic laparoscopy), punch biopsy (such as done for skin lesions), and fine needle aspiration (core biopsy of thyroid nodules). This information could be critical because some tumors are treated with chemotherapy and radiation before the definitive surgery. The disadvantages are that it can be invasive and has potential for disruption and spreading of a contained tumor. Typically, incisional biopsies are done for tumors in which disruption does not affect recurrence, and the incisional biopsy site can be later excised at the time of the definitive procedure.

An excisional biopsy refers to the removal of the entire suspicious lesion, often including an additional surgical margin of uninvolved tissue around the lesion. This can be done as a surgical procedure (such as a lymph node dissection) or during the initial diagnostic exam (such as a polypectomy during a colonoscopy). The disadvantages include the invasiveness of the procedure (which is typically considered a minor procedure). The advantages include the definitive diagnosis and the avoidance of additional procedures leading up to the definitive surgery.

A sentinel lymph node biopsy is a particular type of excisional biopsy, which refers to the injection of a marker material (blue dye or radioactive material) near the tumor to identify the first node in the drainage system. By doing this, the nodal status of the tumor can be ascertained by excising a single node instead of completing a total excision of all of the regional lymph nodes. This reduces the morbidity associated with compromise of the lymphatic system (such as lymphedema after axillary lymph node dissection).

Several of the nuances of biopsy procedures are listed in Table 22-1.

CANCER STAGE CLASSIFICATION SYSTEM

The stage classification system refers to the formal categorization of the extent of tumor progression. For tumor types other than those derived from blood cells (leukemia, lymphoma, etc.), the stage classification system is broken down into T, N, and M to represent tumor, nodal, and metastases. The criteria for each TNM designation (0 to 4) are defined differently for each cancer type, and a staging manual should be consulted for specific cancers. Of note, the terminology “X” for a staging variable (such as T1NXM0) was originally designed to indicate that the variable was unable to be evaluated; however, for most tumor types, this should be avoided and the status be based on the best information available.

The “T” staging variable relates to the extent the original tumor has progressed in the organ in which it started. The T parameter typically is broken down into subcategories (0 to 4) based on such characteristics as the following:

- Size (maximum diameter)
- Depth of penetration into organ or tissue or origin (melanoma, colon cancer, etc.)
- Invasion into neighboring tissues or organs
- Location within the organ of origin (i.e., lung cancers close to the trachea are T3, but those involving the trachea are T4)

The “N” staging parameter involves the extent of nodal spread and is typically separated in subcategories (0 to 3) based on:

- The number of lymph nodes involved with cancer
- The location of the lymph nodes that are involved with cancer

The “M” staging parameter relates to presence (M1) or absence (M0) of systemic metastases (occurring via the blood stream) to other parts of the body. Under some circumstances, lymph node metastases that are outside of the expected drainage of the original tumor are considered as M1.

The varying combinations of TNM parameters are then clustered into stage classifications ranging from I to IV based on prognosis for each tumor type. This is determined by the American Joint Committee on Cancer (AJCC) and published as the AJCC staging manual. As a result, the stage classification offers very important prognostic information, with the best prognosis occurring with stage I and the worst prognosis with stage IV. It is critical to recognize that prognosis varies widely.
for each tumor type (e.g., stage IV thyroid cancer is commonly curable, whereas stage III pancreatic cancer is rarely curable), so it is imperative to consult the survival data for each specific tumor type. It is also very important to emphasize that these are survival estimates and that more accurate predictions can be made by taking into consideration overall health, tumor profiling, and response to treatment. There are additional annotations used in the staging terminology to indicate more information about the timing of the staging evaluation and the patient’s history such as pretreatment with chemotherapy or radiation. These annotations are listed in Table 22-2 and may be used in combination (ypT1N1M0).

The stage determination is also very important to determine the treatment plan. Research and clinical trials have provided evidence for cancer treatment and have organized their results by stage so that clinicians could apply the study findings to individuals who are most similar to the patients in the study. As a result, clinical resources have put together “stage-specific” treatment recommendations.

**Clinical Resources for Staging and Treatment Recommendations**

AJCC: American Joint Committee on Cancer  http://www.cancerstaging.org
American Cancer Society  http://www.cancer.org
American Society of Clinical Oncology  http://www.cancer.net
CancerCare  http://www.cancer.org
National Cancer Institute  http://www.cancer.gov

**CANCER STAGING EVALUATION**

The clinical staging evaluation is used to determine the TNM status for the patient based on the physical exam, imaging interpretation, and biopsy results. It is important to realize that staging studies have varying degrees of believability based on the tumor type, other staging information, and the quality of the study. For example, a positron emission tomography (PET) scan that is performed to look for metastases in a patient with a very early appearing primary lung cancer is more likely to give a false-positive result (meaning it considers something to be a metastasis that is really benign) than a truly positive result and therefore should not be done. On the other hand, microscopic spread to lymph nodes may be too subtle to be detected by imaging studies, and if a patient is felt to be at high risk for lymph node spread, a biopsy may be required.
regardless of a negative imaging study. These examples are meant to illustrate the complexities of the staging strategy. It is not a “one size fits all” evaluation for each tumor type. Knowing when to “believe” an imaging result is a critical part of the art of oncology. Therefore, the staging strategy is best formulated in consult with a multidisciplinary tumor board.

A tumor board is an expert team of physicians generally consisting of medical oncologists, radiation oncologists, radiologists, pathologists, surgeons, and other specialists with expertise in the anatomic region from which the cancer arises. The panel discusses cases, best practices, and clinical pathways and comes to a consensus to seek treatment recommendations that provides optimal care for the patient.

The PCC is often very involved in the initial evaluation and fielding of the many questions that arise as a patient is navigating through the staging process. For that reason, each of the imaging modalities are described as follows.

**CT Scan**

CT scanning has become a mainstay of cancer imaging for most regions of the body. The CT scan not only offers information to support a cancer diagnosis (such as lesion density and morphology) but also the image quality is of sufficient resolution to allow serial studies to detect growth. Because the volume is a function of the radius, an increase in the diameter by 25% represents a doubling of the volume of the lesion. Most cancers double on the order of every 50 to 200 days. CT also offers important information regarding the size of a lesion, the relationship of the lesion to neighboring structures such as blood vessels or other organs, and regional lymph node status (with lymph nodes greater than 1 cm on their shortest axis being suspicious) and is used to survey common sites of metastatic disease such as liver, lungs, and brain (therefore providing TNM staging information). CT scanning is vulnerable to false positives, such as cysts in the liver, benign adenomas in the adrenal glands, and reactive lymph nodes, all of which could easily be mistaken for metastases. Abnormalities in these areas may require further imaging to clarify these processes.

**Strengths:**
- Detail about TNM staging categories
- Detail of surrounding anatomy that could impact the surgical operation (such as proximity to major blood vessels)

**Limitations:**
- Resolution—does not detect subtle changes in lymph nodes and organs prone for metastases
- Specificity—several benign lesions detected and cannot be distinguished from malignant
- Radiation exposure
- Intravenous contrast—if patient has allergy to the contrast material or renal impairment issues

**PET Scan**

PET scanning is a form of imaging that capitalizes on the tumor’s propensity to metabolize sugar. A radiolabeled glucose molecule (known as FDG or 2-deoxy-2-[18F]fluoro-D-glucose) is administered intravenously. Once the radioactive FDG enters the cell, the FDG molecule is chemically altered and becomes trapped within the cell. The more active a cell is, the more radioactive molecules accumulate, and, therefore, more radiation is emitted from that area of the body. Certain tissues have a high baseline glucose need (brain, heart, liver, etc.) and will emit a signal in the absence of tumor. The PET scan takes the background of these areas into consideration when calculating uptake, and the output is converted into a standardized uptake value (SUV). The value that is the most clinically discussed is the maximum SUV, or max SUV, which represents the maximum uptake averaged over an area of interest. Typically, a max of SUV greater than 2.5 has been considered worrisome for malignancy; however, this is a gross oversimplification. The max SUV can be influenced by the size of the lesion, and very small lesions that are quite active may not emit sufficient signal to be registered. Most would consider the test inadequate for lesions less than 1 cm. Many PET radiologists prefer to communicate in terms of low, intermediate, and high FDG uptake or avidity and should note the likelihood of malignancy in the impression portion of the imaging report. The PET scan can also be falsely positive because of infection or inflammation. For example, lymph nodes that drain a tumor may become inflamed or “reactive” and light up on PET scan despite being free of cancer. More recently, PET scans have been combined with a CT scan to offer more precise localization of the abnormal uptake.

**Strengths:**
- Staging information for N and M variables (not as much with the T parameter). Emerging evidence indicates that the “hotter” or higher the SUV on PET scan, the more aggressive it is.

**Limitations:**
- Resolution—Most lesions need to be at least 1 cm to be detected.
- Subject to false positives from infection and inflammation
- Radiation exposure

**MRI**

MRI is a modality that uses magnetic fields to create images of the body. An intravenous infusion of gadolinium enhances the ability to distinguish various tissue types.

**Strengths:**
- Particularly good at distinguishing borders between the tumor and surrounding structures
- Many lesions have distinct features by MRI that are sufficiently compelling to declare them malignant or benign (i.e., adrenal adenoma vs. an adrenal metastases).
- Gadolinium is an alternative intravenous contrast to iodinated CT scan contrast with less renal interaction.

**Limitations:**
- Patients with metallic fragments or metal devices in their bodies often are excluded from use because the magnets may interact with ferrous metal.
- The closed space, noise, and time to acquire images may be difficult for some patients to tolerate (although “open” MRI machines have improved this for many patients).

**Ultrasound**

Ultrasound is an imaging modality based on the pattern reflection of sound waves to distinguish tissues of varying densities. Ultrasound may be used to distinguish suspicious lesions from certain benign conditions such as hemangiomas or cysts. The ultrasound may also be used to guide needle aspirations.

**Strengths:**
- Absence of radiation
- Useful to localize lesions for biopsy
Special Considerations

Each of the imaging modalities requires some degree of preparation to optimize study quality and safety, which are summarized in Table 22-3. Any study that requires radiation to a pregnant patient poses risk to the fetus. Strategies to minimize risk are available and should be discussed with an obstetrician.

### TABLE 22-3 Clinical Staging Studies

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Role in Cancer Evaluation</th>
<th>Preparation</th>
<th>Special Considerations</th>
</tr>
</thead>
</table>
| CT scan          | Diagnosis: tumors originating in brain, chest, abdomen, or extremities  
                  Staging: to detect metastastic spread to brain, lungs, liver, or lymph nodes | Nothing by mouth 4 h before the exam | - Patients with known or suspected allergies to iodinated contrast who require IV contrast should be premedicated with steroids and antihistamines.  
- Use of IV contrast with serum creatinine $>1.5 \text{mg/dL}$ poses risk for contrast nephrotoxicity (unless on hemodialysis).  
- Metformin may need to be held in certain patients to prevent renal complications (lactic acidosis).  
- Test time: if oral contrast, 90 min, otherwise 30–45 min |
| PET scan         | Diagnosis: may elevate suspicion of cancer in lesion detected by CT scan (occasionally used for lung nodules)  
                  Staging: to detect metastastic spread to most organs and tissues of the body (lungs, liver, lymph nodes, bones, skin) but not brain | Only water and medications are allowable by mouth within 6 h prior to test. | - Patients with diabetes are to have regimen titrated to maintain blood sugar $<200 \text{mg/dL}$ at time of injection.  
- No insulin for 6 h prior to exam.  
- Test time: 2–2.5 h |
| Ultrasound       | Diagnosis: may identify lesions in liver, extremities, or thyroid  
                  Staging: to detect metastastic spread to liver or lymph nodes | For abdomen, water only by mouth 4 h before the exam | — |
| MRI              | Diagnosis: tumors originating in brain, chest, abdomen, or extremities  
                  Staging: to detect metastastic spread to brain, lungs, liver, or lymph nodes and to characterize invasion into surrounding structures | Nothing by mouth 4 h before the exam | - No ferrous metals (iron containing) because of magnet in MRI. History of working with metal (welder) or trauma with metal object (gunshot wound) should be followed up with X-rays to exclude metal fragments. Many joint replacements, heart valves, and aneurysm clips are okay, but some are not; therefore, they should be noted and specific make and model be confirmed with scanning facility.  
- No pacemakers because of MRI interference with pacemaker.  
- Test time: 45–120 min |
| Bone scan        | Diagnosis: rarely may identify tumors originating in bones  
                  Staging: to detect metastases to bones | | - Avoid scheduling within 4 d of barium study or taking bismuth (Pepto-Bismol) because barium and bismuth may interfere with results.  
- Relative contraindication in pregnancy because of radiation.  
- Test time: 3–6 h |
| Mammogram        | Diagnosis: breast cancers or precancerous lesions  
                  Staging: N/A | - Schedule 1 wk after completing menstrual period (less discomfort).  
- Do not wear powder or antiperspirant because metallic particles may cause artifacts. | - Possible restrictions or limitations with breast implants but must be confirmed with imaging center.  
- Relative contraindication in pregnancy because of radiation and density of breast tissue |
| Lymphangiogram   | Diagnosis: N/A  
                  Staging: to identify lymph nodes drainage patterns | None | — |

*Premedication strategy: prednisone $50 \text{mg}$ by mouth $13 \text{h}$, then $7 \text{h}$, and then $1 \text{h}$ prior to exam. Plus diphenhydramine $50 \text{mg}$ (IV, IM, or PO) $1 \text{h}$ prior to exam. Other strategies are listed at [http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual/FullManual.aspx](http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual/FullManual.aspx)

CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; N/A, not applicable.
and oncology team. Patients who are morbidly obese may also pose a challenge because many tables for imaging (CT, PET, MRI, or for fluoroscopy) have maximum weight tolerances between 350 and 450 lb. For any patient that is more than 300 lb, the PCC should ensure that the imaging facility is able to accommodate the patient.

THE PRIMARY CARE CLINICIAN—MULTIDISCIPLINARY COLLABORATION

More and more patients with cancer are surviving their disease in part because of the better and earlier diagnosis and treatment advances. Surveillance in the first years of therapy is critical because the risk of disease recurrence is highest. Regular history and physicals are very important in detecting early signs of recurrence for the years that follow an initial cancer diagnosis and course of treatment.

The patient with cancer is faced with a wide array of medical, personal, and social issues that are optimally managed by a multidisciplinary team. Although the urgency of the cancer workup and treatment tends to take precedence over other aspects of the patient’s life, the optimal diagnostic, staging, and treatment plan involve a close collaboration with the clinician who knows the patient best and is most familiar with their malignancy. In this way, all cancer-related decisions take in consideration the patient’s personal and medical status, whereas the oncologic evaluation is streamlined by a team of cancer experts.

References

Management and Treatment of the Patient with Cancer
With the transition of cancer care to the outpatient setting and improved survival of patients with cancer, primary care clinicians are increasingly confronted with patients experiencing complications of their underlying tumor or its treatment. The diverse complications of cancer encompass virtually every organ system and often require urgent or emergent management (Table 23-1). Patients may present to their primary care clinician with acute cancer-related complications as the first manifestation of their disease, in the setting of a delayed recurrence of cancer, or for urgent care while undergoing active oncologic treatment. Thus, the prompt diagnosis of a cancer-related complication by primary care clinician, with appropriate initial management and referral to specialists or an acute care facility, is essential in preventing morbidity and mortality from undiagnosed or untreated complications of cancer. Even in the setting of terminal disease, appropriate management of emergent complications of cancer can significantly improve quality of life.

The emergent and urgent complications of cancer are categorized as structural, paraneoplastic (hematologic or metabolic), and chemotherapy related (see Table 23-1). An oncologic emergency is defined as an acute complication of cancer or its treatment that requires immediate intervention to prevent irreversible morbidity or mortality. The “classic oncologic emergencies” include spinal cord compression, neutropenic fever, superior vena cava (SVC) syndrome, hypercalcemia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and tumor lysis syndrome. However, it is important to recognize that virtually any complication of malignancy can present as a true emergency (see Table 23-1), whereas the classic oncologic emergencies of SVC syndrome or hypercalcemia often do not mandate urgent intervention.

In this chapter, we focus on common oncologic emergencies that are likely to be encountered by the primary care clinician, including epidural spinal cord compression, neutropenic fever, and hypercalcemia as well as the classic oncologic emergency, SVC syndrome. Tumor lysis syndrome, although a true oncologic emergency, is chemotherapy induced and generally managed by oncologists, and thus it is not included in this chapter. Venous thromboembolic disease is perhaps the most important cancer-related complication in terms of incidence, morbidity, and mortality and is discussed separately in Chapter 32. Although a comprehensive review of the diverse array of cancer-related complications is beyond the scope of this chapter, we have provided references for each complication listed in Table 23-1 for further reading.

**EPIDURAL SPINAL CORD COMPRESSION**

**KEY POINTS**

- Epidural spinal cord compression (ESCC) is an oncologic emergency that requires immediate evaluation and treatment to preserve neurologic function.
- Delay in diagnosis and treatment of ESCC can lead to irreversible neurologic deficits and negatively impact quality of life and survival.
- Back pain is usually the earliest symptom of ESCC and should be urgently evaluated in patients with cancer.
- Initial evaluation of patients suspected of ESCC requires an MRI of the total spine.
- Initial treatment in most patients is dexamethasone and urgent radiation therapy.
- Surgical intervention is the initial intervention in specific circumstances.

**Introduction**

Epidural spinal cord compression (ESCC) is an important complication of malignancy that can lead to irreversible paralysis and loss of bowel and bladder function. Early recognition and treatment are essential in preventing or mitigating the devastating impact of this event on quality of life and survival.

**Definition**

ESCC occurs when a malignant lesion in the epidural (extradural) space compresses and damages the spinal cord (or cauda equina). One commonly accepted definition of ESCC is as follows: “Compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumor mass. The minimum radiologic evidence for cord compression is indentation of the theca at the level of clinical features.
Clinical features include any or all of the following: pain (local or radicular), weakness, sensory disturbance, and/or evidence of sphincter dysfunction.

**Pathophysiology**

Approximately 90% of cases of ESCC are caused by the direct extension of tumor into the epidural space from a metastatic bony lesion in an adjacent vertebra (Fig. 23-1). In 10% of cases, paravertebral tumor enters the epidural space through the intervertebral foramen in the absence of bony metastases (e.g., lymphomas, germ cell tumors) (see Fig. 23-1). As the mass grows in the epidural space, it exerts pressure on the thecal sac and the epidural venous structures and mechanically compresses the cord. This results in edema of the cord with compromise of spinal cord blood flow and, ultimately, spinal cord infarction and permanent neurologic deficits.

Metastases directly to spinal cord parenchyma (intramedullary metastases) are rare. Progressive intramedullary metastases cause a neurologic syndrome identical to ESCC (see Fig. 23-1). The notable difference in presentation of intramedullary metastases from classic ESCC is absence of back pain.

The site of ESCC reflects the characteristic distribution of metastatic disease throughout the vertebral column. The thoracic spine accounts for 60% to 80% of vertebral metastases, whereas the lumbosacral and cervical spine account for 15% to 30% and <10%, respectively. Moreover, thoracic lesions are more likely to cause symptomatic ESCC because of the comparatively small diameter of the thoracic spinal canal. Of particular importance in the initial evaluation of ESCC is that as many as 50% of patients have disease at multiple sites throughout the spine at the time of initial presentation. This highlights the importance of a total spine magnetic resonance imaging (MRI) in the initial evaluation, as detailed later in this chapter.

**TABLE 23-1** Oncologic Emergencies and Urgencies

<table>
<thead>
<tr>
<th>Structural</th>
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</thead>
<tbody>
<tr>
<td>Central nervous system:</td>
</tr>
<tr>
<td>Spinal cord compression&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain metastases: intracranial pressure&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain metastases: seizures&lt;sup&gt;3,4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiotoracic:</td>
</tr>
<tr>
<td>Superior vena cava syndrome&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pericardial effusion and tamponade&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Airway obstruction&lt;sup&gt;6-7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Massive hemoptysis&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Malignant pleural effusion&lt;sup&gt;10,11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gastrointestinal and urologic:</td>
</tr>
<tr>
<td>Bowel obstruction&lt;sup&gt;12-14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Biliary obstruction and cholangitis&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>Malignant ascites&lt;sup&gt;16,17&lt;/sup&gt;</td>
</tr>
<tr>
<td>Urinary obstruction&lt;sup&gt;18,19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paraneoplastic metabolic</td>
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<tr>
<td>Hypercalcemia&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<td>SIADH&lt;sup&gt;20-22&lt;/sup&gt;</td>
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<td>Hypoglycemia&lt;sup&gt;23,24&lt;/sup&gt;</td>
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<tr>
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<tr>
<td>Paraneoplastic hematologic</td>
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<td>VTE and PE&lt;sup&gt;27-32&lt;/sup&gt;</td>
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<td>DIC&lt;sup&gt;33-35&lt;/sup&gt;</td>
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<tr>
<td>Hyperviscosity syndrome&lt;sup&gt;39&lt;/sup&gt;</td>
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<tr>
<td>Microangiopathic hemolytic anemia&lt;sup&gt;40-42&lt;/sup&gt;</td>
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<tr>
<td>Chemotherapy induced</td>
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<tr>
<td>Neutropenic fever&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thrombocytopenic hemorrhage&lt;sup&gt;43-45&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tumor lysis syndrome&lt;sup&gt;46,47&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diarrhea&lt;sup&gt;48,49&lt;/sup&gt;</td>
</tr>
<tr>
<td>Neutropenic enterocolitis&lt;sup&gt;50,51&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cytokine release syndrome&lt;sup&gt;52,53&lt;/sup&gt;</td>
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<tr>
<td>Anaphylactic hypersensitivity reactions&lt;sup&gt;54,55&lt;/sup&gt;</td>
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</table>

<sup>a</sup>Reviewed in this chapter.

SIADH, syndrome of inappropriate secretion of antidiuretic hormone; VTE, venous thromboembolism; PE, pulmonary embolism; DIC, disseminated intravascular coagulation.

FIGURE 23-1. Anatomy of spinal cord lesions. This figure illustrates the common mechanisms of epidural spinal cord compression (ESCC). In most cases, ESCC occurs because of the direct extension of a metastatic bony lesion into the epidural space (C, E). Less commonly, paravertebral tumors enter the epidural space through the intervertebral foramen (D). Rarely, intramedullary metastases (A) can mimic ESCC. (Reproduced from Byrne TN. Spinal cord compression from epidural metastases. *N Engl J Med*. 1992;327[9]:614-619, with permission.)
Incidence
ESCC is common and occurs in various malignancies at varying frequency. Overall, in the last 2 years of life, ESCC affects 2.5% to 5.0% of patients with cancer.60,65,66

Although ESCC can occur in any patient with bony metastases or a paraspinal mass, the incidence is greatest in lung cancer, prostate cancer, breast cancer, multiple myeloma, renal cell cancer, and non-Hodgkin lymphoma.65,66 Together, lung, breast, and prostate cancer account for around 60% of cases.63,65,67 This is because of the increased incidence of bony metastasis in these diseases, which increases the likelihood of vertebral involvement. In fact, lung, prostate, and breast cancer each accounts for about 15% to 20% of ESCC events.60,61 Additionally, 20% of cases of ESCC occur as the first symptom of malignancy.67 Thus, careful attention should be paid to new or changing back pain or any new neurologic complaints among these patients. However, keep in mind that lymphoma may present without pain because of the extension through neural foramen from a paravertebral mass rather than bony metastasis.

Of note, when evaluating a patient with cancer with new back pain or neurologic symptoms, the absence of known bone metastases does not preclude a diagnosis of ESCC because it may be the presenting manifestation of bony metastases. Therefore, although the diagnosis is often considered in patients with known metastatic disease, it should also be included on the differential diagnosis of patients with known malignancy and the appropriate symptoms.

Clinical Presentation
The signs and symptoms of ESCC can vary depending on the severity and anatomic location(s) of compression. Delay in treatment has a significant impact on outcomes. One study suggests that 30% of patients who presented to a general practitioner remained ambulatory at the time of treatment compared to 68% who presented directly to a regional cancer center.68 This, correlated with delay in treatment, underscores the importance of early recognition of ESCC.

Back Pain
New onset or increasing back pain is the initial symptom of ESCC in most patients, occurring in >90% of patients,56,60,69 and is caused by the bony vertebral metastases and/or spinal nerve root compression. Given the devastating complications of untreated ESCC, any patient with a known cancer history with new or changing back pain, as detailed in the following text, requires a thorough and prompt evaluation to rule out an early ESCC.56,68,69 The location and quality of the back pain (localized, diffuse, radicular) and exacerbating factors are highly variable. Thus, the specific characteristics of the back pain are not useful diagnostically.

Neurologic Symptoms
Usually, a crescendo pain syndrome over weeks precedes the onset of neurologic dysfunction, although rarely, patients present with acute onset of neurologic symptoms. As spinal cord injury progresses, the “classic” ESCC symptoms of weakness, sensory symptoms, and autonomic dysfunction appear. Weakness usually affects the lower extremities because of the preponderance of thoracic ESCC, and is often described by patients as “heaviness” or difficulty climbing stairs. Weakness usually precedes sensory disturbances of diminished sensation or paresthesias. Loss of autonomic function, that is, incontinence or urinary retention, is a late manifestation of ESCC. Full-blown ESCC is characterized by paraplegia (or quadriplegia for high cervical ESCC), loss of sensation below the affected sensory level, and loss of bowel and bladder autonomic function.

Physical Examination
Although physical examination may be helpful if classic findings are present, it cannot rule out the presence of cord compression and should not delay urgent imaging for diagnosis. The most important part of the examination in suspected ESCC is the neurologic examination. Weakness, hyperreflexia, a sensory level (i.e., decreased sensation below a dermatome/spinal level), and diminished anal sphincter tone are classic signs of ESCC. If the thecal sac is compressed below the level of the conus medullaris, patients may present with a cauda equina syndrome—painful lumbosacral radiculopathy with patchy sensory deficits, variable leg weakness, and hyperreflexia. Compression at the conus medullaris (S5) is associated with “saddle” anesthesia or the perineum and impaired anal sphincter tone with intact lower extremity strength and sensation.

Diagnosis
A patient with a known oncologic history who presents with any symptoms of ESCC should be evaluated rapidly with the goal of early diagnosis and intervention. Diagnosis of ESCC requires imaging of the epidural space with an MRI of the total spine. Bone scans or plain films should not be used in the workup of suspected ESCC because they do not allow visualization of the epidural space.

Widespread access to MRI has greatly simplified the diagnosis of ESCC and facilitated early diagnosis prior to the onset of neurologic symptoms or signs. MRI should be performed emergently if patients have any neurologic symptoms or signs. In patients with new onset or changing back pain in the absence of any neurologic symptoms or signs, elective imaging should be obtained expeditiously. Given the high incidence of involvement of multiple areas of the spine, MRI of the total spine is always indicated in evaluating possible ESCC.60,64,71 In patients with a contraindication to MRI, computed tomography (CT) scan of the total spine is an acceptable substitute.

Treatment
Most patients with ESCC can be treated nonsurgically with corticosteroids and radiotherapy.56,57,60,72–74 Surgical decompression or a spinal stabilization procedure may be indicated in specific circumstances. Rarely, chemotherapy for exquisitely chemosensitive tumors is an effective primary therapy (Fig. 23-2).

Corticosteroids
If there is suspicion of ESCC, corticosteroids should be initiated immediately.56,57,60 Corticosteroids are highly effective in ameliorating pain. In addition, corticosteroids reduce vasogenic edema of the cord and may transiently delay progressive spinal cord injury and improve neurologic symptoms. Dexamethasone is preferred because of its relative lack of mineralocorticoid effects, long half-life, and excellent oral bioavailability. “Low-dose” dexamethasone (10 to 20 mg)
# NEUTROPENIC FEVER

## KEY POINTS

- Fever in a patient with neutropenia is a true oncologic emergency requiring urgent and empiric administration of intravenous antibiotics.
- Neutropenic fever (NF) is defined as a single temperature >101°F or sustained temperature >100.4°F for >1 hour in a patient with an absolute neutrophil count (ANC) <500 cells per microliter.
- Any patient undergoing myelosuppressive chemotherapy is at risk for NF and, if febrile, should be urgently evaluated for neutropenia and need for empiric antibiotics.
- A broad-spectrum antipseudomonal β-lactam agent should be administered as soon as possible after a patient with NF has been pancultured and expeditiously evaluated. Other antibiotics may be added in specific situations as clinically indicated.
- The broad-spectrum antipseudomonal β-lactam agent should be continued until the patient is no longer neutropenic. Thereafter, antibiotics can be discontinued or narrowed to cover specific isolates.

## Introduction

Neutropenic fever (NF) is a frequent and known complication of chemotherapy. In the absence of rapid initiation of appropriate antibiotics, the patient with neutropenia can rapidly succumb to overwhelming infection and sepsis, especially from gram-negative organisms. Time to initiation of treatment is critical and antibiotics should be started <2 hours from initial fever because the clinical course may progress rapidly. By following an algorithm for empiric antibiotic treatment, NF can be effectively managed with a low incidence of mortality.

## Definition

Neutropenia is defined as an absolute neutrophil count (ANC) <500 or <1,000 cells per microliter, with a predicted nadir of <500 cells per microliter. Severe neutropenia is an ANC <100 cells per microliter. The ANC is calculated by multiplying the total white blood cell count by the percentage...
of bands and neutrophils. A patient with neutropenia is considered febrile when he or she has a single temperature >101°F or sustained temperature >100.4°F for >1 hour. In clinical practice, any patient at risk for neutropenia with a temperature >100.4°F should be brought in to an urgent care setting or hospital for evaluation and determination of neutrophil count.

It is important to recognize that patients with neutropenia with life-threatening infection may not always present with fever, particularly if they are elderly or are receiving corticosteroids or antipyretic agents. Thus, clinical deterioration, including hypothermia, hemodynamic instability, or altered mental status, in a patient with neutropenia is a clear indication to treat with empiric broad-spectrum antibiotics (see the following text) even in the absence of fever.

**Risk Factors for Neutropenia and Neutropenic Fever**

Neutropenia is a common complication of myelosuppressive chemotherapy occurring in 10% to 50% of patients with solid tumors and >80% of patients with hematologic malignancies. In general, neutropenia occurs 7 to 14 days after chemotherapy. Certain chemotherapy regimens, such as those used for early-stage breast cancer, stem cell transplantation, acute leukemia, or non-Hodgkin lymphoma carry a particularly high risk of neutropenia.

When assessing a patient who is undergoing myelosuppressive chemotherapy, there are several factors that increase the risk of NF. These risk factors include the following: age older than 65 years, rapid decline in ANC, severe neutropenia (<100 cells per microliter) or prolonged neutropenia (>7 days), bone marrow involvement by tumor, poor performance status, impaired skin or gastrointestinal (GI) barrier (recent surgery, skin breakdown, mucous membrane compromise such as mucositis, colitis), uncontrolled or refractory malignancy, hypogammaglobulinemia, compromised immune system from disease (i.e., cancer, HIV infection), or immunosuppressive medications (steroids, certain chemotherapeutics including fludarabine and high-dose alkylating agents). The presence of any of these risk factors should not delay urgent evaluation of a febrile patient who has recently been treated with myelosuppressive chemotherapy.

**Pathophysiology of Neutropenic Fever**

NF is usually caused by bacterial infection caused by translocation of the patient’s endogenous bacterial flora into the bloodstream. With the onset of chemotherapy-induced neutropenia, the body’s innate defenses against the normal bacterial flora of the gut and skin are compromised, leading to seeding of the bloodstream. Although cultures are positive in only 30% of patients with NF, the presumed origin of fever is transient bacteremia. Importantly, a history of an infectious exposure is rarely elicited in patients with NF.

**Bacterial Pathogens**

The predominant organisms responsible for NF are aerobic gram-negative bacilli and gram-positive cocci. Gram-negative bacilli are the most dangerous pathogens because of their association with sepsis. It is the risk of gram-negative sepsis in patients with neutropenia that underscores both the emergent nature of NF and the need for empiric broad-spectrum gram-negative coverage. Fourteen percent to twenty-two percent of bloodstream isolates in patients with cancer are gram-negative bacilli, including *Pseudomonas, Escherichia coli, Klebsiella, Enterobacter,* and *Serratia.*

Gram-negative bacteria are especially associated with severe syndromes such as sepsis, necrotizing pneumonia, and necrotizing enterocolitis (typhilitis).

**Gram-positive cocci** including *Staphylococcus aureus, Staphylococcus epidermidis,* and *streptococci are now the most common isolates in NF.* Gram-positive organisms are identified in 60% to 70% of culture-positive infections. The rising incidence of gram-positive infections is attributed to the widespread use of indwelling catheters as well as prophylactic fluoroquinolones that are active against gram-negative bacilli. The gram-positive organisms are not as virulent as their gram-negative counterparts and usually do not cause sepsis. However, viridans streptococcal infection in patients with neutropenia may be associated with a toxic shock-like syndrome or adult respiratory distress syndrome (ARDS); risk factors for this syndrome include severe neutropenia or mucositis and antimicrobial prophylaxis with fluoroquinolone or trimethoprim-sulfamethoxazole.

Anaerobic organisms are isolated much less commonly and do not typically cause sepsis. Thus, empiric anaerobic coverage is unnecessary unless the patient has a clinical syndrome associated with anaerobic infection (see the following text).

**Nonbacterial Pathogens.** Fungal and viral pathogens are uncommon unless neutropenia persists for >7 days or the patient is profoundly immunosuppressed (e.g., bone marrow transplant or allograft recipients). Thus, empiric coverage of nonbacterial pathogens is generally not indicated at initial presentation of NF. However, in the appropriate clinical setting, such as thrush, esophagitis, or apparent herpes simplex or varicella-zoster infection, antifungal or antiviral therapy should be considered.

**Evaluation and Management**

When a patient at risk for neutropenia presents or calls with a documented temperature >100.4°F, he or she should urgently be entered into the treatment algorithm for NF (Fig. 23-3). Patients with suspected NF should be evaluated as soon as possible in an emergency or urgent care setting or admitted directly to a medical floor. The initial evaluation and workup, as described in the steps that follow, should be immediate upon presentation and should not delay the initiation of empiric antibiotics.

**Step 1. Rapid evaluation:** Check vital signs, take a “targeted” history, and quickly examine the patient. A detailed history and thorough examination can be completed after initiation of antibiotics (see Step 3 in the following text). If there are signs of hemodynamic instability, a sepsis protocol should be started immediately.

Key aspects of the initial history and physical exam (H&P) should include antibiotic allergies, concurrent medications that may impact on antibiotic choice (e.g., fluoroquinolones), recent infections, assessment of indwelling catheter for infection, and signs of anaerobic infection as detailed in the following text.

**Obtain an immediate (stat) complete blood count** to determine whether the patient is neutropenic as well as full metabolic profile including liver function tests and urine.
The empiric use of vancomycin in the nonpenicillin allergic patient has not been shown to confer clinical benefit.\textsuperscript{77,80,85} Thus, the empiric use of vancomycin should be restricted to the following indications: (1) methicillin-resistant \textit{Staphylococcus aureus} (MRSA) colonization, (2) prophylaxis with ciprofloxacin, (3) erythema or tenderness at a catheter site, (4) substantial chemotherapy-induced mucosal damage, and (5) risk for overwhelming sepsis with viridans strep (ciprofloxacin prophylaxis plus H\textsubscript{2} blockers, severe mucositis).\textsuperscript{77,80}

Specific anaerobic coverage is generally not necessary except in situations where the risk of anaerobic infection is high.\textsuperscript{80} This include diagnoses of necrotizing mucositis, sinusitis, typhlitis, perirectal abscess or cellulitis, intra-abdominal/pelvic infection/abscess, or anaerobic bacteremia.

\textbf{Step 3. Comprehensive evaluation:} Once empiric antibiotics have been initiated, a detailed history and thorough physical examination should be performed. \textit{Important aspects of the history} include the timing and type of chemotherapy (risk of mucositis, duration of neutropenia, immunosuppressive effects), concurrent medications that may alter endogenous flora (fluoroquinolones) or are immunosuppressive (steroids, immunosuppressants), analysis with culture. \textit{At least two sets of blood cultures should be drawn.} In patients with an indwelling central venous catheter, a set of blood cultures should be drawn from each port or lumen in addition to a peripheral site. In patients without an indwelling catheter, a set should be obtained from at least two separate venipuncture sites. Additionally, any areas of suspected infection discovered by history or physical examination should be cultured.

\textbf{Step 2. Start empiric antibiotics:} Given the risk of gram-negative sepsis, antibiotics should be started immediately after cultures are drawn. The antibiotic regimen must provide broad gram-negative coverage, including antipseudomonal coverage.\textsuperscript{77,80} Based on the Infectious Diseases Society of America (IDSA) guidelines, \textit{initial therapy must include one of the following antipseudomonal \textbf{\beta}-lactam antibiotics:} cefazidine, cefepime, imipenem, meropenem, piperacillin/tazobactam.\textsuperscript{77}

Combination therapy for dual gram-negative coverage has not been shown to improve clinical efficacy or mortality and thus is not recommended unless there is suspicion of antimicrobial resistance. In the case of a \textit{penicillin allergy}, the initial choice is aztreonam with vancomycin or ciprofloxacin with clindamycin.\textsuperscript{77}
and any localizing or chemotoxicity symptoms (mouth sores, odynophagia, diarrhea, abdominal pain, respiratory symptoms). Such findings may necessitate additional empiric coverage if there is concern of viral or anaerobic infection. However, most patients with NF will not have localizing symptoms.

On examination, careful attention to the oropharynx for mucositis, abdomen for tenderness, and skin for infectious lesions (rash, cellulitis, ulcers, furuncles, herpetic eruptions) is important. Although examination of the perineum with perianal palpation is essential to evaluate for perirectal abscess, a rectal examination should not be performed on a patient with neutropenia.

Any indwelling lines or catheters should be carefully inspected for erythema and palpated for any tenderness. Remember, the absence of the classical signs of infection does not necessarily correlate with absence of infection because the inflammatory response is blunted in patients with neutropenia.

Any sites that are of concern for infection (e.g., vesicular lesions, mucosal ulcers, pustules, catheter exit-site drainage) should be cultured. Vancomycin, anaerobic coverage, or antiviral agents can be added to the initial empiric antibiotic if indicated based on new findings (see indications for vancomycin or anaerobic coverage in the previous text).

Step 4. Imaging: All patients should have a chest radiograph. Additional imaging should be tailored to the clinical picture. For example, a patient with severe diarrhea and abdominal pain should undergo computerized axial tomography (CAT) scan of the abdomen and pelvis to rule out enterocolitis (typhlitis).

Step 5. Risk stratification: At the time of diagnosis, patients with NF can be stratified into high- and low-risk groups.79,80,86 High-risk patients are those with severe neutropenia (ANC <100 cells per microliter), neutropenia expected to last >7 days, or medical comorbidities (e.g., hemodynamic instability, pneumonia or hypoxemia, GI or neurologic symptoms, hepatic dysfunction). Risk stratification is helpful in predicting the risk of documented infection as well as severity of infection.

In selected low-risk patients, outpatient management with oral antibiotics can be considered, but this is not a routine practice.80,86

Step 6. Subsequent care: The initial triage and rapid initiation of antibiotic therapy are the key first steps in the management of NF. Once admitted and stabilized, the patient needs to be closely monitored because the risk of sepsis remains high in the initial period.

The need for subsequent modification of the initial empiric antibiotic regimen will be dictated by the specific clinical scenario, including hemodynamic instability, persistent unexplained fever, and positive blood cultures or identification of a specific infection. However, the initial empiric antibiotic for broad-spectrum gram-negative coverage must not be discontinued until the patient is no longer neutropenic. If drug allergy is suspected while the patient is neutropenic, an alternative antibiotic selected from the approved list (see previous text) should be substituted.

Step 7. Duration of antibiotics: The duration of antibiotic treatment is dictated by the ANC (<500 cells per microliter versus >500 cells per microliter) and by the clinical course (persistent fever, source of infection, hemodynamic instability) as follows77,80:

- ANC >500 cells per microliter: If the cultures are negative and the patient is afebrile and otherwise clinically well, antibiotics may be safely discontinued when the patient is no longer neutropenic.
- If cultures are positive, or a specific infection is identified, and the patient is improving clinically, antibiotic coverage can be narrowed once the ANC is >500 cells per microliter. The patient should then be treated with the appropriate antibiotic for the indicated duration for the specific infection.
- If cultures are negative but the patient remains febrile, other causes of fever should be considered, including drug allergy, viral syndrome, etc. Consider stopping the antibiotics and repeating the cultures in patients who are stable and clinically well.
- ANC <500 cells per microliter: The initial empiric gram-negative antibiotic coverage must be continued until the ANC is >500 cells per microliter. This principle applies even if cultures are negative and the patient defervesce or if a specific infection is identified that could be treated with narrowed coverage.

If cultures are negative and fever persists for ≥3 days, the patient requires thorough reassessment, including repeat cultures, imaging studies for specific symptoms, and additional antibiotics if indicated (e.g., vancomycin or anaerobic coverage). After 4 to 7 days of persistent fever without a clear source, empiric antifungal therapy should be initiated in patients who are expected to have neutropenia for >7 days.77 Caspofungin is a reasonable choice for initial empiric antifungal therapy because of its equivalent efficacy and improved tolerability compared to liposomal amphotericin in patients with persistent NF.77 If these interventions do not lead to response, a drug fever should be considered and a change in antibiotics may be needed, with the caveat that a broad-spectrum antipseudomonal antibiotic from the approved list must be included until neutropenia has resolved.

**HYPERCALCEMIA OF MALIGNANCY**

**KEY POINTS**

- Hypercalcemia of malignancy (HCM) is the most common metabolic complication of cancer.
- The predominant symptoms of HCM are gastrointestinal and neurologic and are related to both the degree of hypercalcemia and rate of rise in the serum calcium level.
- Severe or symptomatic HCM requires urgent treatment with intravenous hydration and bisphosphonates, although active treatment of hypercalcemia in patients with terminal refractory cancer may not be appropriate.

**Introduction**

Hypercalcemia is the most common metabolic derangement associated with malignancy. Patients may be asymptomatic or present emergently with stupor and coma. In some cases,
hypercalcemia may precede the diagnosis of malignancy and represent the initial manifestation of an occult cancer. In the era of bisphosphonates, hypercalcemia of malignancy (HCM) can be effectively treated in most patients, although in patients with terminal cancer, treatment may be futile and inappropriate. The urgency of treatment is dictated by the absolute degree of hypercalcemia, severity of symptoms, and appropriateness of intervention.

**Incidence and Risk Factors**

Hypercalcemia occurs in up to 30% of patients with malignancy. It is the most common cause of hypercalcemia in the hospital setting. The cancers most commonly associated with hypercalcemia are multiple myeloma, epidermoid cancers (squamous cell lung cancer, head and neck cancer, urothelial cancer), breast cancer, renal cancer, and lymphoma. Of note, although prostate cancer frequently involves the bone, it is uncommonly associated with hypercalcemia. HCM may be precipitated by bed rest, initiation of hormonal therapy (“flare phenomenon”), dehydration, thiazide diuretics, lithium, and overzealous ingestion of calcium supplements. Unfortunately, hypercalcemia is often encountered in patients with end-stage cancer, and the short-term (30 days) mortality in hospitalized patients with hypercalcemia is 50%. 

**Pathophysiology**

The major mechanism of HCM is the release of calcium from bone caused by inappropriate bone resorption by cytokine-activated osteoclasts with concomitant suppression of bone formation. Bone resorption in malignancy is driven by three mechanisms: paraneoplastic secretion of parathyroid hormone (PTH)–related protein (PTHrP) (referred to as humoral hypercalcemia of malignancy), local stimulation of osteoclasts by osteolytic bone metastases, and paraneoplastic secretion of 1,25 dihydroxyvitamin D (calcitriol).

PTHRP-mediated humoral hypercalcemia of malignancy (HHM) is the underlying cause of hypercalcemia in up to 80% of patients with HCM. HHM occurs most often in squamous cell, urothelial, and renal cancers and is also seen in breast and ovarian cancer, melanoma, and non-Hodgkin lymphoma. Tumor-associated PTHrP is homologous to endogenous PTH and mediates similar effects via the PTH receptor in bone and kidney tissue, including stimulation of bone resorption, increased calcium reabsorption in the distal tubules, and decreased renal phosphate reabsorption in the proximal tubules. In the setting of HHM, endogenous PTH levels are suppressed and calcitriol levels are normal. Patients with PTHrP-mediated HCM often have advanced disease and a poor prognosis, and HHM is relatively resistant to bisphosphonate therapy.

Osteolytic metastatic disease to the bone is a common mechanism of hypercalcemia, occurring in approximately 20% of patients. It is the predominant mechanism of HCM in multiple myeloma and breast cancer. The incidence may be decreasing because of the widespread use of bisphosphonates and denosumab (the receptor activator of nuclear factor–κB ligand [RANKL] inhibitor) to prevent skeletal-related events in multiple myeloma and some cases of non-Hodgkin lymphoma. Calcitriol causes hypercalcemia by increasing intestinal calcium absorption as well as promoting osteolysis. It can be diagnosed by demonstrating a high calcitriol level with suppressed endogenous PTH levels. Calcitriol-mediated hypercalcemia is responsive to corticosteroids.

Irrespective of the underlying mechanism, hypercalcemia perpetuates a cycle of increasing serum calcium levels. Calcium disrupts antidiuretic hormone (ADH) function in the kidney, causing a diuretic effect. The nephrogenic diabetes insipidus is often associated with symptoms. However, age, renal function, fluid status, and rate of calcium rise all impact on the acuity and severity of symptoms. Decisions regarding treatment, including the need for hospitalization, should be guided by the clinical presentation rather than the absolute serum calcium level.

In patients with HCM, the clinical manifestations are dominated by GI and neurologic symptoms. Anorexia, nausea, vomiting, and constipation or obstipation are common and easily confused with side effects of chemotherapy or narcotics. The neurologic symptoms include fatigue, lethargy, confusion, and, ultimately, stupor and coma. Seizures or focal neurologic signs are rare and should precipitate a search for other diagnoses. Often, a history of polyuria and nocturia can be elicited because of hypercalcemia-induced nephrogenic diabetes insipidus. The symptoms of hypercalcemia invariably lead to decreased oral intake of fluids, thereby exacerbating the volume contraction and further accelerating the inappropriate compensatory renal resorption of calcium.

**Diagnosis**

The diagnosis of hypercalcemia is readily confirmed with serologic testing, including an ionized calcium level or a total serum calcium level corrected for hypoalbuminemia. In most cases of HCM, the diagnosis will be obvious based on a known cancer diagnosis in the setting of hypercalcemia. However, it must be kept in mind that any patient presenting with lethargy or confusion with only mild hypercalcemia should be evaluated for other causes of altered mental status.

In cases where the etiology of hypercalcemia is unclear, for example, no known cancer diagnosis or a cancer that is rarely associated with hypercalcemia, a PTH level will distinguish primary hyperparathyroidism from HCM. Suppression of PTH is consistent with HCM, granulomatous disease, or other causes of hypercalcemia. PTHrP or calcitriol levels will provide further confirmation of the etiology of hypercalcemia, but these tests are rarely necessary for diagnosis and do not affect treatment.

_Tumor-associated 1,25 dihydroxyvitamin D (calcitriol) mediates HCM in Hodgkin lymphoma and some cases of non-Hodgkin lymphoma. Calcitriol causes hypercalcemia by increasing intestinal calcium absorption as well as promoting osteolysis._
TREATMENT

The goals of treatment are to lower the calcium level and alleviate the symptoms and to prevent subsequent episodes. The urgency of treatment should be guided by both the severity of symptoms and the degree of hypercalcemia. In general, any patient with either severe hypercalcemia (Ca > 14 mg per dL) or symptomatic moderate hypercalcemia (Ca 12 to 14 mg per dL) should be treated urgently and preferably on an inpatient basis as outlined in the following text. Importantly, the decision to treat HCM should always be made in the context of the prognosis of the underlying malignancy.97

The **first step** in the treatment of hypercalcemia is to treat the intravascular volume depletion that inevitably accompanies hypercalcemia.87,95,97 Volume repletion with IV saline at an initial rate of 200 to 500 mL per hour will restore renal perfusion, which in turn leads to enhanced renal calcium excretion and a modest decrease in serum calcium.87,95,97 Previously, furosemide was often used in conjunction with “hyperhydration” to force a calciuresis. However, in the era of the highly potent bisphosphonates, this strategy is rarely necessary; and the primary goal of initial aggressive IV hydration is the restoration of euvoolemia.95,97

The **second step** in the treatment of hypercalcemia is pharmacologic inhibition of bone resorption with bisphosphonates and/or calcitonin. In the absence of renal failure, IV bisphosphate, either pamidronate or zoledronic acid, is administered concurrently with hydration.87,90,95,97 Zoledronic acid at a dose of 4 mg is preferred, given its greater efficacy and shorter infusion time (15 minutes vs. >2 hours) compared to pamidronate.99 The serum calcium usually declines by 2 to 4 days and nadirs at 4 to 7 days after bisphosphonate treatment.98 In patients with severe symptomatic hypercalcemia (>14 mg per dL), initial administration of salmon calcitonin at a dose of 4 IU per kg subcutaneously or intramuscularly is appropriate, given its rapid onset of action within hours and absence of nephrotoxicity. Calcitonin can be dosed at 6- to 12-hour intervals, but importantly, efficacy is generally limited to <48 hours because of rapid tachyphylaxis.

In the setting of severe renal insufficiency (e.g., glomerular filtration rate [GFR] < 30 mL per minute or creatinine >3 mg per dL), bisphosphonates are relatively contraindicated because of the risk of nephrotoxicity and should be used with caution. In this setting, hydration in conjunction with calcitonin may improve renal function, permitting subsequent administration of bisphosphonates to achieve a more durable hypocalcemic effect. Hemodialysis rarely may be indicated in patients with severe renal insufficiency and malignancy-associated hypercalcemia.

Other agents that are used infrequently to treat HCM include glucocorticoids and gallium nitrate. Glucocorticoids are an effective adjunctive therapy in the setting of calcitriol-mediated HCM, whereas gallium nitrate has a limited role in treating patients with bisphosphonate-resistant HCM when treatment is indicated.99

The **third step** in managing HCM is the prevention of recurrent hypercalcemic events. This is best accomplished by treating the underlying malignancy if possible, because recurring episodes of HCM are inevitable in the setting of tumor progression. In addition, patients with bony metastases will receive monthly IV bisphosphonates or denosumab to prevent skeletal-related events and, as a result, recurrent HCM may be prevented.

SUPERIOR VENA CAVA SYNDROME

KEY POINTS

- SVCS is a complication of cancer that only rarely presents as a true emergency.
- More than 90% of cases of SVCS are caused by lung cancer or non-Hodgkin lymphoma.
- A histologic diagnosis should be obtained prior to initiating chemotherapy or radiotherapy, and invasive diagnostic thoracic procedures can usually be performed safely.
- Endovascular stent deployment can provide immediate palliation of symptomatic SVCS.

INTRODUCTION

Malignancy-associated SVC syndrome (SVCS) is an uncommon complication of malignancy caused by obstruction of the SVC from malignant compression or invasion. Because most patients with SVCS present without a known cancer diagnosis, primary care clinicians are often involved in the diagnosis and initial workup. Although described as a “classical oncologic emergency,” SVCS usually develops insidiously over weeks and rarely presents as an emergency with symptomatic increased intracranial pressure. Thus, emergent radiation in the absence of a tissue diagnosis is no longer recommended. Moreover, the use of endovascular stents has facilitated rapid palliation of severely symptomatic SVCS.

ETIOLOGY AND INCIDENCE

SVCS is caused by compression or invasion of the SVC by intrathoracic malignancy in 60% to 85% of cases.100–103 Approximately 80% of cases of malignancy-associated SVCS are caused by lung cancer, particularly small cell and squamous cell histologies, and 10% to 20% are caused by non-Hodgkin lymphoma, particularly lymphoblastic lymphoma and primary mediastinal diffuse large B-cell lymphoma. Less than 5% of cases are caused by other primary mediastinal tumors (germ cell tumors, thymoma) or solid tumors with mediastinal lymph node metastases. Malignancy-associated SVCS is an uncommon complication of cancer in the modern era; only 2% to 4% of patients with lung cancer or non-Hodgkin lymphoma develop this complication.100

An increasing cause of SVCS is thrombosis associated with long-term use of indwelling central venous catheters or cardiac pacemakers. In recent series, up to 40% of cases of SVCS were related to intravascular devices.101 Nonmalignant causes (e.g., goiter, granulomatous diseases, idiopathic fibrosis) are rare.101

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

The thin-walled SVC is vulnerable to extrinsic compression or invasion from adjacent masses arising in the right lung, lymph nodes, or mediastinum. Altered blood through the compressed SVC may lead to in situ thrombosis, which exacerbates the obstructive process. The rise in venous pressure proximal to the SVC leads to blood flow through collateral networks with venous return to the right atrium via the azygous system or the inferior vena cava. Collateral blood flow rapidly decompresses the increased venous pressure from SVC obstruction, and

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although it may take weeks to fully accommodate SVC blood flow through collateral systems, life-threatening increases in intracranial pressure with associated brain edema are rarely encountered.100

Approximately 60% of patients with SVCS present without a known cancer diagnosis.104 In most cases, the onset of SVCS is insidious over weeks to months. The clinical signs include distended and prominent collateral veins of the chest wall, edema of the hands and arms, facial plethora or swelling, chemosis, and periorbital edema. Patients may complain of headaches or head pressure, dizziness, and nasal congestion. Stridor, hoarseness, dysphagia, hemoptysis, dyspnea, and cough can result from edema of aerodigestive structures or the direct effects of the tumor mass. Hemodynamic compromise from SVCS is rare and usually reflects tumor-related mass effect on the heart.100–104

Diagnosis

The diagnosis of SVCS is suspected from the clinical signs and symptoms. The chest radiograph is usually abnormal, showing a mediastinal mass or widening; pleural effusions are present in most patients. A CAT scan of the chest with contrast is the most useful diagnostic test to confirm the diagnosis because the site of obstruction, collateral drainage, and underlying cause (thrombosis vs. mass effect or both) can be delineated from a CAT scan. Alternatively, MR venography can be used in patients who cannot receive iodinated contrast.

A histologic diagnosis will be necessary in those patients who present with SVCS in the absence of a prior cancer diagnosis (60% of cases).105 Because SVCS is rarely an emergency, and optimum therapy depends on the histologic diagnosis, empiric radiotherapy simply to alleviate symptomatic SVCS should almost never be started prior to obtaining a biopsy.101–105 If necessary, diagnostic thoracic procedures (bronchoscopy, mediastinoscopy, video-assisted thoracoscopy) can be performed if a definitive diagnosis cannot be made by other means (bone marrow or peripheral lymph node biopsy, sputum or pleural fluid cytology) because concerns about increased risk of complications in this setting have not been validated in multiple recent studies.101–105 The only exception to this strategy of delaying radiotherapy pending a tissue diagnosis is in cases of impending airway obstruction or coma from increased intracranial pressure.

Treatment

Treatment of SVCS is directed toward alleviating the symptoms of SVCS and optimally treating the underlying malignancy. As noted previously, emergent radiotherapy is rarely indicated, and recent consensus guidelines focus on obtaining a histologic diagnosis, defining the stage, and initiating the optimum stage-specific treatment of the underlying malignancy.100,105,106 In severely symptomatic patients, the early use of endovascular stents can provide dramatic resolution of symptoms in >90% of patients while the diagnostic workup proceeds.100,105,107–109

The specific treatment of SVCS depends on the underlying diagnosis, stage, and prognosis. Chemosensitive tumors (non–Hodgkin lymphoma, small cell lung cancer, germ cell tumors) are treated with chemotherapy alone according to stage-specific consensus guidelines. Symptomatic improvement with initiation of chemotherapy is usually rapid, and the presence of SVCS does not adversely impact outcome.109 Non–small cell lung cancer, by contrast, is relatively resistant to chemotherapy; the use of radiotherapy, with or without concurrent chemotherapy, is often advocated, although chemotherapy alone is an option in patients with stage IV disease. Placement of an endovascular stent for symptomatic SVCS is indicated for patients with non–small cell lung cancer or treatment-refractory malignancy (e.g., mesothelioma, recurrent malignancies). When thrombosis accompanies SVC compression, local thrombolytic therapy or thrombectomy should be considered as well as long-term systemic anticoagulation to prevent rethrombosis. The role of corticosteroids and diuretics is largely unproven. However, a course of high-dose corticosteroids is reasonable in patients undergoing emergent radiotherapy because of impending airway obstruction.

References


Pain in patients with cancer may be caused by the cancer itself, related to the cancer (e.g., muscle spasm, lymphedema, constipation, bed sores), related to anticancer treatment (e.g., chronic postsurgical scar pain, chemotherapy-induced mucositis), or caused by a concurrent disorder (e.g., osteoarthritis). Patients may often experience pain because of a combination of these categories. The cancer itself can cause pain through extension into soft tissues, visceral involvement, bone involvement, nerve compression, nerve injury, and by raising intracranial pressure.\(^1\)

**ASSESSMENT**

Pain assessment is critical to optimal pain management and should be ongoing, individualized, and documented. Assessment should occur at each clinical encounter, at regular intervals after initiation of treatment, after parenteral drug therapy, and 1 hour after oral administration.\(^2\) The WILDA (Words, Intensity, Location, Duration, Aggravating/Alleviating factors) approach ensures that the five key components to a pain assessment are incorporated into the process.\(^3\)

**Words**

**Neuropathic Pain.** This type of pain can be described as burning, shooting, tingling, radiating, lancinating, and numbness. Sometimes, patients say that their pain is like a fire or an electrical jolt. This type of pain can be caused by nerve disorders, nerve involvement by a tumor pressing on nerve plexus, postherpetic neuralgia, or peripheral neuropathies secondary to treatment (chemotherapy, radiation fibrosis).

**Somatic Pain.** Described as achy, throbbing, or dull, somatic pain is typically well localized. Somatic pain accompanies arthritis, bone or spine metastases, low back pain, and orthopedic procedures.

**Visceral Pain.** Pain described as squeezing, pressure, cramping, distention, dull, deep, and stretching is visceral in origin. Visceral pain is manifested in patients after abdominal or thoracic surgery, secondary to liver metastases, bowel or venous obstruction, and also celiac plexus pain because of cancer or chronic pancreatitis.

**Intensity**

The ability to quantify the intensity of pain is essential when caring for persons with acute and chronic pain. Although no scale is suitable for all patients, Dalton and McNaull\(^4\) advocate a universal adoption of a 0 to 10 scale for clinical assessment of pain intensity in adult patients. Inquiring about the pain level acceptable to the patient will help clinicians understand the patient’s goal of therapy. The Wong/Baker faces rating scale is a visual representation of the numerical scale.\(^5\)

Although the faces scale was developed for use in pediatric patients, it has also proven useful with elderly patients and patients with language barriers.

**Location**

Patients may have more than one site of pain.

**Duration**

Patients need to be asked, “Is your pain always there, or does it come and go?” or “Do you have both chronic and breakthrough pain?” Breakthrough pain refers to a transitory exacerbation or flare of pain occurring in a patient who is on a regimen of analgesics for continuous stable pain.\(^6\)

**Aggravating/Alleviating Factors**

Asking the patient to describe the factors that aggravate or alleviate the pain will help plan interventions. Other details to include in the pain assessment are the presence of contributing symptoms or side effects associated with pain and its treatment. These include nausea, vomiting, constipation, sleepiness, confusion, urinary retention, and weakness. Inquiring about the presence or absence of changes in appetite, activity, relationships, sexual functioning, irritability, sleep, anxiety, anger, and ability to concentrate will help the clinician understand the pain experience in each individual. A detailed history and careful physical examination...
must be performed to determine the cause of the pain so as to initiate appropriate therapy.

**PHARMACOLOGIC MANAGEMENT OF CANCER PAIN**

A combination of pharmacologic and nonpharmacologic methods is often most effective. Nonetheless, analgesics and a limited number of other drugs are the mainstay of cancer pain management.

The **WHO Pain Ladder** was developed in 1986 as a conceptual model to guide the management of cancer pain (Fig. 24-1). There is now a worldwide consensus promoting its use for the medical management of all pain.

The first step is a non-opioid. If this does not relieve the pain, an opioid for mild-to-moderate pain (Table 24-1) should be added. When an opioid for mild-to-moderate pain in combination with a non-opioid fails to relieve the pain, an opioid for moderate-to-severe pain should be substituted. Only one drug from each of the groups should be used at the same time. Adjuvant drugs should be used for specific indications.1 Table 24-2 lists some of the commonly used adjuvant analgesics.

If a drug ceases to be effective, do not switch to an alternative drug of similar efficacy but prescribe a drug that is definitely stronger (e.g., from codeine to morphine).1 Morphine has been the drug of first choice for 25 years for treating moderate-to-severe cancer pain for reasons of familiarity, availability, and cost. No important differences have been demonstrated between morphine, oxycodone, and hydromorphone administered orally, and any one of these three drugs can be used as the first choice step 3 opioid for moderate-to-severe cancer pain.7

**Opioid Dosing**

There are no standard doses for opioids. The “right” dose is the dose that relieves the patient’s pain. Drugs used for mild-to-moderate pain have a dose limit in practice because of formulation (e.g., combined with acetaminophen, which is toxic at high doses) or because of a disproportionate increase in adverse effects at higher doses.1 The appropriate dose is the amount of opioid that controls pain with the fewest side effects. Dose titration should continue until good pain relief is achieved or intolerable side effects develop that cannot otherwise be controlled.

Most patients with cancer pain require fixed-schedule dosing to manage the constant pain and prevent the pain from worsening.8 The appropriate dosing interval is determined by the opioid and formulation used. The analgesic effects of short-acting oral opioids such as morphine, hydromorphone, codeine, and oxycodone begin within a half hour after administration and last for approximately 4 hours. The dosing interval of these drugs is usually 4 hours. Short-acting opioids are generally recommended when opioid therapy is being initiated for the first time or when patients are medically unstable or the pain intensity is highly variable. Once stable, patients can be switched to a controlled-release or slow-release formulation. This is more convenient and promotes compliance.2 Many patients will continue to experience breakthrough pain or transitory increases in pain above the baseline level. For such pain, PRN “rescue doses” of a short-acting opioid should be available as needed that should start at 10% to 20% of the total scheduled daily opioid dose.

Patients on chronic opioid therapy may at times require relatively large dose increments to control acute exacerbations of pain. A parenteral infusion pump with a device for self-administration of extra doses of medication every few minutes (patient-controlled analgesia [PCA]) should be used if available. The PCA bolus or demand dose can be as high as the hourly infusion rate during the titration phase and when incident pain is a concern. The continuous basal rate should be frequently adjusted based on the PCA usage and patient’s report. When venous access is problematic, the subcutaneous route can be used. Once the acute pain exacerbation is controlled, the medication should be changed to the oral or transdermal route if possible. Long-term intravenous and subcutaneous opioid administration is possible in patients outside the hospital.

In patients given controlled-release formulations of morphine or oxycodone, relief should begin in 1 hour, peak in

<table>
<thead>
<tr>
<th>WHO Step I/II Opioids</th>
<th>Usual Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine (with acetaminophen or aspirin)</td>
<td>60 mg PO q3–4h</td>
</tr>
<tr>
<td>Tylenol #2 (15 mg codeine)</td>
<td></td>
</tr>
<tr>
<td>Tylenol #3 (30 mg codeine)</td>
<td></td>
</tr>
<tr>
<td>Tylenol #4 (60 mg codeine)</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone (with acetaminophen or aspirin)</td>
<td>10 mg PO q3–4h</td>
</tr>
<tr>
<td>Lorcet, Lortab, Vicodin, Zydone, others</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10 mg PO q3–4h</td>
</tr>
<tr>
<td>Roxicodone (single entity)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone (with acetaminophen or aspirin)</td>
<td></td>
</tr>
<tr>
<td>Percocet, Percodan, Tylox, others</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg PO qid</td>
</tr>
</tbody>
</table>

**TABLE 24-1 Commonly Used Opioids for Cancer Pain**

*WHO, World Health Organization; q, every; qid, four times a day.*

2 to 3 hours, and last for 12 hours; these formulations are usually prescribed in 12-hour intervals. The analgesic effect of transdermal fentanyl begins approximately 12 hours after the application of the patch, peaks in 24 to 48 hours, and lasts for approximately 72 hours. Patches are therefore changed every 72 hours. Do not start transdermal fentanyl in opioid-naïve patients, such as when taking less than 45 mg daily oral morphine. See Table 24-3 for transdermal fentanyl dose calculation based on daily oral morphine equivalents (DOME). In a select group of patients who consistently experience end-of-dose failure despite increases in the patch doses, the dosing interval can be increased to every 48 hours (10% of patients on fentanyl patches).2

When switching from one opioid drug to another, dose conversion ratios can be recommended (Table 24-4). These conversion ratios are specific for patients in whom analgesia from the first opioid is satisfactory. Therefore, when the opioid is switched because of unsatisfactory analgesia, excessive side effects, or both, clinical experience suggests that the starting dose should be lower than that calculated from published equianalgesic ratios. In all cases, the dose needs to be titrated in accordance with clinical response.7

### Routes of Administration

For the patient with cancer pain, the oral route of opioid delivery should be the first choice. If the oral route cannot be used because of gastrointestinal obstruction or severe nausea/vomiting, the rectal (or ostial route) is equivalent. Whether the oral or rectal route is used, long-acting oral preparations should be used around the clock, with “immediate” release preparation available to treat breakthrough pain. Another noninvasive alternative to the oral route is the transdermal

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### Table 24-2: Commonly Used Adjuvant Analgesics

<table>
<thead>
<tr>
<th>Classification</th>
<th>Usual Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic Pain</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>25–75 mg PO at bedtime</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25–50 mg PO at bedtime</td>
</tr>
<tr>
<td>Desipramine</td>
<td>25–75 mg PO qd</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>25 mg PO qd</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30–60 mg PO qd</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5–75.0 mg PO bid to tid</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg PO qd to tid</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>50 mg PO tid</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100 mg PO bid</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>300 mg PO bid</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>25 mg PO qd</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25 mg PO qd to bid</td>
</tr>
<tr>
<td>α₂-Adrenergic agonists</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1 mg PO qd to bid</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>2–4 mg PO tid</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>5–10 mg PO bid</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>4–16 mg PO qd</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td></td>
</tr>
<tr>
<td>Lidocaine transdermal</td>
<td>5% patch × 12 h qd</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>150 mg PO qd</td>
</tr>
<tr>
<td>Topical agents</td>
<td></td>
</tr>
<tr>
<td>Capsaicin cream</td>
<td>Apply tid</td>
</tr>
<tr>
<td>N-methyl-D-aspartate (NMDA) receptor antagonists</td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>30 mg PO tid</td>
</tr>
<tr>
<td>Methadone</td>
<td>2.5 mg PO bid to tid</td>
</tr>
<tr>
<td>Memantine</td>
<td>5 mg PO qd</td>
</tr>
<tr>
<td>Amanitadine</td>
<td>100 mg PO qd</td>
</tr>
<tr>
<td>Ketamine</td>
<td>5 mg PO tid to qid</td>
</tr>
</tbody>
</table>

### Table 24-3: Daily Oral Morphine Equivalents (DOME) → Transdermal Fentanyl (μg/h)

<table>
<thead>
<tr>
<th>DOME (mg)</th>
<th>Transdermal Fentanyl (μg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60–134</td>
<td>25</td>
</tr>
<tr>
<td>135–224</td>
<td>50</td>
</tr>
<tr>
<td>225–314</td>
<td>75</td>
</tr>
<tr>
<td>315–404</td>
<td>100</td>
</tr>
<tr>
<td>405–494</td>
<td>125</td>
</tr>
<tr>
<td>495–585</td>
<td>150</td>
</tr>
</tbody>
</table>

### Table 24-4: Equianalgesic Dosing

<table>
<thead>
<tr>
<th>From → To</th>
<th>Oral:Oral Ratio</th>
<th>IV:IV Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine → hydromorphone</td>
<td>4:1</td>
<td>6:1</td>
</tr>
<tr>
<td>Morphine → oxycodone</td>
<td>1.5:1.0</td>
<td>—</td>
</tr>
<tr>
<td>Morphine → methadone</td>
<td>10:1</td>
<td>6:1</td>
</tr>
<tr>
<td>Morphine → fentanyl</td>
<td>—</td>
<td>100:1</td>
</tr>
<tr>
<td>Morphine → oxymorphone</td>
<td>3:1</td>
<td>10:1</td>
</tr>
</tbody>
</table>

*C* Methadone equianalgesic potency varies relative to dose of opioid.  
*Morphine 1 mg IV is equivalent to fentanyl 10 μg IV.*

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route, which at present is available only for continuous administration of fentanyl. For treatment of breakthrough pain in a patient unable to take oral or rectal medications, a transmucosal preparation of fentanyl is now available. For those patients in whom oral, rectal, and transdermal opioids are not appropriate, subcutaneous PCA is effective and provides approximately 80% bioavailability of administered opioids. It does not require intravenous access and is relatively easy to administer. Intravenous administration of opioids is an option in those patients in whom no other route is available and who have intravenous access.

Methadone is a synthetic opioid agonist with high oral bioavailability. Dosing recommendations for methadone are complex because of the drug’s potency and prolonged elimination half-life. Half-lives as long as 120 hours have been described in the outpatient setting. Extreme caution is recommended when switching from other opioids to methadone, especially in patients who are already highly opioid tolerant. Morphine to methadone dose ratios are actually much higher than those suggested in the published equianalgesic tables because these tables are based on single-dose studies and were not intended for chronic opioid administration. High-dose methadone therapy has been linked to cardiac abnormalities such as prolongation of the QT interval and torsades de pointes. Clinicians should be aware of the potential cardiovascular effects and weigh the benefit-to-risk ratio for each patient based on individual risk for arrhythmia.

**TOLERANCE, DEPENDENCE, AND ADDICTION**

A comprehensive understanding of these three distinct phenomena is vital in many areas of pain management.

*Tolerance* is characterized by the need to use escalating doses of a drug to maintain the same effect. When the underlying disease process is clearly stable and when there is no evidence for either addiction or drug “diversion,” the need for increased doses can, with reasonable confidence, be attributed to this phenomenon. In some cases, switching to another opioid, for which a patient may have only partial cross-tolerance, can be useful. In actual practice, however, once a chronically effective dose has been well established in the treatment of a stable disease process, it is unusual for subsequent tolerance to be an important clinical problem. In the patient with cancer, however, the underlying disease process may not be stable, and when increased doses are needed to achieve the same analgesic effect, the clinician’s primary suspicion should always be disease progression. If disease progression is in fact the cause, then further increases in the dose of the current opioid may be effective.

*Physical dependence* is characterized by symptoms of withdrawal following abrupt discontinuation of the drug and can be a severe problem in the context of chronic use of significant doses of opioids. In the palliative care context, clinicians rarely if ever consciously stop chronic opioids abruptly. Nonetheless, serious withdrawal syndromes can become manifested in the terminal phase of illness if the route of administration of chronic opioids is suddenly no longer available—as in the case of a patient taking opioids orally who becomes moribund and unable to swallow. In this situation, it is important to find an alternate route to administer a minimum of the 25% of the previous daily dose of opioid that is generally regarded as required to prevent withdrawal symptoms and reduce dose by 25% per day. The antihypertensive drug clonidine can also be used to treat opioid withdrawal symptoms.

Addiction is characterized by psychological dependence on the involved drug, compulsive use, loss of control, associated loss of interest in other pleasurable activities, and, most importantly, continued use in spite of evident harm. It is rare for this to be a problem in pain management in the setting of terminal illness, especially in patients with no preexisting history of addiction or substance abuse. For patients with such a preexisting history, the risks of addiction must be carefully assessed and proactively addressed in planning any pain management regimen. Concern about these risks, however, must not lead to plans of care that leave a dying patient with inadequate symptom relief.

Common misperceptions among patients about opioid therapy include confusion between physical dependence and addiction, the perception that all patients receiving long-term opioids become addicted, concerns that opioids may cause persistent sedation and cognitive blurring, and the belief that tolerance inevitably makes opioids ineffective over time. A complete evaluation at the initial visit can help the clinician understand patients and any concerns they may have regarding opioid therapy. When biases and prejudices that may inhibit opioid therapy are discovered, they are best addressed through counseling that covers intended outcomes and foreseeable or potential adverse effects. This requires that clinicians have a working, in-depth knowledge of both opioid pharmacology and the specific medical, psychological, and social aspects of each patient they are treating.

**OPIOIDS, RESPIRATORY SUPPRESSION, AND EFFECT ON SURVIVAL**

When high (or at least increasing) doses of opioids are required for effective pain control, clinicians are often concerned about respiratory depression and decreased survival. Although it is true that respiratory suppression can be a primary drug effect of opioids, it is in fact far less common than many physicians believe they “know” from their own clinical experience.10–12 Azoulay et al., in a retrospective observational study conducted in 114 consecutive hospice patients, found that opioid usage, even at high doses (mean opioid dose 146 + 245 mg/d) had no effect on survival among advanced patients with cancer in a hospice setting.13 Tachypnea is a frequent manifestation both of acute pain and of anxiety, and the decreased respiratory rate that almost always follows administration of an opioid in the setting of intense, acute pain is in most cases a secondary result of the drug’s primary analgesic and anxiolytic effects. When a life-threatening opioid overdose is suspected, naloxone, an opiate antagonist, should be given intravenously. Patients on chronic opioids are more sensitive to naloxone than opioid-naive patients, and a dilute naloxone solution is recommended for use in this setting. The 0.4 mg ampule of naloxone can be diluted in 10 mL of normal saline and injected slowly, with titration bringing the dose to effect, so as to prevent precipitation of severe withdrawal symptoms and return of pain.

**OPIOID SIDE EFFECTS**

Common opioid side effects that will be addressed briefly here include constipation, nausea, vomiting, sedation, and delirium. For all of these except constipation, tolerance may develop, and patients should be counseled that even if the...
undesirable effects are significant with initial doses, a trial of at least a few days may be warranted before deciding that an alternative medication should be used or that the dose of the opioid can be reduced. In the meantime, symptoms should be monitored closely and vigorously treated.

**Constipation** is a predictable effect of chronic opioid use. In the patient who is terminally ill and who frequently has markedly reduced levels of physical activity and other serious comorbidities, it is even more significant and can become a cause of significant abdominal discomfort. A proactive bowel regimen designed to prevent constipation using stool softeners and/or bowel-stimulating laxatives, with daily monitoring of its effectiveness, is a mandatory component of chronic opioid therapy in this setting. Bulk-forming laxatives should generally be avoided because they can predispose to obstruction and impaction.

**Nausea and vomiting** can be treated with various pharmacologic agents including trials of prochlorperazine, haloperidol, metoclopramide, and ondansetron. If tolerance to these adverse effects does not develop, alternative opioids should be tried. It is important to keep in mind, however, that many palliative care patients are suffering from illnesses or taking other medications, which may themselves be the cause of the nausea or vomiting, and the opioid may be only partially to blame.

**Delirium** is a common problem for patients in the terminal setting, with estimated prevalence rates ranging from 25% to 85%. Many of these patients are receiving opioids, but even when administration of the opioid is the precipitating factor, the cause is frequently multifactorial. When evidence of delirium is detected, a comprehensive evaluation of potentially contributing factors is warranted, with efforts to treat the underlying causes. Changing the opioid can be useful. In addition, various pharmacologic agents can be used to treat delirium. Haloperidol has generally been considered the drug of choice.

### PHYSICAL MODALITIES FOR PAIN MANAGEMENT

Generalized weakness, deconditioning, and musculoskeletal pain associated with cancer diagnosis and therapy may be treated by local application of heat, cold, and by exercise. Repositioning the immobilized patient frequently helps to maintain correct body alignment, to prevent or alleviate pain, and to prevent pressure ulcers. Transcutaneous nerve stimulation (TENS) applies controlled low-voltage electrical stimulation to large myelinated peripheral nerve fibers via cutaneous electrodes to inhibit pain transmission.

### PSYCHOLOGICAL INTERVENTIONS

Cancer pain can be intensified by psychological distress, especially mood disturbance, depression, fear, and anxiety as shown by the large majority of 19 studies reviewed by Zaza and Baine. Cognitive behavioral therapy, behavioral interventions such as biofeedback and relaxation, meditation, hypnosis, and music therapy are helpful in treating pain and psychological distress.

### INTEGRATIVE MODALITIES

Several complementary treatment modalities such as acupuncture and therapeutic massage have some supportive empirical evidence or promising preliminary data. Acupuncture has been found to be helpful in managing various pain conditions.

### REGULATORY ISSUES

State and local laws often restrict the medical use of opioids to relieve cancer pain, and third-party payers may not reimburse for noninvasive pain-control treatments. Thus, clinicians should work with regulators, state cancer pain initiatives, or other groups to eliminate these health care system barriers to effective pain management. The U.S. Food and Drug Administration Amendments Act of 2007 requires manufacturers to provide risk evaluation and mitigation strategies (REMS) for long-acting and extended-release opioid drugs (e.g., fentanyl extended-release transdermal system, methadone, morphine extended-release tablets, oxycodone extended-release tablets) to ensure that benefits outweigh risks. A major component of REMS requires prescribers to obtain training so that these drugs can be safely used.

### References

Nausea and vomiting in persons with advanced cancers are perhaps two of the most common symptoms encountered by primary care clinicians, palliative subspecialists, and oncologists alike. These two entities, although common, can present treatment challenges to the clinicians. Their prevalence in patients with cancer with advanced disease is estimated at 60% and 30% for vomiting and nausea, respectively. Symptoms of nausea and vomiting increase in prevalence as the underlying disease itself progresses, thus serving as a potential prognosticator of shortened survival.

Initial treatment regimens include prokinetic agents such as metoclopramide and/or dopamine receptor antagonists such as haloperidol. For persistent symptoms, schedule the antiemetics and, if one agent only partially relieves symptoms, a second agent can then be added.

For the purpose of this chapter, the focus will be on therapeutic interventions that most primary care clinicians should be able to comfortably employ, realizing that other tertiary treatment modalities exist that can be implemented by the oncologists. The scope of this text limits further discussion about the antiemetic regimens used for patients suffering from cancer-induced nausea and vomiting (CINV) and radiation-induced nausea and vomiting (RINV). These therapies range from single-dose regimens to multidose cocktails depending on the emetogenic potential of the chemotherapeutic agents and are usually prescribed by the oncologists. For further readings, please review “Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update.”

We must first define nausea and vomiting and differentiate it from other symptoms that patients might be experiencing and interpreting as nausea and/or vomiting. Nausea is the unpleasant subjective experience of the need to vomit that can be associated with other autonomic symptoms such as pallor, cold sweats, tachycardia, and diarrhea. Vomiting, however, is a physical function where there is rapid, forceful evacuation of gastric contents from the stomach occurring in retrograde fashion through the mouth. Other associated clinical entities that should be considered when patients report nausea and vomiting are dyspepsia, regurgitation, rumination, and posttussive expectoration or emesis.

The approach to all patients with complaints of nausea and vomiting begins with a thorough history and physical examination because the etiology can be found in approximately 75% to 90% of cases. It is important to ask about mitigating/alleviating symptoms as well as provocative phenomena such as eating, smells/odors, and induction by movement. In addition, one should assess the duration (acute vs. chronic), severity, and frequency of nausea and vomiting, whether either occurs alone or together.

In addition, a careful review of medications, prescribed and over-the-counter ones, is of utmost importance. If any offending agents are found, these should be avoided, eliminated, or changed to another appropriate and less provocative agent. The basic metabolic panel may also be helpful. Laboratories should include calcium, sodium, glucose, and renal function because these derangements can provide clues to potentially reversible or correctible causes of nausea and vomiting.

Once the history and physical assessment have been obtained, then therapy can be initiated. Commencing pharmacologic therapy for nausea and vomiting can be done either empirically or mechanistically. Whereas a more mechanistic or etiologic approach is based on the understanding the
principles of neurotransmitter physiology, a more empiric approach does not. There is evidence, however, suggesting that the empiric approach to treatment is more feasible because of the limitations of the mechanistic approach that follows the antiemetic pathway. Response rates have ranged from 56% to 93% in various studies measuring effectiveness of antiemetic therapy using the etiologic approach.\(^3,14,15,20\)

Some studies suggest that multiple causes of nausea and vomiting in the patient with advanced cancer occurs in approximately 25% of that population.\(^3,15,20\)

To more fully understand the mechanistic or etiologic approach, one must have a basic understanding of the physiology of nausea and vomiting. It has been demonstrated that nausea and vomiting, like many other biologic functions, are mediated through various neurotransmitters that have their effect centrally. Research has identified more than 17 potential neurotransmitters or receptors.\(^3\) Neurotransmitters such as dopamine, serotonin, histamine, acetylcholine, and neurokinins exert their effects in various areas of the brain stem: the two most important of which are the chemoreceptor trigger zone (CTZ) and the vomiting center (VC).

### Antiemetic Drug Therapies

Although the following antiemetic drug therapies do not represent all of the available agents and dosing must be based on age, renal function, and hepatic function, it should be used as a guide to consider potential treatment options. The drug regimens in the following text should be considered as primary and perhaps secondary interventions for nausea and vomiting in patients with advanced cancer. Again, for those patients experiencing symptoms of nausea and vomiting while undergoing active chemotherapy or radiation therapy, tertiary antiemetics can be implemented by the oncologist.

Because delayed gastric emptying and gastric stasis are common causes of nausea and vomiting in those with advanced cancer, the use of prokinetic agents is useful in the management of these symptoms.\(^3,14,21\) The most widely available agent is metoclopramide. The evidence for its use, however, is conflicting. Compared to placebo in the treatment of cancer-associated dyspepsia, metoclopramide was superior to placebo but not in opioid-induced nausea.\(^4,22,23\) Despite this evidence, it remains a mainstay of therapy for the treatment of opioid-induced gastrointestinal dysmotility. Metoclopramide exerts its effect via proserotonergic activity in the upper gastrointestinal tract, primarily the stomach and the proximal small bowel. In addition, metoclopramide has central antispasmodic activity in the upper gastrointestinal tract relieving gastroparesis. Metoclopramide and other prokinetic agents should be avoided in the setting of complete bowel obstruction, perforation, or gastrointestinal hemorrhage because stimulation of muscular contraction might adversely affect the gut.\(^4\) Metoclopramide is dosed 10 mg orally or intravenously three times daily, 1.5 hours before meals and at bedtime.\(^4,14\) It should be dose reduced in the elderly and those with impaired renal function. Special note should be made of the black box warning that this drug carries, highlighting the risk of tardive dyskinesia particularly in populations treated beyond 12 weeks.

Dopamine receptor antagonists such as haloperidol and olanzapine exert their antiemetic effect in the area postrema of the CTZ, thus proving their efficacy in chemical causes of nausea and vomiting.\(^5,6,7,14,15\) In addition, it is noted that these agents may have some prokinetic activity by producing vagal blockade.\(^5\) Haloperidol is dosed 1.5 to 5.0 mg orally two to three times daily or 0.5 to 2.0 mg intravenously every 8 hours. Special populations to consider when prescribing include those with Parkinson disease because haloperidol may exacerbate extrapyramidal symptoms.\(^4\) In addition, there is potential prolongation of the QT interval and it should be used with caution in those individuals prone to dysrhythmias.\(^1\) The atypical antipsychotic olanzapine is also useful in the treatment of nausea and vomiting. It blocks multiple receptors including dopaminergic, serotonergic, histaminic, and muscarinic, typically causing less extrapyramidal side effects and lowers incidence of QT prolongation.\(^3,4,24,25\) It is sometimes used as a second-line agent in those suffering from refractory nausea. Usual starting doses of olanzapine is 2.5 to 5.0 mg orally or sublingually twice daily.\(^1,4,26\) Although there are no randomized controlled trials of the use of olanzapine for chronic nausea in the palliative care setting, small, uncontrolled studies have shown efficacy in this context.\(^3,20,27\)

More than two decades ago, nausea and vomiting were adverse side effects of chemotherapy that precluded up to 20% of patients with cancer from continuing with treatment.\(^20\) Research in this arena yielded a newer class of antiemetic agents, the selective serotonin antagonists, of which ondansetron is the oldest agent. These antiemetics are the mainstay for treatment of CINV or RINV.\(^26\) As such, they should be reserved as third-line strategies but are frequently used empirically by clinicians to treat non–chemoradiation-induced symptoms.\(^3,21\) Their mechanism of action is mediated both centrally via the CTZ and peripherally.\(^3,21\) Peripherally, selective serotonin antagonists block the release of serotonin from enterochromaffin cells in the small bowel wall that occurs after chemotherapy, thereby mitigating the effects of nausea and vomiting. Constipation and prolonged QT intervals are important side effects for which to monitor.

Other pharmacologic considerations: Please also note Table 25-1.

1. Antihistamines—work centrally on the VC in the brain stem;\(^3,5\) note should be made that these therapies can potentially negate the effects of prokinetic agents and should not be used simultaneously
2. Benzodiazepines—anticipatory (anxiety) nausea and vomiting
3. Corticosteroids—chemotherapy-induced symptoms both prophylactically and as adjuvant therapy;\(^2,21\) by reducing the permeability of the area postrema and the blood–brain barrier, malignant bowel obstruction, and increased intracranial pressure
4. Octreotide—malignant bowel obstruction by reducing gastrointestinal and pancreatic secretions, reducing gastrointestinal motility\(^4,30\)
5. Cannabinoids—chemotherapy-induced symptoms via binding brain stem receptors and μ-opioid receptors; limited by side effects\(^5,31,32\)

Because pharmacologic therapy is the mainstay for treatment of nausea and vomiting in patients with advanced cancer, it should also be noted that there are several nonpharmacologic strategies that also would be helpful. Behavioral modification such as relaxation and distraction may decrease psychological arousal and may be particularly beneficial in those with anticipatory nausea and vomiting.\(^5,9,33\) Simple dietary changes to avoid foods with strong tastes, such as spicy and salty foods,
or smells as well as consuming small but frequent meals may also mitigate these symptoms. Not only has it been recommended to avoid foods with strong smells but also reducing malodor from wounds or ulcers has been advocated.3 Those individuals suffering from symptoms related to malignant bowel obstruction may experience temporary relief from gastric decompression via nasogastric tube insertion or more long term from placement of a venting percutaneous endoscopic gastrostomy.1,2 There is a growing body of literature that identifies the use of complementary modalities such as acupuncture and acupressure, particularly related to alleviating symptoms of chemotherapy-induced vomiting or anticipatory nausea.3,4,34

When considering which antiemetic agents to use in the treatment of nausea and vomiting, it is important to be thorough in the history and physical examination looking for the potential etiology of the symptoms. Once this is done, reviewing medications, both prescription and over the counter, can provide clues as well to the cause. Other reversible causes such as metabolic derangements should be identified and corrected. Once these potential contributing factors have been corrected and/or ruled out, pharmacologic antiemetic therapy can begin.

### TABLE 25-1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (dopamine receptor antagonist)</td>
<td>0.5–5.0 mg or 0.5–2.0 mg</td>
<td>PO</td>
<td>Bid to tid</td>
</tr>
<tr>
<td>Metoclopramide (prokinetic agent)</td>
<td>10 mg</td>
<td>PO/IV</td>
<td>Every 4–6 h</td>
</tr>
<tr>
<td>Ondansetron (selective 5HT3-receptor antagonist)</td>
<td>4–8 mg</td>
<td>PO/IV</td>
<td>Every 6–12 h</td>
</tr>
<tr>
<td>Promethazine (antihistaminic agent)</td>
<td>25 mg</td>
<td>PO/IV</td>
<td>Every 4–6 h</td>
</tr>
<tr>
<td>Octreotide (somatostatin analog)</td>
<td>100 μg</td>
<td>SC</td>
<td>Every 8 h</td>
</tr>
<tr>
<td>Dexamethasone (corticosteroids)</td>
<td>4–8 mg (up to 16 mg/24 h)</td>
<td>PO/IV/SC</td>
<td>Every 6–12 h</td>
</tr>
</tbody>
</table>

*Bid, twice a day; tid, three times a day.*

### References


KEY POINTS

- Establish and maintain appropriate nonpharmacologic interventions.
- If diarrhea or constipation becomes intractable or is severe at presentation, initiate laboratory workup, consider abdominal imaging, and notify the patient’s oncologist.
- Constipation
  - Prevention and maintenance plans are the keys to management.
  - Be alert to diagnoses such as impaction, bowel obstruction, and pseudo-obstruction.
- Diarrhea
  - Loperamide is first line for cancer treatment-induced diarrhea (CTID).
  - Consider enterotoxin-producing bacterial colitis prior to initiating antimotility therapy.
  - Be alert to diagnoses such as impaction causing overflow diarrhea, infectious colitis, diarrhea occurring during a neutrophil nadir, graft-versus-host disease, and GI syndrome in patients with colon cancer.

http://www.cancer.gov/cancertopics/coping/chemo-side-effects/constipation
http://www.cancer.gov/cancertopics/coping/chemo-side-effects/diarrhea

CONSTIPATION

Constipation is a common and potentially serious problem in patients with cancer, particularly in later stages of their primary disease. Untreated, it can lead to obstipation, bowel obstruction, and death.

Constipation is defined as a decrease in the frequency of the passage of formed stools and characterized by stools that are hard and difficult to pass. Its prevalence in this population suggests that assessment of bowel function in patients with cancer should be included routinely as part of any patient contact. A recent consensus guideline recommends evaluation for constipation a minimum of every 3 days in persons with advanced illness. Table 26-1 lists common causes of constipation in patients with cancer. Table 26-2 describes important aspects of exam and workup.

Nonpharmacologic Management

Prevention and attention to maintenance are the mainstays of constipation management. Patients in care facilities and inpatients should have standing orders for bowel care. Caregivers and patients at home should have a clearly written regimen for outpatient maintenance of regular bowel movements.

The most effective physical strategy to encourage regular bowel movements combines attention to patient privacy, upright positioning ideally with knees higher than hips to aid angle of egress and Valsalva, and attempting defecation preferably after breakfast to capitalize on the stronger gastrocolic reflex that time of day offers. If appropriate, increased physical activity can be suggested. Estimate intake of fluids and solids and encourage fluids as tolerated. Use of fiber or bulk-forming laxatives with inadequate fluids (<1.5 L per day) can precipitate bowel obstruction and is not recommended in seriously ill patients.

Pharmacologic Management and Opioids

It is widely recommended to begin a daily bowel regimen when opioid therapy is initiated. Polyethylene glycol (PEG; MiraLAX) may be started with opioids, and dose can be titrated to efficacy up to three times daily. A stimulant laxative such as senna or bisacodyl may be needed and can be started in addition to the PEG. Enemas may be started with opioids, and dose can be titrated to efficacy up to three times daily. A stimulant laxative such as senna or bisacodyl may be needed and can be started in addition to the PEG. Enemas may be administered with acute symptoms or impaction but should not be used routinely; if enemas are needed often, titrate the oral regimen more aggressively. Exercise caution or avoid rectal agents in patients with neutropenia or severe thrombocytopenia. Note that docusate is considered ineffective when used as a sole agent.

Intermittent (non-opioid) constipation can be treated...
as discussed earlier as well, with early initiation of PEG and stimulant laxatives when needed. Promotility agents such as metoclopramide and erythromycin can also be considered.

Failing these routine measures, management may include opioid rotation. Transdermal fentanyl and oral methadone are less likely to cause constipation than morphine or hydromorphone. Methadone is a well-absorbed, effective oral opioid with lower incidence of constipation as a side effect. Pharmacist consultation for dosing and titration is recommended for those unfamiliar with methadone’s use; methadone has known effects on cardiac conduction system that require consideration as well.

For opioid-related constipation refractory to standard therapies, opioid antagonists such as naltrexone or methylnaltrexone may be indicated. Methylnaltrexone is U.S. Food and Drug Administration (FDA)—approved in opioid-induced constipation refractory to standard care. Because of its restricted ability to cross the blood–brain barrier, it does not affect analgesic efficacy. It is contraindicated when bowel obstruction is suspected and in cases where integrity of bowel is in question, such as primary gastrointestinal (GI) cancers and ulcers, because there is increased risk of bowel perforation.

Naltrexone is a similar opioid antagonist; however, it can cause reversal of analgesia and carries a risk of hepatotoxicity. Naltrexone can be started at a dose of 0.8 mg twice a day with dose doubling every 2 to 3 days until laxative effects are achieved or dose-limiting reversal of analgesia occurs. See Tables 26-3 and 26-4 for summary listings of medications used in treatment of constipation.

### DIARRHEA

The clinical approach to diarrhea in patients with cancer must include consideration of the patient’s cancer diagnosis, surgical history, current and past chemotherapy, and radiation treatment regimens (Table 26-5). Determination of a cause is a

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**TABLE 26-1**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Malignancy</th>
<th>Metabolic</th>
<th>Neurogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Bowel obstruction</td>
<td>Diabetes</td>
<td>Autonomic neuropathy</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Ogilvie syndrome</td>
<td>Uremia</td>
<td>Cerebral or spinal cord lesions</td>
</tr>
<tr>
<td>TCA’s</td>
<td>Rectal outlet</td>
<td>Hypokalemia</td>
<td>Parkinson disease</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Tumor burden</td>
<td>Hypercalcemia</td>
<td>Intestinal dystrophy</td>
</tr>
<tr>
<td>– Carbamazepine</td>
<td>Previous bowel surgery</td>
<td>Pheochromocytoma</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Poor PO intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Fluids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Fiber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO iron supplements</td>
<td>Food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Reduced activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Vincristine</td>
<td>Radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Cisplatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 26-2**

<table>
<thead>
<tr>
<th>Exam and Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>History:</td>
</tr>
<tr>
<td>*Estimate PO intake, physical activity level, toileting practices (bedpan versus toilet, positioning during defection)</td>
</tr>
<tr>
<td>*Elicit caregiver concerns such as problems with assisting; inquire about home equipment such as bedside commode</td>
</tr>
<tr>
<td>*Current medications, active cancer treatments, and bowel regimen</td>
</tr>
<tr>
<td>*Cancer diagnosis and chemotherapy or radiation treatments</td>
</tr>
<tr>
<td>*Surgical history, history of bowel obstruction</td>
</tr>
<tr>
<td>Abdominal exam:</td>
</tr>
<tr>
<td>*Bowel sounds, distension, area of tenderness, palpable masses</td>
</tr>
<tr>
<td>*Severe constipation can cause obstructive uropathy</td>
</tr>
<tr>
<td>Rectal exam:</td>
</tr>
<tr>
<td>*Avoid if possible in patients with neutropenia</td>
</tr>
<tr>
<td>*Impaction *Tumor</td>
</tr>
<tr>
<td>*Sphincter tone *Perianal skin: fissuring, abscess</td>
</tr>
<tr>
<td>Blood and stool testing:</td>
</tr>
<tr>
<td>*If no clear cause determined for constipation or symptoms are severe, lab work is indicated:</td>
</tr>
<tr>
<td>– Basic metabolic panel (electrolytes, BUN, creatinine, glucose)</td>
</tr>
<tr>
<td>– Complete blood count with differential</td>
</tr>
<tr>
<td>– Calcium and albumin or ionized calcium</td>
</tr>
<tr>
<td>– Thyroid-stimulating hormone</td>
</tr>
<tr>
<td>– Magnesium: especially in renal dysfunction or use of magnesium citrate in patients with gastritis, colitis, proctitis</td>
</tr>
<tr>
<td>*Stool studies for diarrhea include osmotic gap, cultures, fungal organisms, Clostridium difficile assay, hemoccult, leukocytes</td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen.


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**TABLE 26-3**

<table>
<thead>
<tr>
<th>Causes of Constipation in Patients with Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Opioids</td>
</tr>
<tr>
<td>Anticholinergics</td>
</tr>
<tr>
<td>TCA’s</td>
</tr>
<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>– Carbamazepine</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Antiemetics</td>
</tr>
<tr>
<td>PO iron supplements</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
</tr>
<tr>
<td>– Vincristine</td>
</tr>
<tr>
<td>– Cisplatin</td>
</tr>
<tr>
<td>Thalidomide</td>
</tr>
</tbody>
</table>

**TABLE 26-4**

<table>
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<tr>
<th>Exam and Workup</th>
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<tbody>
<tr>
<td>History:</td>
</tr>
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<td>*Bowel sounds, distension, area of tenderness, palpable masses</td>
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<td>*Severe constipation can cause obstructive uropathy</td>
</tr>
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<td>Rectal exam:</td>
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<td>*Avoid if possible in patients with neutropenia</td>
</tr>
<tr>
<td>*Impaction *Tumor</td>
</tr>
<tr>
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</tr>
<tr>
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<tr>
<td>– Magnesium: especially in renal dysfunction or use of magnesium citrate in patients with gastritis, colitis, proctitis</td>
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<tr>
<td>*Stool studies for diarrhea include osmotic gap, cultures, fungal organisms, Clostridium difficile assay, hemoccult, leukocytes</td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen.

# TABLE 26-3  
## Laxative and Enemas

<table>
<thead>
<tr>
<th><strong>Osmotic Laxatives</strong></th>
<th><strong>Dose</strong></th>
<th><strong>Onset</strong></th>
<th><strong>Contraindication</strong></th>
<th><strong>Side Effects</strong></th>
<th><strong>Note</strong></th>
<th><strong>Cost Drugstore.com</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene glycol 3350 (MiraLAX)</td>
<td>17 g PO in 8 oz water qd or up to tid, titrate to efficacy</td>
<td>1–3 d</td>
<td>None</td>
<td>Mild: Bloating</td>
<td>Safe and effective for long-term use</td>
<td>$10 for 15 (17 g) doses of powder</td>
</tr>
<tr>
<td>Lactulose</td>
<td>15–30 mL bid Maximum 60 mL bid</td>
<td>1–2 d</td>
<td>None</td>
<td>Cramps Flatulence Nausea</td>
<td>Use in hepatic encephalopathy. Sorbitol is less nauseating.</td>
<td>$10 for 15 (20 g) doses of solution Rx required</td>
</tr>
<tr>
<td>Magnesium citrate</td>
<td>150–300 mL PO qd</td>
<td>1–6 h</td>
<td>Renal failure, gastritis, colitis, ulcer disease: risk of underexcretion/overabsorption of magnesium Do not use with neuromuscular disease</td>
<td>Cramping Diarrhea</td>
<td>Separate dose from bisphosphonates. Do not use with sorbitol. Can reduce blood levels of mycophenolate</td>
<td>Approximately two 150 mL doses in a 10-oz bottle: $0.72/dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Stimulant Laxatives</strong></th>
<th><strong>Dose</strong></th>
<th><strong>Onset</strong></th>
<th><strong>Contraindications/Warnings</strong></th>
<th><strong>Side Effects</strong></th>
<th><strong>Note</strong></th>
<th><strong>Cost Drugstore.com</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisacodyl</td>
<td>5 or 10 mg tablet PO qd 10 mg PR suppository</td>
<td>15 min to 1 h</td>
<td>Bowel obstruction</td>
<td>Cramping</td>
<td>Tablets cannot be chewed or crushed.</td>
<td>$0.18/tablet $0.25/suppository</td>
</tr>
<tr>
<td>Senna</td>
<td>15 mg PO qd up to maximum 70–100 mg, divided bid</td>
<td>6–12 h</td>
<td>Bowel obstruction</td>
<td>Cramping</td>
<td>Liquid formulation can be mixed with juice.</td>
<td>$0.18/25-mg tablet $0.22/8.6-mg tablet dose</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10 mg PO up to qid, 30 min prior to meals and at bedtime Renal dosing applies</td>
<td>30–60 min</td>
<td>Bowel obstruction, perforation, hemorrhage, peptic ulcer; history of seizures Can cause AV block, bradycardia</td>
<td>Cramping Acute dystonic reaction Extrapyramidal symptoms Parkinsonian-like symptoms</td>
<td>Consider limiting use to 8–12 wk; risk of tardive dyskinesia</td>
<td>$13 for quantity 30 generic tablets $15 for 240 mL of 5 mg/5 mL solution</td>
</tr>
<tr>
<td>Erythromycin (base)</td>
<td>125–250 mg PO tid to qid May require initial IV dose</td>
<td>Varies with formulation</td>
<td>Allergy to macrolides QTc prolongation or patients at risk for abnormal cardiac repolarization Do not use with cisapride, pimozide, ergotamine, dihydroergotamine, terfenadine, astemizole</td>
<td>Abdominal pain, cramping Risk of pseudomembranous colitis/ Clostridium difficile infection</td>
<td>Multiple drug interactions, including chemotherapeutics; recommend pharmacist consultation</td>
<td>Erythromycin base: $65 for 30 tablets of 250 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Enemas</strong></th>
<th><strong>Dose</strong></th>
<th><strong>Onset</strong></th>
<th><strong>Contraindications</strong></th>
<th><strong>Side Effects</strong></th>
<th><strong>Note</strong></th>
<th><strong>Cost per Enema Drugstore.com</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate (fleet)</td>
<td>1 bottle (4.5 oz) PR</td>
<td>1–5 min</td>
<td>Renal disease Megacolon Heart failure Bowel obstruction</td>
<td>Diarrhea Electrolyte disturbance Mucosal irritation</td>
<td>Not recommended PO; risk of electrolyte disturbances</td>
<td>$2.99/one-dose bottle</td>
</tr>
<tr>
<td>Lubricant – Mineral oil</td>
<td>60–100 mL PR</td>
<td>Up to 1 h</td>
<td>Ulcerative colitis Diverticulitis Colostomy</td>
<td>Anal leakage of oil Mucosal irritation</td>
<td>Not recommended PO</td>
<td>$2.99/one-dose bottle</td>
</tr>
<tr>
<td>Osmotic – Sorbitol</td>
<td>120 mL as 20%–30% solution PR</td>
<td>¼ to 1 h</td>
<td>Avoid concomitant use of magnesium-containing laxatives.</td>
<td>Mucosal irritation</td>
<td></td>
<td>473 mL of 70% solution: $18.00.</td>
</tr>
<tr>
<td>Irritants – Soap suds – Tap water</td>
<td>500–1,000 mL PR</td>
<td>1–5 min</td>
<td></td>
<td>Epithelial cell damage</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>
## TABLE 26-4  Opioid Antagonists

<table>
<thead>
<tr>
<th>Opioid Antagonists</th>
<th>Dose</th>
<th>Onset</th>
<th>Contraindications</th>
<th>Notes</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylnaltrexone[^30] (FDA approved for opioid-induced constipation)</td>
<td>Maximum one dose per 24 h Dosing is weight based Renal dosing applies</td>
<td>30–60 min in patients who respond</td>
<td>Rule out bowel obstruction Risk of GI perforation Do not use in patients with impaired bowel wall: Ogilvie syndrome, tumor, or ulcers</td>
<td>Only for use in opioid-related constipation refractory to usual treatments, in patients with advanced illness</td>
<td>High</td>
</tr>
<tr>
<td>Naltrexone[^8] (Not FDA approved for opioid-induced constipation)</td>
<td>Start: 0.8 mg PO bid Titrate: Double dose every 2–3 d until laxation or reversal of analgesia[^1] Formulation: can be compounded from 50-mg tablets at compounding pharmacies into capsule or liquid</td>
<td>Black box warning for hepatic impairment</td>
<td>Only for use in opioid-related constipation refractory to usual treatments, in patients with advanced illness</td>
<td>50 mg tablet, 30 each is $103.99</td>
<td></td>
</tr>
</tbody>
</table>

[^30]: FDA, U.S. Food and Drug Administration; GI, gastrointestinal; bid, twice a day.

## TABLE 26-5  Possible Contributions to Diarrhea in Cancer

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid syndrome</td>
<td>Celiac plexus block</td>
<td>Capecitabine, cisplatin, cytosine arabinoside, cyclophosphamide, daunorubicin, docetaxel, doxorubicin, 5-fluorouracil, interferon, irinotecan, leucovorin, methotrexate, oxaliplatin, paclitaxel, topotecan, lopatinib</td>
<td>Irradiation to the abdomen, para-aortics, lumbar, and pelvis</td>
<td>Conditioning chemotherapy, total body irradiation, graft-versus-host disease after allogeneic bone marrow or peripheral blood stem cell transplants</td>
<td>Antibiotics, magnesium-containing antacids, antihypertensives, colchicine, digoxin, iron, lactulose, laxatives, methyldopa, metoclopramide, misoprostol, potassium supplements, propranolol, theophylline</td>
<td>Diabetes, hyperthyroidism, inflammatory bowel disease (Crohn disease, diverticulitis, gastroenteritis, HIV/AIDS, ulcerative colitis), obstruction (tumor-related)</td>
<td>Clostridium difficile, Clostridium perfringens, Bacillus cereus, Giardia lamblia, Cryptosporidium, Salmonella, Shigella, Campylobacter, Rotavirus</td>
<td>Constipation leading to obstruction</td>
<td>Alcohol, milk, and dairy products (particularly in patients with lactose intolerance)</td>
<td>Stress</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Cholecystectomy, esophagogastrectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Gastrectomy, pancreaticoduodenectomy (Whipple procedure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medullary carcinoma of the thyroid</td>
<td>Intestinal resection (malabsorption due to short bowel syndrome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer, particularly islet cell tumors (Zollinger-Ellison syndrome)</td>
<td>Vagotomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^5,18]: Numbered citations in table available at NCI website.

Note: Reproduced from the website of the National Cancer Institute (http://www.cancer.gov).
part of assessment and management; however, the underlying pathophysiology may be multifactorial, with potentially several types of diarrhea present.1,9

Because serious consequences such as dehydration and electrolyte imbalance can develop rapidly and because patients undergoing active treatment may be immunologically vulnerable, in-office evaluation should be prompt and thorough. If admission is not indicated, a well-organized follow-up plan must be communicated clearly to patients and caregivers. It is also important to recognize the emotional distress and caregiving burden associated with severe diarrhea. Printed materials designed to help with self-monitoring, such as patient diaries or logs, as well as repeat counseling during office visits and via telephone are important parts of outpatient management.10

Diarrhea identified as grade 1 or 2 (Table 26-6 for grading scale) without complicating symptoms can be managed closely in the outpatient setting. Initial nonpharmacologic management is composed of discontinuing inciting foods, drinks, and medications where appropriate, along with hydration and dietary recommendations.11 Selected over-the-counter antidiarrheals may be employed and response to treatment monitored. See Table 26-7 for a list of antidiarrheal agents.

### Skin Care

Skin care can be addressed with a barrier cream, ointment, or paste. In cases of incontinence or severe diarrhea, a paste formulation is preferred.12 The paste is superior because ointments and creams tend to come off the skin and onto diaper/garments, thereby creating a less absorptive surface to the diaper with reduced skin protection. The paste is more likely to remain on the skin and does not need to be removed completely with each change: After cleansing area with gentle soap, it can be replaced where needed and over existing paste.

### Enteral Feeding

Enteral feeding has been associated with diarrhea, whether by nasogastric tube, gastrostomy, or jejunostomy.13,14 Formula contamination is commonly the cause and can be addressed with better hand washing prior to handling feeding equipment, changing bag and tubing daily, refrigerating formula, and decreasing the amount of time that the formula hangs unrefrigerated.3 Delivery rate and high formula osmolality may also affect stool frequency.15

### Cancer Treatment–Induced Diarrhea

Chemotherapeutics are common culprits in patients being actively treated and can have acute or delayed presentations. In persons receiving radiation therapy, diarrhea may be acute or occur months or years after treatment. Patients being treated with irinotecan, fluorouracil, and leucovorin for metastatic colon cancer are at greater risk to develop what is described by Benson et al.11 as a GI syndrome, characterized by severe cramping and diarrhea, nausea, anorexia, and vomiting. Early aggressive management of any diarrheal symptoms and prompt notification of the patient’s oncologist is indicated for patients on these regimens. The National Cancer Institute has developed a grading scale (see Table 26-6) to define the severity of diarrhea in patients with cancer.

Neutropenic enterocolitis and graft-versus-host disease (GVHD)–related diarrhea are particularly worrisome adverse events associated with chemotherapy and hematopoietic stem cell transplant, respectively. These represent severe complications of cancer treatment and warrant mention here.

### Neutropenic Enterocolitis

Neutropenic enterocolitis is a complication that usually occurs when absolute neutrophil count is less than 500 cells per microliter. Presenting symptoms may include fever, nausea, diarrhea, vomiting, and abdominal pain (diffuse or localized right lower quadrant [RLQ]); sepsis is not uncommon.9 Abdominal pain may not be present, particularly if the patient has been on steroids.9 The preferred imaging modality for diagnosis is CT scan of abdomen and pelvis.9 Abdominal plain films may show dilation and edema of bowel walls and pneumatosis intestinalis. If neutropenic enterocolitis is suspected, hospitalization for IV fluids, antibiotics, and supportive care is indicated with prompt notification of the patient’s oncologist.

### Graft-Versus-Host Disease

The first sign of GVHD is often a characteristic skin rash: Described as maculopapular, it can be edematous or bullous in appearance with pain or pruritus, starting on nape of neck, spreading to ears, shoulders, and may include palms and soles.9 GI involvement includes diarrhea with cramping abdominal pain. Diarrhea may be profuse (exceeding ≥2 L per day) with severe volume depletion, electrolyte derangement, and, in some cases, hemorrhage requiring transfusion.9 Liver function testing may show an elevated alkaline phosphatase and conjugated hyperbilirubinemia. Diagnosis can be made clinically from signs and symptoms discussed earlier and by rectal biopsy.1 Hospitalization and prompt notification of the patient’s oncologist is indicated.
<table>
<thead>
<tr>
<th>Name</th>
<th>Dose/Route</th>
<th>Contraindication</th>
<th>Adverse Effects/Notes</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotics</td>
<td></td>
<td>Severe immunocompromise, risk of sepsisemia</td>
<td>Abdominal discomfort (mild)</td>
<td><a href="http://www.consumerlab.com">www.consumerlab.com</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caution with short-gut syndrome</td>
<td>Flatulence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Considered safe and effective for prevention and treatment of infectious and antibiotic-associated diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth</td>
<td>Dose</td>
<td>Allergy to subsalicylate</td>
<td>Subsalicylate-containing preparations, caution if on aspirin</td>
<td>Pepto, Kaopectate,</td>
</tr>
<tr>
<td>Pepto-Bismol</td>
<td>Per package instructions</td>
<td>Concurrent influenza or varicella infection because of risk of Reye syndrome</td>
<td>Dose the tetracyclines 2 h before or 6 h after bismuth dose.</td>
<td>multiple formulations</td>
</tr>
<tr>
<td>Kapectate (various</td>
<td></td>
<td>History of GI bleeding or coagulopathy</td>
<td></td>
<td>Tablet, suspension</td>
</tr>
<tr>
<td>formulations)</td>
<td></td>
<td></td>
<td></td>
<td>Readily available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loperamide</td>
<td>4 mg initial dose followed by</td>
<td>Ileus</td>
<td>High dose: may induce ileus that can be life threatening in face of continued secretion</td>
<td>FDA approved</td>
</tr>
<tr>
<td></td>
<td>2 mg q4h or after loose stool</td>
<td>Clostridium difficile colitis</td>
<td></td>
<td>$4–$6 for 18 tablets,</td>
</tr>
<tr>
<td></td>
<td>up to 16 mg/day, continue until</td>
<td>Infection with enterotoxin-producing bacteria</td>
<td></td>
<td>generic drugstore.com</td>
</tr>
<tr>
<td></td>
<td>diarrhea free for 12 h</td>
<td>Acute ulcerative colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>More aggressive: 4 mg followed</td>
<td>Rule out obstruction-related overflow diarrhea.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>by 2 mg q2h or 4 mg q4h until</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diarrhea free for 12 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenoxylate</td>
<td>Diphenoxylate 5 mg qid</td>
<td>Obstructive jaundice <em>C. difficile</em> colitis</td>
<td>May enhance effect of anticholinergic medications:</td>
<td></td>
</tr>
<tr>
<td>(Lomotil)</td>
<td>until control achieved</td>
<td>Infection with enterotoxin-producing bacteria</td>
<td>Monitor for atropinism—dry skin and mucous membranes, flushing, and tachycardia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(maximum: 20 mg/day)</td>
<td>Caution: Renal impairment</td>
<td>Monitor therapy closely for hypotension, respiratory depression.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduce dose as needed; some</td>
<td>Hepatic impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>patients achieve control on</td>
<td>Ulcerative colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>doses of 5 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discontinue if no response after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48 h of therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Use in bile acid malabsorption as</td>
<td>Ileal resection &gt;100 cm</td>
<td>Multiple GI side effects: abdominal pain, biliary colic, duodenal ulcer bleeding, dys-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in patients with ileal resection</td>
<td>Complete biliary obstruction</td>
<td>phagia, pancreatitis, rectal pain, steatorrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of &lt;100 cm</td>
<td>Separate doses from other meds, recommend pharmacist review, especially if the</td>
<td>Long-term therapy may require supplementation of vitamins A, D, E, K; folic acid; and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Start 4 g qd to bid, doses</td>
<td>patient is on cardiac medicines</td>
<td>iron.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mixed in 60–180 mL water</td>
<td></td>
<td>Must drink 60–180 mL liquid with each dose, may also mix in applesauce or crushed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase gradually.</td>
<td></td>
<td>pineapple.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum 24 g/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deodorized tincture</td>
<td>10–15 drops (of 10 mg/mL solution)</td>
<td>Hypersensitivity to morphine or opioids</td>
<td>Note: Care must be taken not to confuse this medication with paregoric (camphorated</td>
<td></td>
</tr>
<tr>
<td>of opium (anhydrous</td>
<td>in water q4h</td>
<td>Absorption is variable; monitor for sedation</td>
<td>tincture of opium). Paregoric is 25 times less potent and is dosed differently.</td>
<td></td>
</tr>
<tr>
<td>morphine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide</td>
<td>100–150 μg subcutaneous tid, up</td>
<td>Hypersensitivity or history of allergy to octreotide</td>
<td>Second line to loperamide</td>
<td></td>
</tr>
<tr>
<td>Consult oncology</td>
<td>to 500 μg subcutaneous tid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>maximum dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravenous: consult GI Oncology</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 26-7** Antidiarrheal Agents

*CFU, colony-forming unit; GI, gastrointestinal; q, every; FDA, U.S. Food and Drug Administration; qid, four times a day; qd, every day; bid, twice a day; tid, three times a day; CID, chemotherapy-induced diarrhea; GVHD, graft-versus-host disease.*

Adapted from Lexi-Comp. Drug information. In: Basow DS, ed. UpToDate. Waltham, MA: UpToDate; 2012; and Drugstore.com, 2012, for pricing.

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References


Dyspnea can be thought of as an “uncomfortable sensation of breathing.” It is a very common symptom that is distressing for both patients and their caregivers. See Table 27-1 for the multitude of terms patients use to describe the sensation of dyspnea. Prevalence ranges from 21% to 71% in all patients with cancer and up to 90% in patients with advanced lung cancer. It is often rated by patients with cancer as their most bothersome symptom.

Dyspnea is a subjective sensation. It may or may not correlate with physical exam findings, oxygen saturation, spirometry, or laboratory values. Although the production of dyspnea involves various physiologic pathways, the perception of dyspnea can be modulated by such factors as psychological distress, anxiety, and pain. Dyspnea has a strong negative correlation with patient satisfaction with quality of life in advanced cancer and has been described as an independent predictor in the will to live.

**PHYSIOLOGY OF DYSPNEA**

The physiology of dyspnea is generally believed to involve the central respiratory center, chemoreceptors and mechanoreceptors, and respiratory muscles (Fig. 27-1). The central respiratory center mediates automatic respiration. Neurons in the medulla receive information from central and peripheral receptors as well as from the cerebral cortex, which is responsible for the actual sensation of dyspnea. Efferent neurons of the central respiratory center stimulate the muscles of respiration, which results in inspiration and expiration.

The receptors that stimulate the central respiratory center are located both peripherally and centrally. Central chemoreceptors in the medulla are stimulated by subtle changes in blood pH and P\textsubscript{CO\textsb{2}}. Peripheral chemoreceptors located on the carotid and aortic bodies respond to more dramatic changes in P\textsubscript{O\textsb{2}}. Also located in the periphery are chest wall and lung mechanoreceptors, which are stimulated by air irritants and stretch.

The muscles of respiration consist of the diaphragm, intercostal muscles, and accessory muscles. These muscles are responsible for promoting gas exchange. Fluctuations in P\textsubscript{CO\textsb{2}} and P\textsubscript{O\textsb{2}} stimulate the central and peripheral chemoreceptors. Respiratory muscles also produce tension, which stimulates the peripheral mechanoreceptors. The physiologic production of dyspnea results from abnormalities in this complex peripheral and central system.

**ASSESSMENT**

The assessment of dyspnea begins with a thorough patient history, including the severity of the symptom using simple scales such as “mild, moderate, or severe”; numeric severity scores from 0 to 10; a visual analogue scale (VAS); and the Edmonton Symptom Assessment System (ESAS). Patients should be asked to describe the extent to which their dyspnea impairs their function and quality of life. Other associated symptoms should also be elicited, including pain, anxiety, depression, cough, pleuritic chest pain, peripheral edema, etc.

Physical exam findings do not always correlate well with the patient’s description or experience of dyspnea. Exam findings may include tachypnea, use of accessory muscles, pursed lips, leaning forward, wheezing, crackles, or hypoxemia. Pulmonary function testing can be helpful in determining the extent and reversibility of an obstructive airway disease; however, these tests do not tend to correlate well with severity of symptoms. Further assessments should be made based on the patient’s history, exam, and his or her desire to pursue a diagnosis or treatment. Pertinent laboratory findings may include brain natriuretic peptide (BNP) for the assessment of congestive heart failure (CHF) or complete blood count (CBC) to rule out anemia.
TABLE 27-1  Patient Descriptions of the Sensation of Dyspnea

<table>
<thead>
<tr>
<th>Difficulty breathing</th>
<th>Heavy</th>
<th>Requires work/effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short of breath</td>
<td>Uncomfortable</td>
<td>Chest feels constricted</td>
</tr>
<tr>
<td>Cannot breathe</td>
<td>Smothering</td>
<td>Rapid</td>
</tr>
<tr>
<td>Cannot take a deep breath</td>
<td>Suffocating</td>
<td>Breathing more</td>
</tr>
<tr>
<td>Cannot take a full breath</td>
<td>Cannot get enough air</td>
<td>Shallow</td>
</tr>
<tr>
<td>Labored</td>
<td>Out of breath</td>
<td>Does not go in all the way</td>
</tr>
<tr>
<td>Tight</td>
<td>Hunger for air</td>
<td>Does not go out all the way</td>
</tr>
</tbody>
</table>


Certain radiographic tools may be very helpful in determining whether a patient’s dyspnea is secondary to a cause that may be amenable to specific treatment. Chest X-ray is often the first study performed and may reveal an infiltration, hyperinflated lungs, or a large mass. Further studies such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) may be warranted based on X-ray findings or clinical suspicion. See Table 27-2 for a list of many of the etiologies of dyspnea in cancer with diagnostic approaches and options for treatment.

Pleural Effusion

A standard chest X-ray is also the first radiographic study performed in the assessment of pleural effusion. As little as 50 mL of pleural fluid can be detected on lateral view. A CT is often subsequently warranted to distinguish malignant from benign pleural disease. Further studies such as MRI or PET have even higher sensitivity and specificity for distinguishing malignant from benign disease. Various factors will determine the need for further testing, including the impact of the effusion on the patient’s quality of life; the type, stage, and availability of treatment of his or her underlying cancer; the impact of biopsy on staging; and the patient’s preferences for treatment of the effusion and the cancer.

The diagnostic test of choice is an ultrasound-guided thoracentesis, with pleural fluid sent for cell count, chemical analysis, and cytology. Unfortunately, the diagnostic yield of cytologic testing can be as low as 60%; therefore, when cytology is negative but malignant pleural effusion is suspected, a pleural biopsy, which has a diagnostic yield as high as 100%, may also be indicated. Patients with cancer may have a pleural effusion from a cause completely unrelated to their cancer, such as tuberculosis, heart or liver failure, or a rheumatologic disease. Additionally, patients with cancer may develop paramalignant effusions because of local and systemic effects of tumor or complications of therapy (Table 27-3). A paramalignant effusion does not contain malignant cells but is a result of malignancy, often from lymphatic obstruction. A large volume thoracentesis may be performed for both diagnostic and therapeutic purposes and may be helpful in determining the effect of removing the pleural fluid on the patient’s dyspnea.

TREATMENT

The treatment of dyspnea should be undertaken with careful consideration of the patient’s goals of care. A patient
with treatable disease and a good prognosis may be willing to undergo repeated invasive and uncomfortable procedures, whereas a patient with advanced disease and a very poor prognosis may wish to focus only on symptomatic treatment. Of course, the reverse may also be true. Treatment of other symptoms such as pain, depression, and anxiety may also improve dyspnea.

**TREATMENT OF SPECIFIC CAUSES**

Many of the causes of dyspnea may be treated with little burden to the patient and may significantly improve function and quality of life. For example, pneumonia may be treated with appropriate antibiotics. Pulmonary embolism can be managed with anticoagulation and/or embolectomy. Chronic obstructive pulmonary disease (COPD) and asthma should be optimally treated with bronchodilators and inhaled or systemic steroids. CHF should be managed with diuretics and antihypertensives. Patients with anemia may benefit from blood transfusions or erythropoietin based on etiology and patient goals. Refer to Table 27-2 for a more comprehensive list of management options for dyspnea in cancer.

**Direct Tumor Involvement**

Primary tumor or metastasis may cause dyspnea by obstruction of the central airway, vascular obstruction, postobstructive pneumonia, or pleural effusion. In many cases, treatment of the primary cancer can help alleviate dyspnea. Treatments include surgical resection of the tumor, which is the primary treatment of early-stage lung cancer. Endoscopic intervention with dilation and/or stent placement may help alleviate a central airway obstruction. Dyspnea caused by tumor obstruction of the upper airway can also be treated with high-dose corticosteroids. Case reports have shown dramatic reductions in stridor and dyspnea with dexamethasone 10 mg intravenously every 6 hours or methylprednisolone 125 mg intravenously every 6 hours. Steroids may also be helpful for patients with carcinomatous lymphangitis, radiation pneumonitis, and superior vena cava syndrome.

Chemotherapy can be particularly helpful in reducing the size of symptomatic lymphangitic tumors. Numerous studies have also demonstrated immediate symptomatic benefits of chemotherapy in non–small cell lung cancer. Unfortunately, dyspnea can also be caused by chemotherapeutics such as bleomycin, whose classic side effect is pulmonary fibrosis. Radiotherapy is often used in association with chemotherapy to improve symptoms of lung cancer or metastatic disease.

As with chemotherapy, however, radiotherapy can cause lung toxicity such as radiation pneumonitis and fibrosis.

**Malignant Pleural Effusion**

Management of a malignant pleural effusion is considered palliative because it has not been shown to improve survival. Therefore, a patient with a small or mildly symptomatic effusion may choose not to undergo invasive therapeutic interventions. Large pleural effusions are often quite distressing, however, and even a patient whose goal is for comfort measures only may elect intervention to treat an effusion. The initial treatment of a malignant pleural effusion is therapeutic thoracentesis. Unfortunately, in 98% to 100% of cases, pleural fluid reaccumulates within 30 days. Repeated thoracenteses may result in adhesions, loculations, and infection and are therefore most appropriate for patients with very short life expectancy or with very slowly reaccumulating effusions.

Additionally, repeated thoracenteses tend to be symptom driven and are therefore typically performed on an urgent basis, putting increased strain on patients, their caregivers, and their health care providers.

For patients with life expectancy longer than 2 to 3 months, there are three major treatment options: chest tube drainage with chemical pleurodesis, video-assisted thoracoscopic surgery (VATS), and an indwelling pleural catheter. Chest tube drainage with pleurodesis is an inpatient procedure performed by a thoracic surgeon. Talc is the most commonly used sclerosing agent and is generally well tolerated. However, the use of talc has been associated with the development of acute respiratory distress syndrome (ARDS). One series reported respiratory failure in as many as 9% of patients receiving talc pleurodesis. VATS usually involves freeing collections of fluid followed by pleurodesis with a sclerosing agent. Thoracoscopic surgery also tends to be well tolerated with a low perioperative mortality rate of <0.5%; major complications include empyema, ARDS, and pulmonary edema. There is no significant data demonstrating an advantage of thoracoscopic surgery with pleurodesis over chest tube drainage with pleurodesis. Both procedures require a week or more of hospitalization and have relatively high success rates. The data on chest tube drainage with pleurodesis reveals a 21% rate of recurrence of effusion. A separate study found the recurrence rate after thoracoscopic surgery with pleurodesis to be 18%.

Placement of a long-term indwelling pleural catheter may be a superior therapeutic option for patients with trapped lung effusions.
for whom successful pleurodesis is not possible, for those with significant surgical risk, and especially for those with short life expectancy. It is typically an outpatient or short-stay procedure, making it preferable for patients wishing to avoid prolonged hospitalization near the end of life. One study shows similar outcomes in improvement of symptoms and quality of life of indwelling pleural catheter compared to chest tube drainage with pleurodesis. The same study reveals that indwelling catheters have a lower rate of effusion recurrence compared to chest tube drainage with pleurodesis (13% compared to 21%) but a higher rate of complication, most commonly, local cellulitis. Patients and their caregivers can be trained to manage symptoms at home by performing pleural drainage when the patient develops dyspnea.

**PHARMACOLOGIC TREATMENT**

**Opioids**

For the symptomatic treatment of cancer-related dyspnea, opioids remain the most effective pharmacotherapy of choice. When used judiciously and systematically, opioids are a safe and efficacious treatment for dyspnea in advanced disease. Several recent studies have found no increased risk of respiratory depression when using low-dose opioids for the symptomatic relief of dyspnea.

Morphine is the most commonly used opioid for the symptomatic treatment of dyspnea, although different opioids are often used based on allergies, intolerances, comorbidities, and patient and provider preference. Dosing for dyspnea is similar to that for pain, with relief of symptoms lasting approximately 4 hours in the case of short-acting oral morphine. A common starting dose for a patient who is opioid naïve is 5 mg of short-acting oral morphine given every hour as needed according to oral morphine’s time to maximal concentration. For patients already taking opioids for pain, a 25% increase in their baseline opioid dose is a reasonable starting point for treating dyspnea. Once an effective 24-hour opioid dose has been established, it can be converted into a long-acting dose for baseline treatment of symptoms. Short-acting doses should still be given for breakthrough symptoms—usually around 10% of the 24-hour long-acting dose—with dosing intervals based on the drug’s time to maximal concentration.

The efficacy of nebulized opioids continues to be studied. Most controlled studies and meta-analyses to date have been small but have found nebulized opioids to be no more effective than subcutaneous opioids in the treatment of dyspnea. However, because opioid receptors are abundant in the lung and nebulized opioids produce minimal systemic effects, the use of nebulized opioids for the treatment of dyspnea remains a hopeful but controversial field of study.

**Benzodiazepines**

It seems intuitive that because anxiety is often involved in the perception of dyspnea, benzodiazepines alone would be an effective pharmacotherapy for treating dyspnea. However, a systematic review found that of the few controlled trials that have studied the use of benzodiazepines in dyspnea, none detected a significant reduction in dyspnea compared with placebo. Although there is little to no evidence to support the use of benzodiazepines as a first-line agent for the treatment of dyspnea, they may be safe and effective when used in combination with opioids. A recent prospective randomized trial found that the combination of around-the-clock morphine and midazolam together was superior to the use of around-the-clock morphine alone or around-the-clock midazolam alone for the treatment of severe dyspnea.

**Oxygen**

In patients with both COPD and hypoxemia, supplemental oxygen has been shown to improve survival, exercise capacity, dyspnea, and quality of life. The evidence for oxygen in cancer-related dyspnea, however, is less certain. Several randomized controlled trials and systematic reviews have been performed on this topic, and the consensus is that supplemental oxygen only improves dyspnea in patients with cancer who are moderately to severely hypoxic. There are some patients, however, who perceive a decrease in dyspnea with the use of a nasal cannula despite having normal blood oxygen levels. For example, a recent double-blind crossover study found that patients with advanced cancer and dyspnea had equally improved dyspnea scores with either oxygen or room air administered via nasal cannula.

**NONPHARMACOLOGIC MANAGEMENT**

A recent Cochrane review found varying levels of evidence to support the use of nonpharmacologic modalities in the treatment of dyspnea in advanced stages of malignant and nonmalignant diseases. Moderate-to-high strength of evidence was found for neuroelectrical muscle stimulation, chest wall vibration, walking aids, and breathing training; however, most of the participants in these studies had COPD and none had cancer-related dyspnea. Small studies have shown that moving room air across the face using a fan or nasal cannula may be helpful in reducing the sensation of dyspnea. Other promising modalities for cancer-related dyspnea come mostly from the lung cancer literature and include nursing interventions such as counseling, breathing training, relaxation techniques, and psychosocial support. An individually tailored nurse-led program appears to be the most successful psychosocial approach to relieving dyspnea.

**References**


CHAPTER 28
Fatigue, Depression, and Anxiety

David Spiegel, MD • Michelle B. Riba, MD, MS • Thomas L. Schwenk, MD

KEY POINTS

• Cancer may be viewed as a trauma—an acute stress disorder (ASD) or posttraumatic stress disorder (PTSD).
• The psychiatric conditions in cancer include depression, anxiety (panic, PTSD, phobias), adjustment disorders, and delirium.
• The specific choice of an antidepressant medication is especially important for patients with cancer treated with tamoxifen because of metabolic genotypic issues.
• Adaptive coping in cancer may be divided into three types: information focused, emotion focused, and problem focused.
• There are several psychotherapies and pharmacotherapies that are useful including cognitive behavioral therapy, group therapy, mindfulness and coping skills training, individual psychotherapy, and electronic technology–based interventions.

ASSESSING PSYCHOSOCIAL PROBLEMS

A wide range of psychiatric and psychological problems affect patients and families before, during, and after cancer care and treatment. Studies in adults treated in outpatient cancer clinics and into survivorship demonstrate that 40% to 50% of patients with cancer experience clinically relevant levels of distress.1,2 Psychiatric assessment is complicated by the fact that many physical symptoms of cancer and its treatments overlap with symptoms that are common in many psychiatric conditions.

Understanding Cancer as a Trauma

In the initial stages of diagnosis and early treatment, the use of the term acute stress disorder (ASD) or posttraumatic stress disorder (PTSD) may best encapsulate the psychological problems that occur. In one study of patients with breast cancer after treatment, 5% to 10% met full diagnostic criteria for PTSD,3 and there was little change in their status over the ensuing year.4 As patients move through the various stages of cancer care, so too does the response to trauma—from acute stress to more chronic PTSD.5–7

Common Psychiatric Disorders

Although there are many psychiatric disorders that occur in patients with cancer, the more commonly diagnosed are depression, anxiety (panic, PTSD, phobias), adjustment disorders, and delirium. Patients may have cognitive changes related to the underlying cancer or to the chemotherapeutic agents with some regimens altering the efficiency with which the brain processes information storage and retrieval.8

Screening for Psychological Problems

There are numerous screening tools that are available for clinical as well as research purposes.9–12 The National Comprehensive Cancer Network developed a tool for patients to mark their level of distress on a visual analog: the distress thermometer (Fig. 28-1). Psychosocial screening provides an opportunity to determine baseline distress and then prospectively evaluate response to psychosocial treatments.13

Coping

Moos and Schaeffer14 summarize coping challenges as the need to preserve reasonable emotional balance, maintain a sense of competence and mastery, sustain relationships with family and friends, and prepare for an uncertain future. Previous coping strategies may no longer be appropriate or productive.15–18 Adaptive coping has been divided into three types: information focused, emotion focused, and problem focused.19,20 Some studies have shown that avoidance strategies may be less adaptive in the long run than task-oriented and approach strategies,16,21 although coping is situation specific and patient specific.22,23 Adaptive coping skills are critical for facing these situations, including facing rather than fleeing, altering perception, coping actively, expressing emotion, and mobilizing social support (Table 28-1).

Survivorship

Survivorship is becoming an increasingly important aspect of comprehensive cancer care and primary care practice as cancer survival improves. There are now some 12 million survivors...
of cancer in the United States. Provision of supportive services should continue after active oncologic treatment is completed. Domains of intervention include surveillance for recurrence and dealing with anxiety about potential recurrence; surveillance for the late effects of treatment such as cardiotoxicity and second cancers; genetic issues such as the implications for children; overall health maintenance and reducing lifestyle risks unrelated to the original cancer such as smoking, obesity, and diabetes; attention to psychiatric, social, behavioral, and financial problems; and other factors that affect quality of life.

TREATMENT INTERVENTIONS

Psychosocial

The appropriate treatment for psychological symptoms associated with cancer can be determined by clarifying the nature of emotional distress, the use of pharmacotherapy to relieve acute and chronic symptoms, and the selection of appropriate psychosocial interventions for treating problems related to anxiety, depression, existential concerns, somatic symptoms, and social or communication problems.

The efficacy of psychosocial treatments for depression and anxiety in patients who are medically ill, particularly brief psychodynamic, educational, supportive, and interpersonal therapies; hypnosis; and behavioral and cognitive behavioral methods, has been supported by numerous outcome studies.

Psychoeducational Interventions

Medical knowledge enhances the sense of control and mastery a person has over his or her disease, and educational interventions generally yield positive outcomes. Interventions for medical patients are usually more effective when they provide cues for using the knowledge related to their disease and daily management or with some emotion-focused components, which helps them to adjust and live through the different phases of the illness. Anticipatory guidance is an important component of these interventions, helping patients to prepare to respond to future as well as current disease-related problems. The evaluation of outcomes of psychoeducational interventions indicates consistent if modest improvement.
Coping Skills Training

Education-based group interventions that provide informational support can facilitate the initial adjustment of patients with early-stage breast cancer by improving self-esteem, body image, and perceived control and by reducing uncertainty about the illness. One cognitive behavioral stress management group program proposed a multimodal type of intervention combining 20 hours of therapy focused on relaxation training, coping skills training, cognitive restructuring, assertiveness and anger management training, and social support for women with breast cancer. Patients improved in self-reports of their ability to identify how having cancer had contributed to their lives and in general optimism, but no improvement on the distress measures was found. In this study, the greatest changes in positive benefits were reported by women who were low in optimism. An eight-session educational intervention, providing training in stress management, problem solving, goal setting, and assertiveness, produced improvements in general quality of life as well as specific competence in managing emotional, financial, and legal problems.

Mindfulness Training

Mindfulness-based stress reduction is an adaptation of Zen Buddhist meditation techniques taught in weekly courses. The focus is on enhancing the ability to live in the moment and to tolerate stresses as real but transient phenomena while more comfortably relating to one’s body. Such techniques have been used to good effect with patients with cancer. A meta-analysis of 10 studies documented a significant (moderate effect size $d = .48$) overall improvement in quality of life and possible benefit for various aspects of physical health. Other studies have shown that a combination of such techniques with more traditional group therapy produced reductions in intrusive thinking and other posttraumatic stress symptoms as well as reduced depression and fear of recurrence and produced higher energy among women with breast cancer. Such intervention has also been shown to result in lower cortisol, reduced T-helper cell 1 (Th1) (proinflammatory) cytokines, and lower systolic blood pressure, as well as improved natural killer cell cytotoxicity.

Cognitive Behavioral Therapy

The cognitive behavioral approach is built on the assumption that previous social learning, developmental history, and significant experiences lead people to form a unique set of meanings and assumptions, or cognitive schemas, about themselves, the world, and their future. These schemas are then used to organize perception and to govern and evaluate behavior. When specific schemas are activated, they directly influence the content of a person’s perceptions, interpretations, associations, and memories from a given time. Cognitive behavioral therapy (CBT) was developed as a short-term (12 to 20 sessions) intervention for depression, targeting patients’ thoughts and their relation to behavior and affect. CBT for patients with cancer generally features a multicomponent intervention incorporating coping skills training, stress management, and an intervention designed to enhance cognitive and behavioral processes that will be useful in adjusting to illness. The efficacy of CBT as a treatment for depression is well established. A review of empirically supported treatments for psychosomatic disorders determined that CBT is efficacious for chronic pain management and some cancers.

Group Psychotherapy

Group intervention in various forms has become an increasingly popular, effective, and efficient means of providing psychosocial support for patients with cancer. Groups of different types may encompass theoretical approaches that include the psychodynamic, supportive expressive, existential, educational, and cognitive behavioral, among others. Factors associated with reluctance to join include less favorable views of such groups, feeling less control over their cancer, using less active coping styles, and having less distress. Although men may initially be more reluctant than women to openly discuss emotional problems relating to cancer, cognitive aspects of coping can be a good starting point, and men with prostate cancer report information sharing with other patients as a helpful aspect of group experience. Clinical trials have demonstrated the benefit of group therapy for patients with breast cancer, with notable reductions in pain and emotional distress. A systematic review of the literature that included two meta-analyses and nine well-designed randomized controlled trials indicated that psychoeducational interventions not only enhance patients’ knowledge about their cancer and its treatments but also reduce depression, anxiety, nausea, and pain.

Electronic Technology–Based Interventions

Technology-assisted interventions have been proven highly effective. A peer-modeling videotape shown to patients shortly after diagnosis produced increases in vitality and posttraumatic growth and decreases in depression and intrusive thoughts. A combined home visiting and telephone intervention resulted in reduced pain. Computer-based patient support tools provided information, decision support, and interaction with other patients and produced not only increments in knowledge but also better patient–doctor interactions.
and enhanced social support. Support groups have been adapted to the Internet with remarkably good effect. Real-time leader-conducted groups for patients with breast cancer have produced significant reductions in depression and pain.

Excellent Internet resources for information about various types of cancer and their treatments as well as supportive services are now available, including websites maintained by the National Cancer Institute, the American Cancer Society, Wellness Community website maintained by the Cancer Support Community, and the Breast Cancer Connections.

**PSYCHOTROPIC MEDICATION**

### Antidepressants

Depression that arises in the context of cancer is responsive to antidepressant treatment. Antidepressants decrease depressive symptoms, improve functional capacity, reduce cachexia, ameliorate some menopausal symptoms, and reduce pain. Fisch et al. found that treatment with fluoxetine significantly improved depressive symptoms and some measures of quality of life when compared to placebo in patients with cancer with various tumors with an expected survival of 3 to 24 months. Importantly, these patients were recruited based on meeting the criterion of being bothered by depressed mood at a severity of “somewhat” or greater and not by meeting criteria for full major depression. Another large trial compared paroxetine to placebo in patients with cancer and fatigue and found that the antidepressant significantly lowered depressive (but not fatigue) symptom scores. In double-blind trials, fluoxetine, paroxetine, and venlafaxine have been shown to reduce hot flashes, and mirtazapine and the anticonvulsant gabapentin have been reported to decrease pruritus in patients with cancer. Venlafaxine, bupropion, and the tricyclic antidepressants have been shown to relieve neuropathic pain, which frequently accompanies cancer and its treatment. Trazodone, a tetracyclic antidepressant, which in low doses (50 to 150 mg) is often used as a sedative-hypnotic drug that does not produce dependency, has also been used to treat various adjustment disorders among patients with breast cancer. Patients with cancer treated with cytokines such as interferon-α often become significantly depressed, with a substantial increase in suicidal ideation and acts. Pretreatment of such patients with selective serotonin reuptake inhibitors (SSRIs) actually reduces the risk of developing depression. There are increasing data that suggest that depression-specific symptoms may significantly contribute to morbidity and mortality in the context of medical illness.

These findings may also provide an explanation for the oft-repeated observation that agents with catecholaminergic activity are generally more effective than SSRIs in the treatment of neurovegetative and somatic symptoms, such as pain and fatigue, even when these symptoms occur outside the context of a diagnosable mood disorder. Combination treatment may also be especially helpful in more severe depressions. Evidence that proinflammatory cytokines contribute to the development of depression, even in medically healthy individuals, may explain the use of combined serotonin-norepinephrine or dopamine treatment, such as adding desipramine or bupropion in conjunction with an SSRI or using a serotonin-norepinephrine reuptake inhibitor such as venlafaxine or duloxetine. These approaches may be more effective than selective serotonin agents alone in the treatment of major depression, especially when comorbid pain is present. Stimulants such as amphetamine, methylphenidate, and modafinil can also be used effectively either alone or in combination with antidepressants, especially to provide more rapid onset. They rarely trigger anorexia in this population, and they are also agents of choice for patients with cancer with short expected survival periods.

### Tamoxifen and Selective Serotonin Reuptake Inhibitors

The specific choice of an antidepressant is especially important for patients with cancer treated with tamoxifen. Tamoxifen continues to be used as an important selective estrogen receptor modulator (SERM) to reduce the risk of recurrence in estrogen receptor–positive patients with postmenopausal breast cancer. To be clinically active, tamoxifen is converted to 4-hydroxy-N-desmethyl-tamoxifen (endoxifen) and other active metabolites by cytochrome P450 (CYP) enzymes. More than 80 different major alleles of CYP2D6 genes have been identified, many of which confer decreased or absent CYP2D6 activity, and patients can be divided into poor, intermediate, extensive, and ultra rapid metabolizers based on their genotype.

Patients with breast cancer treated with tamoxifen who were homozygous for a poor metabolizer genotype had significantly lower serum concentrations of endoxifen than those with an active genotype. In a review of retrospective studies evaluating the effect of CYP2D6 genotype on breast cancer outcomes, Goetz et al. found that patients with estrogen receptor–positive breast cancer, homozygous for the poor metabolizer genotype and treated with tamoxifen monotherapy, were more likely to experience a recurrence of breast cancer than those patients who carried an allele coding for active enzyme. Stearns et al. in a prospective clinical trial, evaluated the effects of the coadministration of tamoxifen and paroxetine—an SSRI (at the time) commonly used to treat depression and hot flashes. The authors found that the use of paroxetine, which inhibits CYP2D6, decreased the plasma concentration of endoxifen, suggesting that the CYP2D6 genotype and drug interactions should be considered in patients treated with tamoxifen. More recently, Kelly et al. in a population-based cohort study, studied postmenopausal women aged 66 years or older living in Ontario who had been treated between 1993 and 2005 with tamoxifen for breast cancer and overlapping treatment with a single SSRI. After adjustment for age, duration of tamoxifen treatment, and other potential confounders, absolute increases of 25%, 50%, and 75% in the proportion of time tamoxifen was used concurrently with paroxetine were significantly associated with 24%, 54%, and 91% increases in the risk of death from breast cancer, respectively. The authors concluded that paroxetine use during tamoxifen treatment is associated with an increased risk of death from breast cancer, supporting the hypothesis that “paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer” regardless of their CYP2D6 genotype.

In addition to paroxetine, sertraline and venlafaxine have also been noted to reduce the metabolism of tamoxifen. Lash et al. found no reduction of tamoxifen effectiveness among patients using citalopram. With the accumulation of studies, Desmarais and Looper provide recommendations that clinicians who are treating patients with breast cancer should carefully evaluate the best, safest, and most up-to-date options for treatment of depression while being mindful of the risks of untreated depression. Table 28-2 by Thekdi et al. provides useful information on antidepressant use, mechanisms of action, dosing, and clinical pearls.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dosing (mg/day)</th>
<th>Clinical Pearls, Side Effects, and Precautions</th>
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<tr>
<td><strong>SSRIs</strong></td>
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| Fluoxetine  | SSRI                | 10–80           | • Minimal risk of discontinuation syndrome because of long half-life  
• Once weekly formulation available at 90 mg  
• Inhibits conversion of tamoxifen to active metabolite  
• High potential for drug–drug interactions via CYP450 enzymes  
• May cause headache, gastrointestinal disturbance, sexual dysfunction, insomnia, restlessness
| Sertraline  | SSRI                | 25–200          | • Few drug–drug interactions  
• Gastrointestinal side effects common
| Paroxetine  | SSRI                | 5–60            | • Inhibits conversion of tamoxifen to active metabolite  
• High potential for drug–drug interactions via CYP450 enzymes  
• High risk of discontinuation syndrome because of short half-life  
• Weight gain, sedation, dry mouth
| Citalopram  | SSRI                | 10–40           | • Few drug–drug interactions
| Escitalopram| SSRI                | 10–20           | • S-enantiomer of citalopram  
• Few drug–drug interactions
| **SNRIs**   |                     |                 |                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Venlafaxine | SNRI                | 37.5–300        | • Least likely to interact with tamoxifen metabolism  
• Used for neuropathic pain and hot flushes  
• Increased blood pressure at higher doses  
• High risk of discontinuation syndrome
| Desvenlafaxine| SNRI              | 50              | • Metabolite of venlafaxine
| Duloxetine  | SNRI                | 20–60           | • Used for neuropathic pain and hot flushes  
• Sedative effects  
• Hepatotoxicity risk, monitor liver function tests  
• Urinary retention
| **Tricyclics**|                  |                 |                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Amitriptyline| SNRI             | 25–150          | • Sedating profile
| Imipramine   | SNRI                | 25–150          | • Activating profile
| Clomipramine | SNRI                | 25–150          | • Activating profile  
• Parenteral administration forms
Antianxiety Agents

Antidepressants have antianxiety properties as well and can be used effectively for the frequent problem of mixed anxiety and depression. Benzodiazepines can provide immediate short-term relief of anxiety symptoms but generally are not a good strategy for long-term treatment, in part because of the problem of habituation and a tendency to produce dependence. In addition, many of the antianxiety agents are used for insomnia with good short-term effect only.

Antipsychotics

Neuroleptics are rarely used among patients with cancer, but they can be highly effective in managing symptoms of delirium and those of the metabolic disequilibrium associated with cachexia, mood disorders, and psychosis associated with steroid treatment and for preterminal delirium. Disorientation to time, place, and person coupled with agitation can be misunderstood as a sign of poor pain management, but increases in opiates and other analgesics, which can be very useful when pain is the problem, may contribute to further delirium. Initially, small but increasing doses of antipsychotics such as haloperidol either orally or intravenously can be very helpful in controlling delirium and agitation.87

CONCLUSION

Psychosocial problems and comorbid psychiatric disorders are common among patients with cancer. They are often overlooked because of overlap with cancer-related symptoms. Such psychiatric problems are detrimental to quality of life, may impair treatment adherence, increase burden to families, and can even worsen prognosis. An array of individual and group psychotherapies, web-based support, and medications can provide effective treatment for cancer-related fatigue, depression, and anxiety.

References


Cancer-Associated Anorexia-Cachexia Syndrome

Christina Brzezniak, DO • Ann M. Berger, MSN, MD

KEY POINTS
- The fall in weight of patients with cancer is a multifactorial process defined by the interplay of anorexia, cachexia, sarcopenia, and increased basal energy expenditure.
- Weight loss affects not only body image and quality of life but also impacts prognosis and response to chemotherapy.
- Reversible symptoms affecting oral intake such as pain, oral thrush, nausea, or vomiting should be addressed.
- Treatment of cancer-associated anorexia-cachexia syndrome can be challenging with corticosteroids and progesterone analogues as the mainstay of therapy.

NORMAL CONTROL OF BODY WEIGHT
Energy expenditure is derived from the interplay between basal metabolic rate, thermogenesis, and physical activity. Up to 70% of total energy loss is secondary to resting energy expenditure. A balance of caloric intake and energy expenditure is maintained to provide weight stability. Both peripheral and central appetite stimulation is needed to maintain this balance. Peripheral appetite stimulation is a process of peripheral hormonal and cytokine-mediated hunger/satiety that is derived from gastric, duodenal, hepatic, pancreatic, and small bowel interplay. Central appetite control, however, is more closely related to energy input/expenditure managed by the hypothalamus and its hormones. Altering peripheral or central stimulation can change how we process, store, or take in calories.

PATHOGENESIS OF CANCER-ASSOCIATED WEIGHT LOSS
The cancer-associated anorexia-cachexia syndrome is a complex process. The balance between energy intake and of normal body homeostasis. Most energy expenditure is shunted toward growth and support of the constant energy demands of a growing malignant process. It is the processes of anorexia (decreased caloric intake) in unison with cachexia (hypercatabolism), sarcopenia (skeletal muscle wasting), and increased basal energy expenditure that leads to the fall in weight of patients with cancer. In total, it is defined as a cancer-associated anorexia-cachexia syndrome. Depending on the tumor type, up to 50% of ambulatory patients with cancer will lose 2% to 5% of their precancer weight. This number is greater with patients who are hospitalized or immobile as well as the percentage of weight loss. This weight loss has implications on almost every aspect of their cancer care.
Increased resting energy expenditure
- Increased thermogenesis in skeletal muscle
- Increased use of energy stores by expanding tumor burden

Loss of adipose tissue
- Increased lipolysis
- Starvation/anorexia

Loss of skeletal muscle
- Decreased protein synthesis
- Increased protein degradation

Loss of adipose tissue
Up to 90% of bodily fuel reserves are stored as adipose tissue. The process of breaking down these stores to provide available energy is termed lipolysis. It is mediated through hormonal signals to maintain stable stores. The hypercatabolic process of cachexia plays a major role in both adipose and skeletal muscle loss. Cancer cachexia is mediated through both hormones and proinflammatory cytokines. Malignant cells produce cytokines constitutively to provide direct support to tumor cell growth and maintenance. Additionally, these tumor-produced cytokines can alter innate cytokine production, dramatically increasing them and leading to an excessive proinflammatory state. As they cross the blood–brain barrier, they affect central homeostatic mechanisms. Thus, patients with cancer will have heightened responses to lipolytic stimuli. Tumor cells also produce tumor-specific mediators such as lipid-mobilizing factors to promote lipolysis or transforming growth factors to sustain tumor growth despite lack of caloric intake and energy deficit. A minor contributor to loss of adipose tissue is the state of starvation secondary to anorexia. It results in loss of fat in excess of muscle mass and mainly affects peripheral appetite regulation.

Loss of Skeletal Muscle
The muscle mass of the adult remains constant unless stimulated via inputs such as exercise. The hypercatabolic state of cancer cachexia produces a dramatic loss of skeletal muscle through decreased protein synthesis and increased protein degradation. This is in contrast to anorexia/starvation alone, which is characterized by a loss of fat in excess of muscle mass. This is a process that is not clearly understood. It is felt that cytokine production by tumor cells, as well as their alteration of normal homeostatic mechanisms, produce these changes to skeletal muscle balance. Similar to the uncoupling of ADP phosphorylation or alteration in lipolysis stimulation, cytokines produced by tumor cells of the patient with cachexia alter the phosphorylation pathways of protein synthesis and degradation.

Each of these processes individually is designed to favor energy production in growth and support of the malignant process without the constraints of our physiologic checks and balances. Even more compelling, the process of anorexia-cachexia syndrome supports and sustains itself. The constant state of inflammation via cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-6 and IL-2β induces anorexia by means of influence on the hypothalamus, which controls appetite and feeding, further affecting the hypothalamus and central processes of energy balance.

CLINICAL SIGNIFICANCE OF WEIGHT LOSS
One of the most obvious manifestations of underlying malignancy can be weight loss. This process is a marker for both progression of the underlying disease as well as prognosis for the patient. Oncologist often use the Eastern Cooperative Oncology Group (ECOG) Performance Status as an independent marker for prognosis (Table 29-2). However, weight loss of greater than 5% of prediagnosis weight is also an
independent predictor of poorer prognosis and earlier mortality.\textsuperscript{13} Weight loss may also be a marker of poorer response to chemotherapy. It affects body image and patient’s quality of life satisfaction. It provides stress for patient and caregiver and is difficult to manage.

A thorough discussion with patients and caregivers is needed to ensure they are informed of the likelihood of weight loss associated with malignancy. The stress of a family member not eating and their loved ones’ perception of “starving to death” can be difficult to combat. Not to mention, patients often become frustrated if every conversation with their caregivers is focused on food intake. Establishing realistic expectations for patients and their loved ones is critical to creating open communication. Because of patient’s appetite suppression, he or she often has little to no control over his or her lack of oral intake. Focusing family activities toward non-food-specific gatherings can help alleviate stress on both caregivers and patients alike. In addition, addressing the effects of depression, feelings of loss of control, anger, or fear for both patients and caregivers can assist in the treatment of this challenging complication of malignancy.

**TREATMENT**

The difficulty in treating cancer-associated anorexia-cachexia syndrome lies in the complex nature of its pathogenesis. Pharmacologic as well as nonpharmacologic interventions are regularly considered in this complex patient population. Reversible confounding symptoms such as oral thrush, pain, nausea, or vomiting must be addressed in conjunction with primary interventions. Providing dietary counseling may help elucidate symptoms interfering with feeding and maximize food enjoyment. Oral supplementation is affordable and noninvasive intervention in the short term. However, replacement of calories alone is not sufficient to reverse the course of cancer-associated anorexia-cachexia syndrome.

When cancer-associated weight loss is secondary to a reversible state, such as curable malignancy or chemotherapy administration, the use of enteral or parenteral feedings or intravenous fluids are common interventions. In this setting, the goal of nutritional support is to restore or maintain both functional and nutritional status.\textsuperscript{14} However, in the metastatic, progressive disease or palliative setting, the goal of any intervention is optimization of quality of life. Parenteral or enteral nutritional replacement often has only limited benefit in this setting.\textsuperscript{13,15,16} In patients who are terminally ill, aggressively providing nutritional interventions often worsens patient’s quality of life.\textsuperscript{14} Central lines for parenteral nutrition carry the risk of infection or thromboembolism. Nasogastric or percutaneously inserted feeding tubes for enteral nutrition can compromise body image and deteriorate quality of life. In general, there has been a demonstrated lack of benefit from these nutritional interventions in both survival and quality of life for patients in the metastatic, progressive disease or palliative setting.\textsuperscript{7-10} An appropriate discussion focusing on goals of interventions is required when considering any nutritional input.

Although there are no known effective treatments to reverse this syndrome, pharmacologic therapy is often employed to manage its effects. Appetite stimulants are the mainstay in palliation despite lack of improvement in overall survival.\textsuperscript{13,15,16} As a result, a thorough discussion of risk/benefit of any treatment strategy must be undertaken for these patients. Other potential areas for pharmacologic intervention include cytokine or metabolic inhibitors (anticatabolism) as well as anabolic agents and other therapies such as metoclopramide (Table 29-3).

A focus on anorexia palliation compromises most phase III data. Both corticosteroids and progesterone analogues can be effective but have no improvement in overall survival or quality of life assessments.\textsuperscript{13,15,16} They are, however, the only agents with any proven benefit in the palliation of cancer-associated anorexia-cachexia syndrome. Corticosteroids’ mechanism of action in this syndrome is not clearly understood. It is felt that they act via anti-inflammatory mechanisms and potentially stimulate appetite centers of the hypothalamus.\textsuperscript{13,15} Yet, they do not provide weight gain in cancer-associated anorexia-cachexia syndrome, and their appetite stimulation tends to be transitory.\textsuperscript{13,15} Acute side effects can include insomnia, hyperglycemia, neutropenia, adrenal insufficiency, pyrexia, or psychosis. Moreover, the side effects from prolonged corticosteroid use, even over a few weeks, can be dramatic. Some such long-term effects can include skin thinning, altered fat deposition, osteoporosis and fracture, insulin resistance, cataract, depression, and hypertension. The progesterone analogue megestrol acetate has been shown to increase both appetite and weight in this patient population.\textsuperscript{20,21} Side effects include increased risk of venous thrombosis, especially if given simultaneous with chemotherapy, as well as suppression of the hypothalamic/pituitary/adrenal axis. This medication is frequently used as upfront therapy.

Legal changes regarding regulation and use of medical cannabis have made both inhaled as well as its oral derivatives a more frequently patient sought intervention. Although dronabinol is U.S. Food and Drug Administration (FDA) approved for weight loss from AIDS anorexia, it has little to no efficacy in cancer-associated anorexia-cachexia syndrome. A North Central Cancer Treatment Group study.\textsuperscript{2} Weight loss may also be a marker of poorer response to chemotherapy. It affects body image and patient’s quality of life satisfaction. It provides stress for patient and caregiver and is difficult to manage.

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**TREATMENT**

The difficulty in treating cancer-associated anorexia-cachexia syndrome lies in the complex nature of its pathogenesis. Pharmacologic as well as nonpharmacologic interventions are regularly considered in this complex patient population. Reversible confounding symptoms such as oral thrush, pain, nausea, or vomiting must be addressed in conjunction with primary interventions. Providing dietary counseling may help elucidate symptoms interfering with feeding and maximize food enjoyment. Oral supplementation is affordable and noninvasive intervention in the short term. However, replacement of calories alone is not sufficient to reverse the course of cancer-associated anorexia-cachexia syndrome.

When cancer-associated weight loss is secondary to a reversible state, such as curable malignancy or chemotherapy administration, the use of enteral or parenteral feedings or intravenous fluids are common interventions. In this setting, the goal of nutritional support is to restore or maintain both functional and nutritional status.\textsuperscript{14} However, in the metastatic, progressive disease or palliative setting, the goal of any intervention is optimization of quality of life. Parenteral or enteral nutritional replacement often has only limited benefit in this setting.\textsuperscript{13,15,16} In patients who are terminally ill, aggressively providing nutritional interventions often worsens patient’s quality of life.\textsuperscript{14} Central lines for parenteral nutrition carry the risk of infection or thromboembolism. Nasogastric or percutaneously inserted feeding tubes for enteral nutrition can compromise body image and deteriorate quality of life. In general, there has been a demonstrated lack of benefit from these nutritional interventions in both survival and quality of life for patients in the metastatic, progressive disease or palliative setting.\textsuperscript{7-10} An appropriate discussion focusing on goals of interventions is required when considering any nutritional input.

Although there are no known effective treatments to reverse this syndrome, pharmacologic therapy is often employed to manage its effects. Appetite stimulants are the mainstay in palliation despite lack of improvement in overall survival.\textsuperscript{13,15,16} As a result, a thorough discussion of risk/benefit of any treatment strategy must be undertaken for these patients. Other potential areas for pharmacologic intervention include cytokine or metabolic inhibitors (anticatabolism) as well as anabolic agents and other therapies such as metoclopramide (Table 29-3).

A focus on anorexia palliation compromises most phase III data. Both corticosteroids and progesterone analogues can be effective but have no improvement in overall survival or quality of life assessments.\textsuperscript{13,15,16} They are, however, the only agents with any proven benefit in the palliation of cancer-associated anorexia-cachexia syndrome. Corticosteroids’ mechanism of action in this syndrome is not clearly understood. It is felt that they act via anti-inflammatory mechanisms and potentially stimulate appetite centers of the hypothalamus.\textsuperscript{13,15} Yet, they do not provide weight gain in cancer-associated anorexia-cachexia syndrome, and their appetite stimulation tends to be transitory.\textsuperscript{13,15} Acute side effects can include insomnia, hyperglycemia, neutropenia, adrenal insufficiency, pyrexia, or psychosis. Moreover, the side effects from prolonged corticosteroid use, even over a few weeks, can be dramatic. Some such long-term effects can include skin thinning, altered fat deposition, osteoporosis and fracture, insulin resistance, cataract, depression, and hypertension. The progesterone analogue megestrol acetate has been shown to increase both appetite and weight in this patient population.\textsuperscript{20,21} Side effects include increased risk of venous thrombosis, especially if given simultaneous with chemotherapy, as well as suppression of the hypothalamic/pituitary/adrenal axis. This medication is frequently used as upfront therapy.

Legal changes regarding regulation and use of medical cannabis have made both inhaled as well as its oral derivatives a more frequently patient sought intervention. Although dronabinol is U.S. Food and Drug Administration (FDA) approved for weight loss from AIDS anorexia, it has little to no efficacy in cancer-associated anorexia-cachexia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action, Typical Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Stimulate hypothalamic appetite centers</td>
</tr>
<tr>
<td>Prednisone</td>
<td>10–40 mg/day in divided doses</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>2–4 mg/day</td>
</tr>
<tr>
<td>Metyprednisolone</td>
<td>Sodium succinate 125 mg/day</td>
</tr>
<tr>
<td>Progesterone analogue</td>
<td>Unclear mechanism of action to stimulate appetite</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>400–800 mg/day</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Increased gastrointestinal motility and reduced nausea 5–10 mg prior to meals</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>No demonstrated efficacy in cancer-associated anorexia 2.5–10.0 mg twice daily</td>
</tr>
</tbody>
</table>


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syndrome.\(^2\) Several randomized double-blinded trials of patients with cancer-associated anorexia found no improvement in weight gain or quality of life.\(^2\)\(^,\)\(^3\) Data for inhaled cannabis in cancer-associated anorexia-cachexia syndrome is lacking.\(^4\) The increased side effects associated with cannabinoid use such as somnolence and confusion, in addition to the available data suggesting lack of efficacy, make their use limited in this setting. Although there is data supporting their use for treatment of nausea and vomiting, the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) do not recommend their use as first-line therapies.\(^5\)\(^,\)\(^6\)\(^,\)\(^7\)

Targeting catabolism can be a complicated process with varying results. There is insufficient data to support the use of any antineoplastic agent for treatment of the cancer-associated anorexia-cachexia syndrome.\(^1\) Some of these agents include eicosapentaenoic acid (EPA), thalidomide, and hydrazine sulfate. EPA is an \(\alpha\)-linolenic (omega-3) fatty acid. Its effects include attenuation of lipolysis and suppression of IL-6. Thalidomide is an inhibitor of the cytokine TNF-\(\alpha\). Hydrazine sulfate inhibits an enzyme involved in gluconeogenesis. Further research is needed before any of these agents become standard treatment approaches.

The goal of anabolic steroidal agents is to increase lean body mass. However, they do not provide significant weight gain. Furthermore, the improvement in lean body mass remains short lived. There are few studies examining its efficacy and little data to support its use. Animal models of growth hormone use have shown skeletal muscle increase despite tumor regression. Yet, patients who are critically ill have higher mortality rates associated with the use of recombinant growth hormones.\(^8\)\(^,\)\(^9\) As such, attempts to target alternative steps along the growth hormone pathway have been studied. Additional research is needed to determine what role any growth hormone or stimulation of the growth hormone pathway may play in treatment of this condition.

Lastly, there are several other pharmacologic strategies that have been attempted to mitigate the effects of anorexia-cachexia syndrome in patients with cancer. All of these therapies require further data to support their use in this patient population. Metoclopramide will increase gastrointestinal motility but has no benefit on improving caloric intake.\(^10\) Olanzapine has been studied given in addition to megestrol acetate with questionable benefits. Insulin therapy, melatonin, or amino acid supplementation all require further inquiry. Mirtazapine, a tetracycline antidepressant with a side effect of weight gain and increased appetite, was studied in both a small, open-label crossover as well as in a small phase II trial of cancer-associated anorexia-cachexia syndrome, suggesting improvement in pain, nausea, anxiety, and appetite with weight gain at low doses of 15 to 30 mg daily.\(^11\)\(^,\)\(^12\) Further studies will clarify its role in this setting.

References


KEY POINTS

- Mucositis is a breakdown in the mucosal barrier that most commonly affects the alimentary tract.
- Chemotherapy and radiation therapy are the most common causes of mucositis.
- Preventive strategies include the use of ice chips, good dental hygiene, and palifermin in patients undergoing autologous stem cell transplantation.
- Treatment is supportive and involves good oral care, pain control (topical or parenteral), and treatment of superimposed infections.

DEFINITION

Mucositis is a breakdown in the mucosal lining and most commonly affects the gastrointestinal tract. It can affect any part of the alimentary tract, from mouth to anus. Less common sites of mucositis include the vagina and nasal mucosa. Symptoms of mucositis include oral ulcerations, dysphagia, odynophagia, gastritis, and diarrhea. Potential complications from mucositis are superimposed infections, translocation of gut bacteria into the bloodstream, bleeding, and impaired nutrition.

ETIOLOGY

Chemotherapy and/or radiation therapy are the most common causes of mucositis. It is estimated to affect 35% to 40% of patients receiving cytotoxic chemotherapy. Up to 75% of patients receiving high-dose chemotherapy and/or radiation conditioning regimens for bone marrow transplantation and up to 80% of patients receiving radiation therapy for head and neck cancer develop mucositis. The pathophysiology of mucositis is complex. Chemotherapy and radiation damage DNA and non-DNA targets via direct effects and reactive oxygen species. This injury leads to a production of proinflammatory cytokines, which accumulate and damage surrounding tissues, causing ulcerations. It is these ulcerations in the gastrointestinal tract that present as mucositis.

RISK

Multiple risk factors influence the likelihood of developing and the severity of mucositis. The chemotherapy agents most commonly associated with mucositis are bleomycin, cytarabine, doxorubicin, etoposide, fluorouracil, and methotrexate.

Preexisting periodontal disease, poor oral hygiene, and radiation therapy to the head, neck, or oral structures can increase the risk and severity of mucositis.

MANIFESTATIONS

The development of oral mucositis progresses through five defined phases:

- Initiation: Radiation and/or chemotherapy damages DNA in basal epithelial cells. Reactive oxygen species are generated that further damage the cells in the submucosa.
- Upregulation and message generation: Chemotherapy and/or radiation induces apoptosis and results in the release of pro-inflammatory cytokines.
- Amplification and signaling: Proinflammatory cytokines lead to further tissue damage and amplify the damage response signaling cascade.
- Ulceration: Tissue destruction leads to loss of mucosal integrity and pain.
- Healing: Proliferation, differentiation, and migration of epithelial cells restore the mucosal barrier.

The clinical signs and symptoms of mucositis usually peak at 7 days after the administration of chemotherapy, although the damage to the mucosa occurs shortly after the administration of chemotherapy and/or radiation. Initially, there may be mild erythema of the oral mucosa that is accompanied by a burning sensation. This stage may be followed by the development of white, slightly painful patches. Further progression can lead to desquamation of the oral mucosa causing shallow ulceration with a pseudomembranous appearance. These ulcerations can coalesce to form large, painful ulcerations. If there is concomitant thrombocytopenia, there may be bleeding from these lesions.

The severity of mucositis can be clinically graded. There are multiple different schema for grading mucositis; one of the most commonly used criteria is the Common Terminology Criteria for Adverse Events (CTCAE v4.0). The clinical grading of mucositis is summarized in Table 30-1.

COMPLICATIONS

Oral mucositis has been demonstrated to lead to worse clinical and economic outcomes in patients. In a prospective trial, patients undergoing bone marrow transplantation who developed oral mucositis were found to have statistically
significant increases in the development of fever, infection, number of days in the hospital, increased costs of care, and increase in 100-day mortality.3,4

The breakdown of the mucosal barrier of the gastrointestinal tract increases the risk of acquiring bacteremia. The incidence and severity of infection rise when the absolute neutrophil count (ANC) is less than 1,000 cells per microliter. In addition to bacteremia, patients are also at risk for developing Candida albicans and herpes simplex virus (HSV) infections of the oral cavity and esophagus.

HSV type 1 reactivation can occur in patients receiving high-dose chemotherapy. It is estimated to occur in 65% to 90% of patients who are seropositive who receive high-dose chemotherapy. In patients with HSV-associated mucositis, the typical vesicular lesions may be absent, and the duration of mucositis is often longer than in patients with mucositis without HSV infection. Because of this, in patients with mucositis and no evidence of oral candidiasis, HSV should be considered in the differential diagnosis. A swab of one of the lesions can be sent to test for HSV, and empiric therapy with acyclovir or valacyclovir should be started.

Patients at high risk for developing reactivation of HSV, such as those undergoing induction chemotherapy for acute leukemia or those receiving high-dose conditioning regimens for hematopoietic stem cell transplantation, should receive antiviral prophylaxis with acyclovir or valacyclovir. Antiviral prophylaxis is started on the day of therapy and continued as prophylactic use of palifermin can be considered in patients undergoing autologous hematopoietic stem cell transplants. There is insufficient data to support the use of prophylactic palifermin in patients who are not undergoing autologous stem cell transplantation.

Glutamine has also been investigated as an agent to prevent mucositis. The data regarding the benefits of oral glutamine for mucositis prevention are conflicting. Two trials have demonstrated no benefit in adults receiving fluorouracil-based chemotherapy.10,11 A newer formulation of glutamine, Saforis (MGI Pharma), has shown promise as a preventive measure. In a prospective phase III trial of 326 women with breast cancer who were slated to receive anthracycline-based chemotherapy, Saforis significantly reduced the incidence of grades 2 and 3 oral mucositis.12 Although this is promising, independent confirmation is needed prior to recommending the routine prophylactic use of Saforis or other glutamine supplementation for the prevention of mucositis.

Amifostine is a drug that is used to prevent xerostomia in patients receiving radiation therapy for head and neck cancers. It is thought to exert its effect by scavenging free radicals generated by radiation therapy. Its efficacy in preventing xerostomia was demonstrated in a trial of 315 patients who received either adjuvant or definitive radiation therapy for head and neck cancer.13,14 Although the trial found a significant reduction in acute and chronic xerostomia, the use of amifostine in the contemporary management of head and neck cancers is uncertain. Its use in patients receiving chemoradiotherapy has yielded conflicting results. Additionally, it is unknown if the benefits of amifostine persist with the use of newer radiation therapy techniques that spare the parotid glands.

### TREATMENT AND SUPPORTIVE CARE

Mucositis is self-limited, and treatment is supportive and symptom guided. The ulcerations of the gastrointestinal tract will begin to resolve spontaneously and are usually completely healed within 14 days. During this time, depending on the severity, the patient may require supportive care, including opiates for pain control and parenteral nutrition, if he or she is unable to maintain adequate intake.
Appropriate oral care can reduce further irritation to the damaged oral mucosa. This includes removal of dentures, gentle toothbrushing, and oral rinses. Oral rinses with a solution of salt and baking soda (½ teaspoon of salt and 1 teaspoon of baking soda in a quart of water) should be done every 4 hours while awake.

Treatment of superimposed oral infections is also indicated. Oral thrush can be treated topically with clotrimazole troches or nystatin suspension. Systemic therapy with fluconazole is usually unnecessary, provided the patient can tolerate topical therapy. In patients at high risk of developing oral candidiasis, prophylactic oral fluconazole has been recommended.

Mucosal barrier agents can provide symptomatic relief of established oral mucositis. There are various agents, such as Gelclair (Alliance Pharmaceuticals Ltd). This is a bioadherent gel that provides a physical barrier over mucosal surfaces to protect denuded areas from the effects of food, liquids, and saliva. MuGard (Access Pharmaceuticals, Inc., Texas) is a U.S. Food and Drug Administration (FDA)–approved mucosal adhesive oral protectant that has demonstrated efficacy in the prevention and treatment of oral mucositis in patients receiving treatment for head and neck cancer. Similar to Gelclair, it forms a bioadhesive protective coating over the oral mucosa.

Sucralfate has also been investigated as an agent to treat and prevent oral mucositis. In patients receiving fluorouracil-based chemotherapy who developed mucositis, treatment with sucralfate suspension did not show any difference in stomatitis severity or duration versus placebo. Similarly, the use of sucralfate suspension as a prophylactic measure has not demonstrated effectiveness in preventing fluorouracil-associated mucositis.

Oral doxepin rinses have been used to reduce the pain of mucositis. Investigators found that doxepin rinses resulted in statistically significant reduction in reported pain, and the recurrence of pain was slower in patients who used the doxepin rinse.

For patients with significant oral pain, topical analgesics are often necessary and can provide significant symptomatic relief. One commonly used analgesic combination, often referred to as “magic mouthwash,” contains combinations of viscous lidocaine, diphenhydramine, sodium bicarbonate, and normal saline. This mixture is swished around in the mouth and then spit out up to six times per day. In very severe cases, the patient may require parenteral narcotics. This is most commonly given via patient-controlled analgesia.

## SUMMARY
Mucositis is the result of breakdown of the mucosal barrier most commonly from chemotherapy and/or radiation therapy. It is a common clinical sequela of chemotherapy and radiation therapy and can lead to increased hospital costs and infections. Clinically apparent lesions usually develop approximately 7 days after chemotherapy administration and will usually resolve within 14 days of chemotherapy administration.

Preventive strategies include thorough dental examination in patients who will receive an autologous stem cell transplant, the use of cryotherapy with ice chips, and palifermin in patients receiving autologous hematopoietic stem cell transplantation (Table 30-2). Treatment of mucositis is supportive and includes treatment of concomitant infections, such as thrush or HSV, topical anesthetics, and parenteral narcotics in severe cases (Table 30-3).

## References


Low blood counts are common in patients with cancer and can be caused both by the malignancy itself and by its treatment. They range in severity from mild, asymptomatic abnormalities to life-threatening cytopenias, which require immediate therapy. They are often encountered by the primary care clinician (PCC) when patients with cancer are seen in between their visits to the specialist and may require further investigation and treatment. Chemotherapy-induced bone marrow suppression varies depending on the regimen used and the patient’s bone marrow reserve. It tends to be cumulative and worsens with subsequent cycles of treatment. For most agents, the blood counts nadir approximately 10 days after chemotherapy. The bone marrow suppression caused by radiation depends on the amount of bone marrow radiated, the dose of radiation used, and whether concurrent chemotherapy is administered. In addition to treatment-induced cytopenias, bone marrow infiltration by the cancer, autoimmune processes, and nutritional deficiencies (especially iron, vitamin B₁₂, and folate) may cause anemia, leukopenia, and/or thrombocytopenia.

**ANEMIA**

When evaluating a patient with anemia, the clinician should ask about the presence of bleeding and the symptoms related to anemia. The presence of symptoms will depend on the patient’s comorbidities, the severity of the anemia, and the rate in which it developed. The clinician should also ask about the patient’s diet and the degree of exposure to chemotherapy, biologic agents, immunotherapy, and radiation therapy. On exam, attention should be paid to signs of hemodynamic instability, bleeding, pallor, jaundice, heart failure, and splenomegaly. Although most patients with active cancer have anemia, the specific causes of the anemia in the individual patient should always be identified. Important pathologies can be missed if the anemia is attributed to the cancer and/or its treatment without a search for additional underlying etiologies (Tables 31-1 and 31-2).

**Management of Anemia in the Patient with Cancer**

Deficiencies of folic acid and/or vitamin B₁₂ should be corrected. It is our practice to offer parenteral vitamin B₁₂ to patients with levels less than 200 pg per mL and to offer oral therapy (1 mg per day) to patients with low normal levels (between 200 and 300 pg per mL). All patients who receive oral repletion of vitamin B₁₂ should have B₁₂ levels rechecked several weeks after initiation of therapy to confirm that they are absorbing the vitamin. Diagnosing iron deficiency in patients with active cancer can be challenging, because in most of these patients, inflammation causes a decrease in the iron saturation and an increase in ferritin. Ferritin is the more reliable indicator in most patients, and we offer oral iron repletion to all patients with symptomatic anemia and ferritin less than 100 ng per mL.

**Transfusion Therapy**

The decision to offer a patient a transfusion of packed red blood cells (PRBCs) requires clinical judgment and should not be made on the basis of hemoglobin and hematocrit levels alone. A transfusion is rarely indicated when the hemoglobin level is above 10 g per dL. The American Association of Blood Banks discourages the use of blood transfusions
TABLE 31-1  Causes of Anemia in Patients with Cancer

<table>
<thead>
<tr>
<th>Type of Effects</th>
<th>Causes of Anemia</th>
</tr>
</thead>
</table>
| Direct effects of the cancer | • Tumor bleeding (tumors of GI tract, bladder, endometrium)  
• Bone marrow infiltration (leukemias, lymphomas, prostate, breast, myeloma) |
| Indirect effects of the cancer | • Anemia of inflammation  
• Nutritional deficiencies (iron, folate, vitamin B₁₂)  
• Coagulopathy- and/or thrombocytopenia-induced bleeding  
• Autoimmune hemolytic anemia  
• Microangiopathic hemolytic anemia  
• Anemia of renal failure |
| Treatment effects | • Chemotherapy, biologic therapy, immunotherapy-induced bone marrow suppression  
• Radiation-induced bone marrow suppression  
• Chemotherapy-induced hemolysis  
  • Autoimmune (e.g., fludarabine)  
  • Microangiopathic (e.g., gemicitabine, mitomycin)  
• Enzymopathies (e.g., G6PD deficiency)  
• Anemia of renal failure  
• Androgen deprivation  
• Hypothyroidism |

GI, gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase deficiency.

When the hemoglobin is above 7 to 8 g per dL in most clinical scenarios.⁶ Patients with asymptomatic or only mildly symptomatic anemia and without significant comorbidities should be monitored. PRBC transfusions can be considered in asymptomatic patients with cardiopulmonary comorbidities and/or a rapid decline in hemoglobin and should be offered to patients with symptomatic anemia and significant comorbidities.⁶⁻⁹

The transfusion of 1 U (300 mL) of PRBC increases the hemoglobin level by approximately 1 g per dL and the hematocrit by 3% in a normal-sized adult who is not experiencing blood loss.⁷ In most instances, PRBCs should be transfused by the unit, and reassessment should be conducted after each transfusion.

**Risks of Transfusions**

Potential risks of transfusions include transfusion-related reactions, congestive heart failure, bacterial and viral infections, and iron overload.⁷⁻¹² The safety of the US blood supply has improved dramatically over the past two decades with the introduction of multiple screening tests for infectious organisms, and the risk of a transfusion-borne viral infection is now in the range of one in a million (Fig. 31-1). Leukocyte reduction using a filter that captures white blood cells can further improve transfusion safety by reducing the incidence of febrile, nonhemolytic transfusion reactions, infections, human leukocyte antigen (HLA) allosensitization, and platelet refractoriness.¹¹ All patients who are chronically transfused, potential transplant candidates, immunosuppressed, and/or have had previous transfusion reactions should receive leukocyte-reduced blood.¹¹ Patients who are immunosuppressed and have not been exposed to the cytomegalovirus (CMV) should receive CMV-negative blood. Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare, but almost always, fatal transfusion complication that occurs in patients who are profoundly immunocompromised such as bone marrow cell transplant recipients and patients receiving nucleoside analogs such as fludarabine. Irradiation of the transfusion product prevents TA-GVHD and should be performed in all patients at risk.¹² Iron overload occurs in patients who are chronically transfused, and iron chelation therapy should be considered after patients have received more than 20 U of blood and/or their serum ferritin is greater than 1,000 ng per mL.¹³

**Erythropoiesis-Stimulating Agents**

Erythropoiesis-stimulating agents (ESA) have been shown to reduce PRBC transfusions in patients with cancer undergoing chemotherapy. However, a consistent quality-of-life benefit has not been demonstrated, and their use has been associated with poorer outcomes in treated patients. Meta-analyses have demonstrated a 17% increased mortality¹⁴ and an increased risk of venous thromboembolism¹⁵ in patients with cancer treated with ESA. A black box warning on the labels of the two available ESAs—epoetin alfa and darbepoetin alfa—states that the drugs should be used only to treat chemotherapy-induced anemia, should be discontinued once the chemotherapy course is complete, and should not be used when the anticipated treatment outcome is cure. The U.S. Food and Drug Administration (FDA) also mandates ESAs to be prescribed for patients with cancer under a risk management program.¹⁶ ESAs are still used in patients with lower risk myelodysplastic syndromes, and available data suggests that they are safe in this population.¹⁷

**LEUKOPENIA**

Neutrophils and lymphocytes are the main circulating white blood cells, and a decrease in their numbers secondary to
Febrile Neutropenia

Febrile neutropenia is a medical emergency requiring prompt administration of broad-spectrum empiric antibiotics. Prior to the era of empiric antibiotic therapy, infections accounted for almost 75% of the mortality related to chemotherapy. Fever in a patient with neutropenia is usually defined as a single temperature $>38.3^\circ C$ (101° F) or a sustained temperature $>38^\circ C$ (100.4° F) for more than 1 hour.18 However, patients with neutropenia and infection do not always present with a fever, especially if they are older or receiving glucocorticoids. Hypothermia, hypotension, confusion, and/or clinical deterioration may indicate infection in these patients and should prompt the initiation of empiric antibiotics. Furthermore, because neutrophils play an important part in the inflammatory response to infectious agents, localizing signs and symptoms of infection such as pain, erythema, swelling, and abnormalities on chest X-ray and other imaging are often minimal or absent in patients with neutropenia.

Management and Risk Stratification of Patients with Febrile Neutropenia

When evaluating patients with neutropenia, a full medication history should always be obtained (including over-the-counter medications and supplements). All patients should be instructed to avoid sick contacts, follow strict hand washing guidelines, monitor their temperature, and seek prompt medical attention when febrile (defined previously). Patient should also follow established food safety guidelines, but neutropenic diets are not recommended.

Categorizing patients with neutropenia and fever as high risk versus low risk for infection is an essential part of the management (Table 31-3). This risk assessment is used to determine the choice of empiric regimen, the mode of administration (intravenous vs. oral), and the venue of treatment (inpatient vs. outpatient).18 Patients with neutropenia as a
result of induction chemotherapy for acute leukemia or allogeneic stem cell transplantation are at particularly high risk for severe infection.

The initial workup of a patient with neutropenia and infectious symptoms is outlined in Table 31-4. An infectious source is identified in only approximately 30% of febrile neutropenic episodes. Although gram-negative organisms predominated a few decades ago, more infections are now documented to be caused by gram-positive organisms. Factors contributing to this trend include use of long-term central venous catheters and prophylactic antimicrobials, which are primarily active against gram-negative pathogens.\(^\text{18}\)

Initial antibiotic selection should be guided by the patient’s risk stratification, history, allergies, symptoms, signs, recent antibiotic use, culture data, and awareness of institutional nosocomial infection patterns (Table 31-5). Vancomycin should not be used as part of the initial regimen unless the patient has suspicion of catheter-related infection, skin or soft tissue infection, pneumonia, or hemodynamic instability. Outpatient therapy can be considered in low-risk patients (Table 31-6).\(^\text{19}\)

If an infectious source of fever is identified, antibiotics should be continued for at least the standard duration for that particular pathogen and site of infection and until resolution of fever and neutropenia. In addition to antibiotics, the central venous catheter should be removed in all patients with catheter-related bloodstream infections caused by \textit{Staphylococcus aureus}, \textit{Pseudomonas aeruginosa}, fungi, and rapidly growing nontuberculous mycobacteria as well as for patients with catheter tunnel or pocket infections. If the source of infection has not been identified, antibiotics can be discontinued once the patient has been afebrile for at least 2 days and the ANC is >500 per microliter and is trending up.

### Granulocyte Colony-Stimulating Factors

Granulocyte colony-stimulating factors (CSFs) (filgrastim, pegfilgrastim, sargramostim) reduce the severity and

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**TABLE 31-3** Risk Stratification of Febrile Neutropenia (ANC <500/μL)

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>ANC &lt;100/μL anticipated to last &gt;7 d and/or: Significant comorbid conditions, Hypotension, Pneumonia, Significant mucositis, Significant diarrhea, Acute abdominal pain, Neurologic changes, Hepatic or renal failure</td>
</tr>
<tr>
<td>Low risk</td>
<td>Brief neutropenia (&lt;7 d) and No or minimal comorbidities</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count.

**TABLE 31-4** Initial Workup of Patient with Febrile Neutropenia

- Physical exam, including mouth, and inspection of rectal area
- Complete blood count with white blood cell differential
- Complete chemistry panel with liver and renal function tests
- Urinalysis and urine culture
- Chest radiograph
- Blood cultures
  - Patient with central venous catheter—culture from each port and one peripheral
  - No central venous catheter—two peripheral blood cultures
  - Sputum culture (if patient has productive cough)
  - Nasal viral swab (if patient has respiratory viral symptoms)
  - Aspiration/biopsy of skin lesions

**TABLE 31-5** Initial Antimicrobial Treatment in a Patient with Febrile Neutropenia

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Antipseudomonal β-lactam agent (cefepime, meropenem, imipenem, piperacillin-tazobactam) or Ceftazidime (if low rate of resistance among gram-negative bacteria)</td>
</tr>
<tr>
<td>High risk, with hypotension, pneumonia, known resistant bacteria</td>
<td>Antipseudomonal β-lactam agent + aminoglycosides, fluoroquinolones, and/or vancomycin</td>
</tr>
<tr>
<td>Suspected catheter-associated infection, skin or soft tissue infection, pneumonia, hemodynamic instability</td>
<td>Antipseudomonal β-lactam agent + vancomycin</td>
</tr>
</tbody>
</table>

Low risk—Inpatient: Antipseudomonal β-lactam agent (cefepime, meropenem, imipenem, piperacillin-tazobactam) or Ceftazidime (if low rate of resistance among gram-negative bacteria) or Rapid transition to outpatient treatment

Low risk—Outpatient: Ciprofloxacin\(^a\) + amoxicillin-clavulanate

\(^a\)Ciprofloxacin should not be used in patients with febrile neutropenia if fluoroquinolone was used as a prophylaxis.

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**TABLE 31-6** Criteria for Outpatient Management of Febrile Neutropenia

- Low risk (anticipated neutropenia <7 d, clinically stable, no medical comorbidities)
- Compliant, motivated patient
- Able to tolerate and absorb oral medications
- Availability of telephone, transportation, caregiver
- Availability of clinician for close medical follow-up

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duration of neutropenia associated with intensive cytotoxic chemotherapy or radiation therapy. However, their use has not been shown to have an impact on survival in most clinical situations. The current guidelines recommend that these growth factors not be routinely administered for primary prophylaxis of febrile neutropenia if the incidence of neutropenic fever is expected to be less than 20% following chemotherapy. When the estimated risk of neutropenic fever is between 10% and 20%, the decision to use granulocyte CSFs should be individualized. Risk factors for increased complications from febrile neutropenia include age older than 65 years, poor performance status, prior episodes of febrile neutropenia, prior treatment with radiation therapy, cytopenias secondary to bone marrow infiltration by cancer, poor nutritional status, open wounds or active infections, and other serious comorbidities. Granulocyte CSFs may also be used to maintain chemotherapy dose intensity in patients treated with potentially curative regimens. There is no established role for granulocyte CSFs in afebrile patients who have already developed neutropenia after chemotherapy or in patients with febrile neutropenia unless they are critically ill.\textsuperscript{18,20,21}

**Antimicrobial Prophylaxis**

Antimicrobial prophylaxis has been shown to reduce the incidence of invasive bacterial, fungal, and herpesvirus infections in patients with severe prolonged neutropenia (ANC $\leq$ 100 per microliter for $>7$ days). This includes patients undergoing allogeneic stem cell transplantation or induction therapy for acute leukemia (Table 31-7). However, for patients with chemotherapy-induced neutropenia, which is expected to be of shorter duration, current guidelines recommend against the routine use of antimicrobial prophylaxis.\textsuperscript{18,22–26} Patients on steroids and/or with defects in cell-mediated immunity (Table 31-8) are at risk for *Pneumocystis jiroveci* infection and should receive prophylaxis with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone.\textsuperscript{27}

**THROMBOCYTOPENIA**

Thrombocytopenia is commonly defined as a platelet count of less than 150,000 per microliter. Spontaneous bleeding is not usually seen until the platelet count drops below 20,000 per microliter, unless the patient is on anticoagulant or antiplatelet agents, or the platelets are dysfunctional secondary to myelodysplasia or uremia. When evaluating these patients, the clinician should ask about bleeding, alcohol consumption, and medication use, including over-the-counter medications and supplements. On physical exam, the clinician should evaluate for hemodynamic stability and evidence of bleeding from mucosal, skin, gastrointestinal, and other sites. The laboratory evaluation should include assessment for other cytopenias and review of the peripheral blood smear and confirmation of the low platelet count. Pseudothrombocytopenia, caused by platelet clumping from the ethylenediaminetetraacetic acid (EDTA) used to anticoagulate the blood specimen, has no clinical significance and should be ruled out before the patient undergoes further workup.\textsuperscript{28} Table 31-9 lists the most common causes of thrombocytopenia in patients with cancer.

### Management of Thrombocytopenia in the Patient with Cancer

Patients should avoid alcohol and antiplatelet agents, including aspirin and nonsteroidal anti-inflammatory agents. Anticoagulants may need to be discontinued. Immune thrombocytopenia

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**TABLE 31-7** Oral Antimicrobial Regimens for the Prophylaxis of Patients with Neutropenia in High-Risk for Infections (ANC $<100/\mu$L for More than 7 d).

<table>
<thead>
<tr>
<th>Antibacterial</th>
<th>Ciprofloxacin 500 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levofloxacin 500 mg bid</td>
</tr>
<tr>
<td>Antiviral</td>
<td>Acyclovir 800 mg bid</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir 500 mg bid</td>
</tr>
<tr>
<td></td>
<td>Famiclovir 250 mg bid</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Fluconazole 400 mg daily</td>
</tr>
<tr>
<td></td>
<td>Voriconazole 200 mg bid</td>
</tr>
<tr>
<td></td>
<td>Posaconazole 200 mg tid</td>
</tr>
</tbody>
</table>

**Note:** Doses presume normal renal and liver function and no significant drug interactions. bid, twice a day; tid, three times a day.

**TABLE 31-8** Patients with Cancer Who Should Receive *Pneumocystis* Prophylaxis

- Patients who are receiving a glucocorticoid dose equivalent to $\geq 20$ mg of prednisone daily for 1 mo or longer
- Patients who undergo allogeneic hematopoietic stem cell transplant
- Select patients who undergo autologous stem cell transplant
- Acute lymphocytic leukemia
- Patients receiving alemtuzumab, temozolomide, purine analogs (e.g., fludarabine)

**TABLE 31-9** Common Causes of Thrombocytopenia in Patients with Cancer

- Chemotherapy
- Radiation
- Medications and over-the-counter agents (heparin, sulfonamides, quinine [in tonic water])
- Immune (especially in hematologic malignancies)
- Bone marrow involvement by the cancer
- Myelodysplasia from previous therapy
- Infections (immune, through disseminated intravascular coagulation [DIC], or bone marrow suppression)
- Hemodilution
- Alcohol abuse
- Hypersplenism
- Acute or chronic disseminated intravascular coagulation
- Nutritional (vitamin B$_{12}$, folate)
- Thrombotic microangiopathy (mucin-producing adenocarcinoma, gemcitabine, mitomycin, bevacizumab, sunitinib)
is usually treated in the adult once the platelet count drops below 30,000 per microliter. First-line agents include steroids and/or immune globulin; and rituximab, splenectomy, and/or thrombopoietin receptor agonists (romiplostim or eltrombopag) are used in refractory or relapsing patients.29

Prophylactic platelet transfusions can prevent life-threatening hemorrhage and should be offered to most patients with severe thrombocytopenia from bone marrow suppression. Table 31-10 lists platelet transfusion thresholds commonly used in clinical practice. However, the decision to transfuse platelets must be individualized, with consideration given to the specific patient’s bleeding risk, comorbid conditions, and goals of care. A platelet pool (usually derived from 6 U of whole blood or one apheresis product) typically increases the platelet count in an average-sized adult by 10,000 to 30,000 per microliter.30

Table 31-10: Transfusion Thresholds for Patients with Thrombocytopenia

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Platelet Transfusion Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable patient with solid tumor or hematologic malignancy</td>
<td>10,000/μL</td>
</tr>
<tr>
<td>Patient with fever, coagulopathy, rapid platelet drop</td>
<td>20,000/μL</td>
</tr>
<tr>
<td>Prior to most invasive procedures (placement of central venous catheter, transbronchial and esophageal endoscopic biopsies, minor surgery)</td>
<td>40,000–50,000/μL</td>
</tr>
<tr>
<td>Active bleeding, prior to major surgery, lumbar puncture</td>
<td>50,000–100,000/μL</td>
</tr>
</tbody>
</table>

References


CHAPTER 32
Hypercoagulable States Associated with Cancer

Jill Lacy, MD • Michal G. Rose, MD • Aleagia Mercer-Falkoff, MD

KEY POINTS
- Cancer is a hypercoagulable state, which predisposes patients to venous and arterial clots.
- Venous thromboembolism (VTE) is a common and preventable cause of death in patients with cancer.
- New extremity edema or respiratory symptoms, as well as unexplained tachycardia or fatigue, should prompt a workup for deep venous thrombosis and/or pulmonary embolism in a patient with cancer.
- The preferred treatment of VTE in most patients with advanced cancer is low-molecular-weight heparin (LMWH) or fondaparinux.
- Disseminated intravascular coagulation, thrombotic microangiopathy, arterial thrombosis, and marantic endocarditis are other cancer-associated hypercoagulable states.

VENOUS THROMBOEMBOLISM

VTE is a leading cause of death in patients with cancer⁴ and occurs in 10% to 20% of patients over the course of their disease.⁵ The risk of VTE is highest in patients with mucinous tumors (pancreas, ovarian, gastric, lung) and malignant brain tumors.⁶ However, given the prevalence of lung, prostate, and colon cancer in the overall population, these three malignancies account for the largest absolute number of VTE events (21%, 18%, and 17% of all cases of cancer-associated VTE, respectively⁷). Additional factors that increase the risk of VTE in patients with malignancy include a recent diagnosis of cancer (within 3 to 6 months), metastatic disease, older age, active systemic therapy (chemotherapy, hormonal therapy, antiangiogenic agents, erythropoiesis-stimulating agents), immobilization, recent surgery, and presence of a central venous catheter.¹⁵,⁶

Clinical Presentation

Although VTE often presents with the well-known classic symptoms of pulmonary embolism (PE) or deep venous thrombosis (DVT), patients with malignancy may have subtle symptoms or signs that appear insignificant or may be confused with other diagnoses. Thus, patients with PE may present with subtle fatigue or mild exertional dyspnea in the absence of the classic findings of tachycardia, tachypnea, pleuritic chest pain, or hypoxemia. Alternatively, patients may have no common symptoms of PE but may have unexplained tachycardia. Given the high risk of VTE/PE in patients with cancer, these subtle presentations should precipitate the appropriate diagnostic workup (see the following text).

DVT of the lower extremities may be easily overlooked because patients with malignancy often have other etiologies for lower extremity edema (hypoalbuminemia, chronic steroid use, immobilization, congestive heart failure). The presence of an indwelling central venous access catheter is associated with increased risk of upper extremity DVT, and thus edema or pain of the arm or neck must not be ignored. Patients with malignancy are at risk for inferior vena cava (IVC) as well as...
extremity thrombosis and thus may present with symmetric bilateral lower extremity edema. In general, any patient with active cancer and new extremity edema should be evaluated for VTE/DVT regardless of symmetry or alternative explanations.

Thrombosis of the hepatic vein (Budd-Chiari syndrome) or the portal and mesenteric veins are complications of myeloproliferative disorders as well as hepatobiliary and pancreatic cancers. Patients with gastrointestinal malignancies are already at risk for ascites, jaundice, and symptoms of hepatic congestion from their underlying malignancy. However, sudden onset of any of these symptoms or change in these symptoms should raise the suspicion for hepatic or portal/mesenteric vein thrombosis.

**Diagnosis**

Screening tests such as the Wells score and D-dimer should not be used to rule out VTE in patients with cancer because they are at high risk based on their diagnosis. Thus, imaging should be performed as soon as the suspicion of VTE is raised by the history or exam. Compression ultrasonography with Doppler is the recommended imaging test for diagnosis of DVT. Both upper and lower extremities can be assessed for DVT with ultrasonography. Ultrasound techniques, however, are not reliable for diagnosis of DVT in iliac veins; and if suspected, contrast venography, computed tomography (CT), or magnetic resonance imaging (MRI) are more reliable modalities. Spiral CT with pulmonary angiography of the chest is the most useful diagnostic test in evaluating patients for PE. Ventilation-perfusion scan can be used if there is a contraindication to CT scan. If the history or exam suggests hepatic or splanchic thrombosis, abdominal Doppler ultrasonography, CT, or MRI venography should be used for diagnosis.

**Treatment**

**Initial Treatment**

Unless there are absolute contraindications to anticoagulation (see the following text), the initial treatment of VTE in most patients is low-molecular-weight heparin (LMWH) (enoxaparin, dalteparin) or fondaparinux. LMWH (or fondaparinux) is preferred to unfractionated heparin (UFH) for the initial treatment of VTE because meta-analyses suggest lower rates of mortality, recurrent DVT, and bleeding in patients treated with LMWH in the acute setting compared to those treated with UFH. In addition, because LMWH can be self-administered and does not usually require laboratory monitoring, most patients can be treated in the outpatient setting. Hospitalization is appropriate, however, in patients with massive proximal DVT, symptomatic PE, significant comorbidities, risk of hemorrhage with initiation of anticoagulation, or severe renal insufficiency. Because UFH can be rapidly reversed with protamine, it may be preferable to LMWH in patients at high risk for bleeding or who require urgent procedures. It is also preferred when the pharmacokinetics of LMWH are uncertain (severe renal insufficiency or morbid obesity) because of ease of monitoring.

**Contraindications to Anticoagulation**

Anticoagulation is contraindicated in patients with active bleeding or who are at risk for serious bleeding. Importantly, the risk of serious hemorrhage must be weighed against the risk of a fatal complication of VTE, and thus the decision to withhold anticoagulation should be made on a case-by-case basis. In addition to active bleeding, anticoagulation may be contraindicated in the following settings: chronic clinically significant bleeding, thrombocytopenia (platelet count <50,000 per microliter), severe platelet dysfunction, recent major surgery, coagulopathy, recent spinal anesthesia or lumbar puncture, and high risk of falls.

Malignant disease of the brain (brain metastases or primary brain tumors) is not a contraindication to anticoagulation in most patients. However, patients with untreated brain metastases from melanoma, renal cell cancer, choriocarcinoma, or thyroid cancer are at high risk of cerebral hemorrhage and should not be anticoagulated. When anticoagulation is contraindicated, an IVC filter should be placed.

**Long-Term Anticoagulation and Secondary Prevention**

The treatment of choice for long-term therapy and prevention of recurrent VTE in patients with active malignancy is LMWH. LMWH is more effective than warfarin in reducing the risk of recurrent VTE in patients with malignancy, albeit with no overall survival benefit, and the risk of hemorrhage with LMWH is the same or reduced compared to warfarin. Based on these data, LMWH is recommended for long-term anticoagulation of VTE in patients with cancer. In addition to superior efficacy, LMWH has the added advantages of absence of drug interactions or need for regular monitoring. At this time, dalteparin is approved by the Food and Drug Administration (FDA) for the treatment of VTE in patients with malignancy and requires once daily dosing. However, enoxaparin may be used as an alternative.
In patients who do not tolerate daily injections, warfarin is an acceptable alternative. However, vigilance in monitoring the international normalized ratio (INR) is mandated in this patient population, given the interactions of warfarin with multiple drugs and herbal supplements. Notably, the oral chemotherapeutic, capetibatide, should not be used concurrently with warfarin. There is limited data regarding the efficacy of the newer anticoagulants including the direct thrombin inhibitors (e.g., dabigatran) and the factor Xa inhibitors (e.g., rivaroxaban) in the treatment of VTE in patients with cancer. Because these are oral agents that do not usually need monitoring and appear to be at least as efficacious as warfarin in most clinical settings, they may become the anticoagulants of choice in patients with cancer.

**Duration of Treatment**

The duration of anticoagulation after the diagnosis of VTE should be decided on a case-by-case basis. As long as the risk factors for VTE persist, including active malignancy, anticoagulation should be continued indefinitely unless there is a contraindication. Thus, many patients with VTE in the setting of cancer will require lifelong anticoagulation.

**DISSEMINATED INTRAVASCULAR COAGULATION**

Activation of the coagulation system in the form of DIC is common in patients with advanced solid tumors (especially adenocarcinomas) and acute leukemias, especially acute promyelocytic leukemia. Patient with acute DIC usually present with bleeding from multiple sites including mucosal surfaces, the gastrointestinal tract, the urinary tract, and/or at sites of intravenous lines. The minority of patients will also have thrombotic manifestations. Laboratory investigation demonstrates prolongation of the prothrombin time (PT) and activated partial thromboplastin time (aPTT), thrombocytopenia, reduced fibrinogen levels, and increased levels of fibrin degradation products (FDPs, including the D-dimer). Patients with chronic DIC are usually asymptomatic, with normal or near-normal PT and aPTT, somewhat reduced platelets and fibrinogen, and presence of FDP. Treatment of DIC is supportive with replacement of clotting factors and/or heparin depending on the predominant clinical manifestation. Successful treatment of the underlying malignancy is usually necessary to reverse the coagulation abnormalities.

**NONBACTERIAL THROMBOTIC ENDOCARDITIS AND ARTERIAL THROMBOSIS**

Nonbacterial thrombotic endocarditis (also called marantic endocarditis and Libman-Sacks endocarditis) is characterized by the development of sterile heart valve vegetations that contain platelet aggregates and fibrin. Patients usually have advanced cancer (most commonly adenocarcinoma) and evidence of systemic embolism and/or PE involving the cerebral, coronary, renal, and/or mesenteric arteries. The diagnosis is established by either transthoracic or, more commonly, transesophageal echocardiography. Patients should be treated with heparin if not contraindicated; however, overall prognosis is poor. Other causes of arterial thromboembolic events that should be considered in patients with cancer include treatment-related arterial clots (see Table 32-1) and the myeloproliferative disorders, particularly essential thrombocytosis and polycythemia vera.

**THROMBOTIC MICROANGIOPATHY**

Thrombotic microangiopathy (TMA) is characterized by a microangiopathic hemolytic anemia, thrombocytopenia, and microthrombi in the vasculature. In contrast to DIC, in these patients, PT, aPTT, and fibrinogen are normal or near-normal; patients have evidence of hemolysis; and the peripheral blood smear shows multiple red cell fragments. The changes in TMA in patients with cancer may also include chemotherapy agents (mitomycin, gemcitabine, bevacizumab, sunitinib) and post-transplant complications. Unfortunately, response to plasmapheresis is poor in these patients.

**References**


KEY POINTS

- The risk of venous thromboembolism (VTE) is significantly increased in patients with cancer who undergo surgery, and aggressive prophylactic measures should be used including consideration of extended prophylaxis after abdominal and gynecologic surgery.
- Chest radiation and chemotherapy may increase the risk of cardiac disease even in younger patients who would ordinarily be thought of as low risk.
- Good exercise tolerance is a strong predictor that patients will tolerate surgery even when they have significant pulmonary findings on imaging.
- Time urgency to proceed to curative cancer surgery limits preoperative interventions to those that will substantially impact the perioperative course.

VENOUS THROMBOEMBOLISM

Patients with cancer have a fourfold to sevenfold increase in the incidence of VTE, and postoperative VTE occurs two to three times more frequently in the patient with cancer. Although lung cancer accounts for the highest absolute number of VTEs, patients with ovarian cancer, pancreatic cancer, lymphoma, and central nervous system (CNS) tumors have the highest rates of VTE. Treatment factors such as antiangiogenic therapy against vascular endothelial growth factor (VEGF), hormonal therapy, and use of erythropoietin are associated with VTE. Additional factors involved in the postoperative hypercoagulable state include immobility, thrombin activation, and low-grade disseminated intravascular coagulation (DIC). Chemotherapy within 30 days of surgery, transfusion of more than 4 U packed red blood cells (PRBCs) within 72 hours of surgery, and type of surgery are also associated with higher rates of postoperative VTE.

The perioperative management of patients with cancer presents distinct challenges for the primary care clinician. Cancer surgery rarely falls into the typical categories of either emergent or elective surgery. Although risk stratification for urgent surgery on patients with cancer may conform to standard guidelines, there is little guidance about the impact of delaying cancer surgery to optimize preoperative health. For example, it is clear that poor diabetes control increases the risk of postoperative complications. What is unclear is if there is a reduction in the success rates of curative cancer surgery if there are delays to improve diabetic control. Similarly, recommendations for preoperative β-blockade recommend gradual up-titration preoperatively, but this could take several weeks. In the absence of associated data specific to patients with cancer, we rarely delay potentially curative cancer surgery for more than 1 week. There are many nuances to managing patients with cancer perioperatively. We have chosen to focus this chapter on three common concerns that have important perioperative implications: venous thromboembolism (VTE), cardiac disease, and pulmonary disease.
175 IU per kg daily, or dalteparin 100 IU per kg twice a day. The last dose of LMWH should be halved and administered 24 hours preoperatively.3

Guidelines for VTE prevention are well known.3,4 Patients with cancer undergoing major pelvic or abdominal surgery more than 45 minutes in duration should be considered high risk for VTE and prophylaxed with LMWH (such as enoxaparin 30 mg subcutaneously twice a day) or unfractionated heparin 5,000 U subcutaneously three times a day with intermittent compression devices. Consideration to pharmacologic prophylaxis should be given in patients with cancer undergoing abdominal and pelvic laparoscopic procedures more than 45 minutes, weighing the risk of bleeding. In spite of adherence to prophylaxis guidelines, high rates of VTE occur in postoperative urologic patients. The incidence of postoperative VTE is 1.0% to 4.7% in patients who undergo prostatectomy, 0.5% to 8.0% in patients who undergo cystectomy, and 0.24% to 1.50% in patients who undergo nephrectomy. The use of screening lower extremity Doppler postoperatively may have a role in this patient population.5

Up to one-third of postoperative VTE events occur after hospital discharge. In spite of adequate prophylaxis, there is a 2.1% incidence of VTE at postoperative day 30.9 Patients undergoing hepatobiliary procedures and esophagectomy are at highest risk.7 Two randomized controlled trials in patients with cancer have shown a decreased incidence of VTE when prophylaxis was extended to 4 weeks postoperatively. The enoxaparin and cancer (ENOXACAN) study showed a 12% reduction in VTE incidence in the extended prophylaxis group.6 More recently, the cancer, bemiparin and surgery evaluation (CANBESURE) study found that VTE complications in major abdominal or pelvic cancer surgery were decreased with use of prophylactic bemiparin for 4 weeks.9 Recent guidelines recommend extended-duration prophylaxis with LMWH in high-risk patients who are undergoing abdominal or pelvic cancer surgery.3

CARDIAC EVALUATION

The core preoperative cardiac evaluation of the patient with cancer is generally the same as that of the noncancer patient. The primary care clinician uses standard cardiac risk indices and algorithmic tools such as the Revised Cardiac Risk Index and the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery.10 (Fig. 33-1). Most surgical oncology procedures for cure pose an interoperative cardiac risk defied by AHA as 1% to 5% risk of cardiac death or nonfatal myocardial infarction. Therefore, it is rare to cancel or significantly delay potentially curative cancer surgery because the mortality risk from cancer is usually greater than the cardiac risk. Typically, patients at risk for cardiac events can be managed with β-blockade perioperatively rather than requiring a delay imposed by revascularization.

Antiplatelet agents such as aspirin or clopidogrel should be stopped 7 to 10 days prior to surgery if they are being used for primary prevention. When antiplatelet drugs are being used for secondary prevention, the increased risk of bleeding must be weighed against the increased risk of vascular events caused by the discontinuation of these medications. Patients who have had a recent vascular event or have had stents placed within the prior 12 months are at increased risk for vascular events off antiplatelets. Although we routinely stop clopidogrel before surgery, many procedures that are low-to-moderate risk for bleeding can be performed safely on aspirin.11 Close collaboration with the surgeon and cardiologist is required to make this determination.

Careful consideration is given to any symptoms or physical exam findings that might indicate cardiovascular pathology; and when indicated, cardiac testing helps to further elucidate and stratify a patient’s level of cardiac risk. Key elements that complicate the evaluation and management of the patient with cancer relate to the potential for cardiovascular pathophysiology resulting from the local or systemic effects of malignancy and the cardiotoxicity of cancer therapies.

Local effects of cancer primarily relate to direct tumor mass effect on the cardiac chambers, great vessels, or other vascular structures, such as with mediastinal tumors. Appropriate imaging studies including chest computed tomography (CT), cardiac magnetic resonance imaging (MRI), or echocardiogram should be used when direct tumor compression of cardiovascular structures is suspected.

Relevant systemic effects of cancer include malignant effusion, in particular, pericardial effusion. Malignant pericardial effusion increases the risk of cardiac tamponade. If tamponade is suspected based on physical exam findings, including hypotension, tachycardia, distended neck veins, or pulsus paradoxus, echocardiography should be performed. Active tamponade must be treated before proceeding to surgery. Malignant pericardial disease can also result in fibrotic changes to the pericardial tissue, thereby resulting in constrictive pericarditis. Constrictive pericarditis generally results in diastolic dysfunction because of decreased filling of the cardiac chambers, and treatment should be addressed prior to surgery.

Various chemotherapeutic agents have cardiotoxic effects. Notably, the anthracyclines, such as doxorubicin, can cause cardiomyopathy in a dose-cumulative fashion, which can, in turn, lead to left ventricular systolic dysfunction and ultimately heart failure.12 Preoperative echocardiography should be considered in patients who have received significant doses of anthracycline to assess ventricular function. The perioperative management of patients with known anthracycline-induced cardiomyopathy follows the same clinical principles for heart failure in general.

Additional chemotherapeutic agents of importance are the angiogenesis inhibitors, also known as the VEGF inhibitors. VGEF inhibitors frequently result in hypertension, likely as a function of increased systemic vascular resistance. Uncontrolled hypertension resulting from angiogenesis inhibitors must be treated with appropriate pharmacotherapy, particularly in the perioperative period, to decrease associated risk of myocardial ischemia. Furthermore, VEGF inhibitors have been associated with impaired wound healing. Therefore, when clinically feasible, VEGF inhibitors such as bevacizumab should be held for at least 6 to 8 weeks prior to elective surgery and should not be started for at least 4 weeks after surgery.13

Patients who have received radiation therapy to the chest are at increased risk for cardiovascular complications, including premature coronary artery disease, valvular thickening and fibrosis, pericarditis, conduction abnormalities, and diastolic dysfunction because of fibrotic changes of the myocardium.14 These risks should be considered as part of the patient’s...
Preoperative Pulmonary Evaluation of a Patient with Cancer

The purpose of preoperative pulmonary evaluation is to optimize resilience and reserve and to reduce postoperative complications including atelectasis, infection, bronchospasm, exacerbation of underlying chronic obstructive pulmonary disease (COPD), respiratory failure, and prolonged mechanical ventilation. The American College of Physicians guidelines do not recommend routine pulmonary function testing, and the use of a screening chest radiograph has rarely

Preoperative Pulmonary Evaluation of a Patient with Cancer

The purpose of preoperative pulmonary evaluation is to optimize resilience and reserve and to reduce postoperative complications including atelectasis, infection, bronchospasm, exacerbation of underlying chronic obstructive pulmonary disease (COPD), respiratory failure, and prolonged mechanical ventilation. The American College of Physicians guidelines do not recommend routine pulmonary function testing, and the use of a screening chest radiograph has rarely
changed management in the perioperative period. The critical part of the evaluation is the history and physical exam. Even with spirometry evaluation, there is no absolute threshold for declaring surgery a prohibitive risk. Pulmonary risk indices such as the cardiopulmonary risk index (based on Goldman criteria for cardiac risk), Brooks-Brunn risk index, and multifactorial risk index (Arozullah index) for postoperative respiratory failure are not widely used.

The issues that are unique to patients with cancer that require consideration are malignant pleural effusion (MPE), pulmonary effects of cancer therapy, and metastatic disease.

MPE is defined as the presence of cancer cells in pleural space. Patients with cancer can also develop pleural effusions as an indirect effect of cancer without evidence of cancer cells in the pleural fluid. The detection of a pleural effusion coincidentally with new malignancy does not establish MPE because 50% of such effusions are nonmalignant. Pleural effusions cause significant mortality and morbidity in patients with cancer. They can be the initial presentation of a malignancy, delayed complication, or may indicate recurrence of a malignancy. Although any kind of malignancy can cause MPE, 75% of MPE is caused by cancers of the lung, breast, ovary, or lymphoma. In the setting of preoperative evaluation, small effusions that are asymptomatic are managed conservatively (without diagnostic intervention) unless the MPE alters tumor staging and decisions on therapy. If patient is symptomatic with decreased exercise tolerance, dyspnea, and cough, additional workup is pursued including CT of the chest to rule out pulmonary embolism and therapeutic thoracentesis to relieve symptoms and to increase patient’s pulmonary reserve.

Certain chemotherapeutic agents and radiation are known to cause pulmonary toxicity that is additive. The main evaluation remains history and physical exam along with preoperative chest radiograph. Bleomycin can cause pneumonitis in 3% to 5% of patients receiving doses of less than 300 mg and in 20% of those receiving doses of greater than 500 mg. Pulmonary fibrosis can also develop several years after completing the bleomycin. Other studies have shown bleomycin morbidly as high as 40% and mortality rates ranging from 2% to 10%. Cyclophosphamide can cause acute pneumonitis or chronic progressive irreversible fibrotic process. Taxanes (paclitaxel and docetaxel) can also cause immediate or delayed interstitial pneumonitis in 1% to 4% of patients. Docetaxel has been implicated in the syndrome of capillary leak, which can cause peripheral edema, noncardiogenic pulmonary edema, and pleural effusion.

For patients with poor functional capacity or symptoms, a chest radiograph and pulmonary function test should be considered. Findings of restrictive lung disease and increased alveolar-arterial oxygen gradient require specialized pulmonologist care. Patients with interstitial metastasis but without clinical signs and symptoms of pulmonary compromise and well-preserved exercise capacity who are undergoing non-lung surgery generally do well without additional testing. If metastatic lesions are large and there is a concern for postobstructive pneumonia or airway compromise, CT scan of the chest should be performed.

References
Primary care clinicians are poised to play an active and important role throughout their patients’ cancer care. They are often responsible for delivering the diagnosis, providing accurate information and support, coordinating specialty care, and managing concurrent symptoms and side effects of treatment. Patients followed by both an oncologist and primary care clinician are more likely to receive appropriate preventive care, more likely to receive treatment of concurrent illnesses, are less likely to visit the emergency room, and more likely to die at home.1,2

Because it is likely that a primary care clinician may have several patients diagnosed with new cancers per year, the need for effective communication skills is paramount. Historically, practitioners were taught that communication skills are largely intuitive behaviors. A survey of oncologists in 1998 showed that fewer than 10% had received formal training in communication, and only 32% had regularly observed communication of bad news during training.3 As a result, most providers report feeling overwhelmed and stressed with the prospect of communicating unwanted or unexpected news. More recently, educators have proven that effective techniques can be learned, and researchers have developed protocols to provide a teaching framework.4 This chapter will outline useful communication techniques and strategies for the primary care clinician.

**KEY POINTS**

- Use SPIKES® protocol when communicating bad news to patients and families.
- Make advanced care planning and establishing goals of care an ongoing part of patients’ cancer care.
- Integrate the shared decision-making model into the communication process.
- Emphasize, maintain, or reframe hope for patients with cancer and their families.

**BREAKING BAD NEWS**

Primary care clinicians often need to communicate bad news to their patients. Studies have shown that most patients prefer to be provided with honest, realistic information regarding their diagnosis and prognosis. It is no longer believed that receiving bad information invariably causes psychological harm. Research shows that patients having such discussions did not experience more anxiety or depressive symptoms.5,6 However, how information is delivered has been shown to affect a patient’s comprehension of information, satisfaction with medical care, level of hopefulness, and subsequent psychological adjustment.3 When clinicians are uncomfortable with or avoid discussing bad news, patients often undergo unhelpful treatments or interventions and are less likely to participate in shared decision making.

The SPIKES tool is a six-step protocol designed to provide a systematic framework for breaking bad news. This strategy, described by Baile et al.,3 helps the clinician achieve the four essential goals from a discussion of bad news: determination of the patient’s knowledge and expectations, to provide information in accordance with the patient’s wishes, to provide support to the patient, and to develop a strategy or treatment plan for going forward.

**Step 1: S—SETTING UP**

Providing a comfortable, private space in which to conduct the conversation is important. The clinician should make every effort to be seated at eye level with the patient. The act of sitting allows the patient to feel some control over the situation and that the clinician is there to listen. Patients also perceive the amount of time spent with the physician as greater when the physician is seated, leading to greater overall satisfaction.4 If possible, involve other family members or friends of the patient to provide support. Make every effort to maintain eye contact. Touch can also be a useful way to connect if the clinician and patient both feel comfortable. Attempt to minimize or avoid interruptions.

**Step 2: P—Assessing the Patient’s PERCEPTION**

Use open-ended questions to determine how much the patient already knows and understands about his or her diagnosis. For example, “What have you been told about your medical
situation so far?” or “What is your understanding of your medical condition?” This allows you to assess and correct any misinformation that the patient may already have. It also allows you to assess denial or unrealistic expectations that the patient may be experiencing. During this part of the conversation, the clinician may also gain some insight into the patient’s overall goals and expectations.

**Step 3: I—Obtaining the Patient’s INVITATION**

As mentioned before, studies over the years have shown that most patients prefer realistic information regarding diagnosis and prognosis. However, some patients may prefer to avoid information either as an effective coping mechanism or a cultural norm. Patients may prefer that you discuss prognostic information with a family member or friend. Questions such as “Are you the type of person who prefers to know all of the information?” or “How would you like me to give you information about your test results?” can elicit how the patient wishes to receive the information. Accept the patient’s right not to know if he or she chooses and asks to speak with a family member.

**Step 4: K—Giving KNOWLEDGE and Information**

Once the clinician has obtained the invitation to disclose, it can be helpful to use a warning statement, which alerts the patient that bad news is coming. Examples include “Unfortunately, I have some bad news to tell you . . . ” or “I’m sorry to tell you . . . ” Once the patient has been warned, proceed with the medical facts, making every attempt to avoid medical jargon. Provide information in small amounts, stopping to assess the patient’s understanding and give him or her time to process or ask questions. Avoid using phrases that are particularly blunt or do not provide hope or useful information, such as “There is nothing we can do for you.”

**Step 5: E—Addressing the Patient’s EMOTIONS with Empathetic Responses**

After receiving bad news, patients may experience a range of emotions. It is important for the clinician to observe and identify the emotion and allow the patient the time to express his or her feelings. Statements such as “I know this isn’t what you wanted to hear . . . ” help validate the emotion. Facilitation techniques such as appropriate silence, nodding in response, and reiterating what the patient said in your own words can provide empathy. Open-ended questions can help if the patient remains silent or his or her response is not clear. Emotions need to be addressed before additional information and treatment plans can be established.

**Step 6: S—STRATEGY and SUMMARY**

Attempt to summarize and establish a plan when the patient is emotionally ready. Patients report feeling less anxious when there is a clear plan for the future. It may simply be to continue the conversation at a later date once the patient has had time to process the news. If possible, discuss treatment options in the context of the patient’s understanding and goals, which were hopefully established during steps 2 and 5. Shared decision making improves patient satisfaction and may also reduce feelings of failure on the part of the clinician if the treatment is not successful. Acknowledge and reassure that other goals such as symptom control and continuity of care will continue to be addressed. Avoid providing false or unrealistic hope.

Often, a conversation where a primary care clinician is breaking bad news is the first step in an ongoing decision making, advance care planning, or establishing goals of care process.

**Shared Decision Making**

Shared decision making has become the preferred method for decision making in the United States. This is a model in which patients and families work with their health care professional(s) when making higher impact decisions. During this process, “patients’ autonomy is respected, patients are helped to establish their values and preferences, and final treatment decisions are reflected through agreement between patients and their practitioner(s) rather than a unilateral decision.”

Sixty-three percent of patients with cancer preferred the shared decision-making process over other methods of decision making in one study. Examples of such higher stakes decisions include selecting treatment options, participation in clinical trials, advance care planning, and end-of-life issues such as transition to hospice.

It is important to realize that primary care clinicians may often be communicating with proxy decision makers either with or instead of their patients regarding decisions. The shared decision-making principle still holds when communicating with proxies. However, studies show that when proxy decision makers perceive family conflict, they tend to favor more aggressive end-of-life treatments rather than palliation and tend to be less accurate or reflective of what their loved one would have wanted. Thus, primary care clinicians should explore the degree of perceived family conflict to better understand a proxy’s tendencies toward end-of-life decisions.

**Advance Care Planning**

Advance care planning is a patient-centered decision-making process based on the patient’s wishes and choices for end-of-life care. This process gives patients a voice about their care when they no longer can communicate. The Agency for Healthcare Research and Quality (AHRQ) recognized that a stepwise, structured approach to advance care planning could be helpful and suggested the following: (1) initiate a guided discussion, (2) introduce subject of advance care planning, (3) prepare and complete advance directive documents, (4) and review patient preferences on a regular basis and update documents. Primary care clinicians are uniquely suited to support these ongoing discussions as part of their routine health care.

**Establishing Goals of Care**

Communication with patients about goals of care should begin prior to the advanced stages of cancer. Advance care planning and establishing goals of care are often intertwined. When primary care clinicians discuss overarching goals of care with a patient with cancer, an assessment of a patient’s values and preferences for care is essential. These discussions take time and need to be done on an ongoing basis similar to advance care planning.

Work in geriatric oncology provides a useful framework for establishing goals of care for hospital admissions. Garman et al. focused on classifying each inpatient admission according to goals set by the health care team and patients as diagnostic, therapeutic, rehabilitative, or palliative. The goals identified were fulfilled in more than 75% of the cases.
This work suggests that “realistic diagnostic, therapeutic, and rehabilitative goals can be identified and achieved in this subgroup of complex patients.”11 Importantly, this work also demonstrates that establishing goals of care prior to end of life can be an effective intervention for patients with cancer.

**PROGNOSTICATION**

Information regarding prognosis is often important in the setting of advance care planning and establishing goals of care. Two key tasks for primary care clinicians in this arena are formulating and communicating prognostic information. There are numerous prognostic tools to assist primary care providers in formulating a prognosis. Communication tips for breaking bad news reviewed earlier in this chapter can be helpful when conveying prognostic information. One unique aspect of communicating prognosis is the issue of uncertainty. Primary care clinicians can use language when speaking with patients and families to reflect this uncertainty, such as “It is my best estimate that you might have . . .” or “It is very difficult for us to say exactly how long you might have . . .” Additionally, it is a good idea to use ranges rather than specific numbers such as days, days to weeks, or weeks to months.

**SUPPORTING HOPE**

Patients with cancer identify hope as an integral component to quality of life, well-being, and coping with adversity.15,16 The primary care clinician is uniquely positioned to influence patients’ hopes, yet many struggle with fostering hope in the face of serious or terminal illness. Many fear that discussions of a poor prognosis will destroy all hope. Hopelessness does appear to contribute to desires for a hastened death17 or interest in physician-assisted suicide.18 However, studies show that patients and families given diagnosis of life-threatening illness often remain hopeful, although what they hope for may evolve as death nears.17,19,20

The challenge is finding the balance between sustaining authentic hope without introducing false hope. Patients not provided with honest, realistic information on prognosis are more likely to choose aggressive anticancer therapy21 and may not complete necessary life tasks or make critical end-of-life decisions. In our “cure-driven” model of care, death is perceived as the enemy and failure. When hope is defined only in curative outcomes, then it is easy to understand that a change from curative options can be viewed as taking away all hope. Patients and health care clinicians describe a spectrum of hope. Hope is not strictly linear, and the focus of hope changes over time.22 Patients may express hope for a miracle or cure but can concurrently acknowledge the terminal nature of their illness.

Behaviors identified by patients and families that negatively affect patients’ hopefulness include the clinician appearing impersonal, nervous, or uncomfortable; giving prognostic information to family before the patient; using euphemisms such as “growth” instead of the term cancer;23 giving blunt, overly detailed information; and withholding of information.20,24

There are strategies to foster coping and nurture hope when discussing prognosis and end-of-life issues (Table 34-1).15,24 Patients want clinicians to demonstrate confident openness and act as supportive coaches.20 Using the framework of “hoping for the best and preparing for the worst” allows the clinician to explain the best that can be expected along with what is likely to occur.10 Exploring a patient’s hopes and reframing hopes that focus on positive and realistic outcomes will help patients find meaningful goals even in the face of dying. Emphasizing what can be done and positive goals such as symptom control, increased energy, healing of relationships, and spending time with significant others will support hope and help patients cope with their illness even in the face of disease progression.22

**TABLE 34-1 Interventions to Support Hope**

<table>
<thead>
<tr>
<th>Interventions to Support Hope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide honest information about disease and prognosis with sensitivity and level of detail that is “tailored” to patient and caregiver.</td>
</tr>
<tr>
<td>Reassurance of up-to-date skilled treatment and availability of specialists.</td>
</tr>
<tr>
<td>Pace information given at rate patients and families can assimilate.</td>
</tr>
<tr>
<td>Explore hopes other than cure.</td>
</tr>
<tr>
<td>Convey sense of caring, empathy, and compassion.</td>
</tr>
<tr>
<td>Being present.</td>
</tr>
<tr>
<td>Active listening and open-ended questions.</td>
</tr>
<tr>
<td>Coordinate with all clinicians involved to deliver consistent message.</td>
</tr>
<tr>
<td>Treatment with dignity and respect.</td>
</tr>
<tr>
<td>Use of shared decision making.</td>
</tr>
<tr>
<td>Give personal recommendations for suggested plan of care.</td>
</tr>
</tbody>
</table>


**TRANSITIONING FROM ANTICANCER TREATMENTS**

As terminal illness progresses, the primary care clinician assists in the transition from curative to palliative to hospice care. Communication regarding discontinuation of anticancer treatment is a difficult conversation for clinicians, patients, and their families. These discussions often unleash a myriad of intense emotions. Because it is so difficult, clinicians lacking communication skills may prescribe third- and fourth-line therapies despite evidence of benefit rather than engage in end-of-life discussions.25 Patients and families may think of the transition to hospice as “giving up” or “not fighting.” They often experience feelings of helplessness, loss of control, and grief. The primary care clinician’s role at this phase is to communicate realistic hope and guidance in choosing appropriate treatments. Strategies to minimize family distress include the following: (1) explain the current medical condition and provide evidence that the treatment is not working; (2) assist in understanding of prognosis in a framework of what is the best that can be hoped for and what is likely to happen; (3) provide information on treatment options including benefit versus burdens; (4) explore patient’s values and goals of care; (5) identify and address fears; (6) engage in shared decision making to best match treatment plan to patient’s goals; and (7) affirmation of continued involvement and nonabandonment.

Patients welcome personal recommendations from their clinicians. However, a recommendation that does not include
a connection to a patient’s goals of care will most likely be rejected. Use a statement such as “Based on the goals and needs you have identified, I feel hospice makes the most sense to help you achieve those goals.” If a patient’s or family’s goals are not yet consistent with a hospice approach, one can propose additional options.

Two strategies that help patients feel less threatened when talking about dying are the use of hypothetical questions or “hope/worry statements.” Hypothetical questions allow patients to discuss possible poor outcomes within an emotional shield from reality. For example, a commonly described plan of care is “Once I get stronger, my oncologist is planning more chemotherapy.” Using the hypothetical question strategy, a clinician may say, “Have you ever thought about what if you are not able to get more chemotherapy?” Hope/worry statements help balance difficult news with hope. A statement of hope is used to acknowledge and encourage hopes and positive thoughts. The simultaneous statement of “worry” introduces the idea of poor outcome in a less threatening yet straightforward approach. Using the hope/worry statement, the clinician may respond by saying, “I am hoping you are able to get stronger and receive chemotherapy, but seeing how you have been getting weaker and not gaining weight over the past few weeks, I worry this may not be possible. I also worry that if you focus on the goal of getting more chemo, you may miss opportunities to focus on other goals that could improve the time you have left such as spending more time with your family.”

There are instances that patients and families have goals or request interventions that the medical team perceives as non-beneficial, unlikely to succeed, or futile. Most situations of perceived futility are the result of poor understanding, differing values, or interpersonal issues between the family and clinicians. Simply allowing the family the opportunity to express themselves combined with active listening and demonstrating presence can help resolve conflict. Instead of taking these requests at “face value,” the primary care clinician should take this as a cue to explore underlying understanding of illness, emotions, and spiritual beliefs. Potential reasons for requests to “do everything” include unrealistic understanding of prognosis, overwhelming feelings of burden of decision making, guilt, anger, secondary gain, fear of dying or abandonment, difficulty in “letting go,” or need for reassurance that all options for best medical interventions have been explored. In this situation, clinicians should consider the use of harm reduction strategies including minimizing discussions focused on limiting or withdrawal of burdensome interventions, identify one clinician to hold these conversations, and use of time-limited trials with clear evaluation points. Clinicians must be prepared to offer their recommendations for care to help lift the burden of decision making from patients or families. If faced with a situation in which the clinician and patient or family are unable to agree, involve the assistance from a consultant, palliative care, or ethics committee.

In summary, providing skilled communication for patients with cancer is an important role for primary care clinicians. The authors have reviewed evidence-based approaches and strategies for breaking bad news through advance care planning, establishing goals of care and end-of-life care, and transitioning from curative-based therapies. Maintaining and reframing hope are vital components to this communication process. The primary care clinician is uniquely suited to provide this communication and work with his or her oncology colleagues throughout his or her patients’ cancer care.

References


KEY POINTS

- Palliative care is the multidimensional assessment; prevention and management of physical, psychosocial, and spiritual distress in patients with life-threatening illness; and support to their families.
- Palliative care is applicable throughout the illness trajectory, and patients with cancer should be screened at regular intervals for palliative care needs.
- Specialized interdisciplinary palliative care teams include palliative care programs that are usually hospital- and home-based hospice care programs.
- In the United States, patients are eligible for hospice care if their estimated life expectancy is 6 months or less.

The field of hospice and palliative medicine is assuming an increasingly important role as leading international and national bodies recognize the immense need and advocate for providing multidimensional support to patients and their families when diagnosed with a life-limiting illness. Among patients with cancer, most experience several physical and psychosocial sources of distress during their illness trajectory, which significantly impact quality of life (QoL). Numerous studies have demonstrated poor control of pain and other symptoms, high psychological distress, and poor communication and social support among patients with advanced cancer or who are terminally ill. Poorly controlled symptoms and poor QoL not only result in considerable suffering but are also predictors of less favorable treatment outcomes for patients with cancer.

Palliative care (from Latin word *palliare*, meaning to cloak) can be viewed as a philosophical concept that encompasses a body of knowledge aimed at the multidimensional assessment, prevention, and management of physical, psychosocial, and spiritual distress in patients and families. This multidimensional holistic approach to care aims to reduce pain and suffering and improve the QoL of patients and should be provided to all patients with cancer at any stage of their illness. It can be delivered by primary care clinicians (PCCs) and oncologists; however, because of the complex and diverse care needs of patients with cancer, an interdisciplinary approach to palliative care is recognized as most effective. Two interdisciplinary palliative care teams, the hospital-based palliative care (referred simply as palliative care) and hospice-based palliative care (referred as hospice care), are available and have expertise in addressing physical, emotional, spiritual, and social issues. Although both palliative care and hospice programs share basic approaches and philosophies of care, the distinction between the two is often confusing to the general public, patients, as well as health care professionals because definitions, services provided, operational characteristics, and eligibility criteria may vary by country and the medical institution in which they are practiced. In the United States, there are important differences in reimbursement between hospital-based palliative care and hospice that may affect patient’s willingness to accept the latter. Some of the differences between hospice care and palliative care are illustrated in Table 35-1. Although both hospice and palliative care programs have dramatically increased, patient referrals to these programs is variable, mostly occurring in the last few weeks of life. Thus, most patients who are terminally ill are cared for in a generalist rather than a specialist palliative care setting. PCCs are uniquely positioned to provide palliative care to their patients because they have an ongoing patient–physician relationship, which can be strengthened as the patient navigates through his or her last moments of life. This delivery of palliative care, referred to as primary palliative care, requires basic skills and competencies in end-of-life (EOL) care, including the management of pain. With adequate training, resources, and referral to specialist palliative care when needed, PCCs can improve the care of patients who are terminally ill.

PALLIATIVE CARE DEFINITIONS

The definition of palliative care has evolved over time and is currently viewed both as a philosophy of care and as an organized, highly structured system for delivering care. In 1990, the World Health Organization (WHO) defined palliative care as “the active total care of patients whose disease is not responsive to curative treatment.” This definition...
In 2002, WHO redefined palliative care as “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. . . .” The WHO has outlined six key principles that underpin the provision of palliative care (Table 35-2), including offering support to patient’s family members. In children, the WHO definition of palliative care is “the active total care of the child’s body, mind and spirit, and also involves giving support to the family. . . .” These WHO definitions have been adopted by the American Academy of Hospice and Palliative Medicine (AAHPM) and the National Comprehensive Cancer Network (NCCN) and highlight that palliative care can be delivered concurrently with life-prolonging care or as stressed that palliative care was applicable when disease was terminal in nature (Fig. 35-1) and went along the traditional view of medical care having two mutually exclusive goals: either to cure disease and prolong life or to provide comfort care. It also supported the Medicare legislative policies to separate reimbursement of regular care from hospice care services, requiring patients to choose one type of care or the other. Newer definitions by the WHO and others have since removed the anchor to terminal disease or EOL and stress that palliative care is applicable throughout the illness trajectory (see Fig. 35-1). Palliative care needs fluctuate during the course of illness. Diagnosis of cancer is associated with significant psychological distress, or the diagnosis may be made on account of the presence of symptoms. Palliative care at the time of diagnosis may help in relieving symptoms and allow patients to better tolerate cancer-directed therapies.

**TABLE 35-1 Differences Between Hospice and Palliative Care in the United States**

<table>
<thead>
<tr>
<th>Hospice Care</th>
<th>Palliative Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When can referral be made?</strong></td>
<td>Can be initiated at any time, ideally at the time of diagnosis. Not dependent on prognosis.</td>
</tr>
<tr>
<td><strong>Can patients receive concurrent curative treatments?</strong></td>
<td>Yes. Patients do not forego curative therapies.</td>
</tr>
<tr>
<td><strong>Setting of care?</strong></td>
<td>Provided mainly in inpatient settings in hospital wards. Community-based outpatient palliative care clinics are on the rise but mainly in major cancer centers.</td>
</tr>
<tr>
<td><strong>Insurance coverage under Medicare?</strong></td>
<td>Covered under traditional Medicare Part A</td>
</tr>
</tbody>
</table>

Old palliative care definition: At end of life

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cancer-directed therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Palliative care</td>
</tr>
<tr>
<td></td>
<td>Hospice care</td>
</tr>
<tr>
<td>Death</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

New palliative care definition: Integrated palliative care

<table>
<thead>
<tr>
<th>Death</th>
<th>6 mo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Bereavement care</td>
</tr>
</tbody>
</table>

**FIGURE 35-1.** Comparison between old and newer definitions of when palliative care is applicable in the cancer trajectory.
the main focus of care. This is compatible with the American Society of Clinical Oncology’s (ASCO) vision of integrating palliative care along with traditional measures of treating (surgery, radiation, chemotherapy) patients with cancer throughout the illness rather than only at EOL.

MODELS OF PALLIATIVE CARE DELIVERY

Leading national organizations advocate for a simultaneous care model with integration of palliative care interventions in all stages of the illness trajectory of the patient with cancer. To achieve this, palliative care should be available to all patients with cancer from the time of diagnosis. Although the best model for delivery has yet to be defined, currently, in the United States, there are three ways to integrate palliative care into the cancer continuum and are discussed in the following text.

Solo Practice Model for Delivering Palliative Care

In many community practice settings where specialist care may be scarce or lacking, PCCs not only have to coordinate oncologic care but also have to address a range of palliative care needs for their patients. This requires clinicians to dedicate adequate time to their patients and have skills in core palliative care competencies (Table 35-3). This includes the assessment and management of pain and other physical, psychosocial, and spiritual disturbances; communication (about diagnosis, prognosis, treatment options); patient-centered decision making (such as goals of care and patient/family preferences); EOL care (support to dying patients and families); and knowledge about community resources for specialist palliative care, psychiatric, and hospice services. Communication approaches at the EOL is addressed in another section.

In many circumstances, the oncologist and PCC together share responsibility for delivering palliative care, and communication between the two is paramount. ASCO’s public policy clearly states that oncologists are responsible for providing care for their patients in a continuum that extends from the moment of diagnosis; and, in addition to appropriate anticancer treatment, this care should include symptom control and psychosocial support during all phases of care, including the last phase of life. However, inadequate training, time constraints, and risk of burnout may be significant barriers to providing effective palliative care to patients.

When the complexity of patient’s suffering and care needs exceeds the experience of the oncologist team, such as in advanced stages of illness, consultation with experts become necessary. This may include a “congress model” approach or a referral to palliative care specialists if available.

Referral to Multiple Disciplines or the Congress Model Approach

Consultation to multiple specialties such as to a pain specialist for pain management, psychiatrist for anxiety symptoms, pulmonologist for dyspnea, and gastroenterologist for chronic nausea is often considered. This model has several disadvantages, such as the risk for fragmented communication or conflicting care plans between multiple disciplines; polypharmacy; and, for patients and families, this approach can be time consuming and exhausting. There is also the disadvantage of increased health care costs.

Referral to Specialist Palliative Care and Hospital-Based Palliative Care Programs

Referral to palliative care specialists may range from a single consultation about a specific issue to several encounters or ongoing involvement until the patient’s death. The integrated care model between the primary oncologist and palliative care team allows the oncologist to focus on all aspects of cancer management while the palliative care team addresses physical and psychosocial symptoms. This collaborative approach can improve the standard of patient care, reduce the risk of oncologist burnout, and increase the likelihood of patient’s family and physician’s satisfaction. Occasionally, this model will require consultation with other specialists especially for palliative interventions (such as placement of intraperitoneal catheters for refractory ascites), but many problems can be managed by the palliative care team, which will result in less risk for polypharmacy and fewer health care visits and costs.

### TABLE 35-2

**Principles of Palliative Care as Defined by the World Health Organization**

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient’s illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated
- Will enhance quality of life and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications

### TABLE 35-3

**Basic Palliative Care Core Clinical Skill Sets**

- Basic formulation of prognosis
- Communication including breaking bad news or death
- Decision making
- Advanced care planning
- Ethical/legal issues including withdrawal/withholding interventions
- Coordination of care
- Knowledge about community palliative care and hospice resources
- Assessment and management of pain and other symptoms
- Recognition and management of oncologic complications
- Counseling
- Psychosocial aspects of care
- Spiritual support
- Care of the imminently dying patient
- Care of the caregivers
- Grief and bereavement

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Chapter 35  /  Principles of Hospice and Palliative Care

EVIDENCE FOR THE BENEFITS OF PALLIATIVE CARE PROGRAMS

Multiple studies have provided evidence for the favorable impact of palliative care programs in the inpatient or outpatient setting, on patient and family-related outcomes such as improvements in symptoms and QoL. The term hospice has its linguistic origins in the Latin word hospes, meaning hospitality, which is traced back to medieval times when it referred to a place of shelter and rest for weary travelers. Cicely Saunders is credited with forming the tenets used in hospices worldwide, including the concept of “total pain,” to describe the physical, emotional, social, and spiritual components to distress and suffering in patients who are terminally ill; timely and appropriate use of opioids; and attention to the needs of family members. In the United States, the first hospice program was developed in 1974. Around this period, political discussions on EOL care and hospice eventually led to the creation of the Medicare hospice benefit (MHB) in 1982, which was made permanent in 1986 by the congress. To be eligible for MHB, patients must fulfill four criteria as shown in Table 35-4.

HOSPICE CARE

The term hospice has its linguistic origins in the Latin word hospes, meaning hospitality, which is traced back to medieval times when it referred to a place of shelter and rest for weary travelers. Cicely Saunders is widely recognized to be the first to apply the name hospice to specialized care for dying patients and developed the first modern hospice, St. Christopher’s, in London in 1967. She is credited with forming the tenets used in hospices worldwide, including the concept of “total pain,” to describe the physical, emotional, social, and spiritual components to distress and suffering in patients who are terminally ill; timely and appropriate use of opioids; and attention to the needs of family members. Soon, the acceptance of the hospice movement gained momentum worldwide.

In the United States, the first hospice program was developed in 1974. Around this period, political discussions on EOL care and hospice eventually led to the creation of the Medicare hospice benefit (MHB) in 1982, which was made permanent in 1986 by the congress. To be eligible for MHB, patients must fulfill four criteria as shown in Table 35-4.

TABLE 35-4  Eligibility Criteria to Receive Medicare Hospice Benefits

<table>
<thead>
<tr>
<th>Eligibility Criteria for Medicare Hospice Benefit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The patient is eligible for Medicare Part A.</td>
</tr>
<tr>
<td>2</td>
<td>The patient’s physician and the hospice medical director use their best clinical judgment to certify that the patient is terminally ill with a life expectancy of 6 mo or less if the disease runs its normal course.</td>
</tr>
<tr>
<td>3</td>
<td>The patient signs a statement electing hospice care instead of standard Medicare benefits.</td>
</tr>
<tr>
<td>4</td>
<td>The patient enrolls in a Medicare-approved hospice program.</td>
</tr>
</tbody>
</table>

All four criteria need to be met.
freestanding agencies, and the remaining are either a part of a hospital system, home health agency, or nursing home. More than 90% of these programs are certified by Medicare.

In 2010, an estimated 1.6 million patients received hospice care services, a number that has steadily been increasing. Of these, an estimated 1.03 million patients died in 2010, accounting for about 42% of all deaths in the United States. Most patient care (approximately 67% in 2010) is provided in patient’s home setting, which may include private residences, assisted living, or a nursing home. About 25% of hospice programs also operate a dedicated inpatient unit or facility. Short-term hospice inpatient care can be made available when pain or symptoms become too difficult to manage at home or the caregiver needs respite. The median length of service in 2010 was 19.7 days, a decrease from 21.1 in 2009. This means that half of hospice patients received care for less than 3 weeks and half received care for more than 3 weeks.

SCREENING PATIENTS FOR PALLIATIVE CARE NEEDS

All patients with cancer should have screening for palliative care needs at the initial visit with frequent reassessments throughout cancer continuum. At the initial visit, clinicians should determine the presence and severity of symptoms, patient and family distress, and concerns about the anticipated course of the disease/treatment. A patient who presents with significant pain, psychological distress, fatigue, or dyspnea, irrespective of the stage of illness, may require intensive palliative services from the outset. A significant proportion of patients present with cancer in late stages of illness and are diagnosed based on cancer-related symptoms. For these patients, palliative care referral should be initiated early on. If the initial screen fails to identify significant physical symptoms or psychosocial concerns, information about available palliative care services should be provided and the anticipation and/or prevention of treatment-related symptoms should be discussed. The NCCN palliative care guideline, first developed in 2001, is a consensus document that is updated annually and aims to help professionals integrate palliative care into general oncology care. It offers guidelines for decision making, palliative care interventions, and timely referral to specialist palliative care teams, taking into account whether the patient’s survival is expected to be measured in years, months to a year, weeks to months, days to weeks, or hours to days.

COMMUNICATING WITH PATIENTS AND FAMILIES AT THE END OF LIFE

Effective and empathetic communication is central to the clinician–patient encounter at the EOL, especially when bad news is being communicated. “Bad news” in the oncology setting is any information that may alter patients’ view of their future and includes information regarding diagnosis, recurrence, treatment failure, and prognosis. Patients and families need adequate information about disease status, prognosis, and the limitations of treatment options before they are ready to make the transition to EOL care. On the other hand, this type of discussion is often perceived as difficult and uncomfortable for health care professionals because of the lack of sufficient time, uncertainty about the patient’s expectations, fear of destroying the patient’s hope, and not feeling adequately trained to manage patient’s emotional reactions when discussing prognosis and EOL concerns. Not surprisingly, considerable unmet communication needs for information regarding extent of disease and prognosis have been identified in patients with cancer. Studies suggest that among patients who are terminally ill, an accurate understanding of their prognosis influences preferences regarding medical treatment. Patients who reported having discussed their wishes for EOL care with a clinician were more likely to receive care that was consistent with their preferences. Among patients who received no life-extending measures consistent with their preferences, their overall distress has been shown to be lower, whereas care that was inconsistent with patient preferences is associated with negative patient outcomes as well as higher health care use costs. Therefore, shared decision making has emerged as the ideal model for complex decision making, according to which health care professionals provide frank information to patients and families and share their opinions regarding decisions, and patients and families make informed decisions regarding their medical care in conjunction with their providers. In one study on decision-making preferences of patients with cancer, 63% of patients with cancer preferred a shared decision-making process with their physicians. The other 37%, however, preferred either an active or more passive approach. This suggests that individual preferences should be elicited. Primary care, oncology, and palliative care are three disciplines that patients and their families expect this from; and the involved disciplines should communicate with one another to avoid giving conflicting information. PCCs are uniquely positioned to assist with shared decision making. This is especially true in areas where specialist care may be limited or unavailable. Likewise, PCCs often have longer relationships with patients and families than the other specialists on the team. These longer term relationships often prove very helpful when patients and families face difficult EOL decisions.

Studies that have explored cancer patients preferences with regards to communication of bad news have identified four key areas important to patients and families: the setting where news is delivered, the manner of communication, what and how much information is provided, and emotional support by the health care team. Having a prepared plan of action can help support all the participants in this difficult discussion. A six-step practical protocol “SPIKES” (Table 35-5) fulfills the four most important objectives of disclosing bad news: gathering information from the patient, providing medical information, providing support to the patient, and developing a treatment plan that is consistent with the patient’s preferences and values. Not every episode of breaking bad news will require all of the steps of SPIKES, but when they do, they are meant to follow each other in sequence. In addition, when transitioning to EOL care, additional approaches should be directed toward eliciting “big picture” goals or values: asking about worries, fears, and concerns; and proposing a care plan that addresses goals, values, and fears/concerns. The ask-tell-ask technique is particularly helpful when patients inquire about their prognosis, but clinicians are unsure how much information the patient wants to hear. Some common questions posed by patients or their families at the EOL may be related to how much time they have to live or if the clinician has given up on them. Such examples with clinician responses are shown in Table 35-6. Some patients may not have previously considered or be ready to articulate about EOL issues. Those patients may simply need some space and
### TABLE 35-5  SPIKES—A Six-Step Protocol for Delivering Bad News

<table>
<thead>
<tr>
<th>6-Step SPIKES Protocol</th>
<th>Details</th>
</tr>
</thead>
</table>
| **S = setting** | - Be prepared before the meeting with patient’s medical information. If other interdisciplinary health care providers are going to be present, discuss relevant issues before the meeting.  
- Physical setting for discussions: private, invite family/caregivers; have seating for all participants.  
- Inform participants about anticipated length of meeting (usually 30–45 min); pagers/phones should be silenced to provide uninterrupted time; if unavoidable, inform participants about possible interruptions. |
| **P = perception** | - Gather information about patient’s understanding of medical condition.  
- Use open-ended questions such as “What have you been told about your medical situation so far?” or “What is your understanding of the reasons we did the scan?” or “What do you think this might be?” and “What are you most afraid of?”  
- Determine if patient is engaging in any variation of illness denial: wishful thinking, omitting essential but unfavorable medical details of the illness, or has unrealistic expectations of treatment. |
| **I = invitation or information** | - Elicit what the patient and family want to know about their diagnosis and prognosis, keeping in mind that most desire full information and want to be fully involved in their treatment options. For patients who do not want to know any bad news, this may indicate a psychological coping mechanism. |
| **K = knowledge** | - Give information in small chunks and allow for time for patient to comprehend and reach to information and ask questions.  
- Avoid using technical words such as metastasis, malignant, and renal failure.  
- Avoid bluntness or statements such as “Nothing more we can do for you.” |
| **E = empathy** | - Use statements that show respect and concern for the patient.  
- Nonverbal communication (body posture, nodding occasionally when listening, slight lean toward the patient) should convey that you are nonjudgmental and attentive.  
- Observe for any emotion and validate.  
- Allow for silence.  
- Use empathetic statements: “I wish there was better news.” “I know this is hard for you to hear.” |
| **S = summarize or strategize** | - Ensure that patient/family have understood the conversations: “Tell me what you are taking away from our talk” or “Does this make sense to you?”  
- Before discussing a treatment plan, it is important to ask patients if they are ready to hear about treatment options.  
- Involve patients in treatment options: “Do you have enough information to make a decision?”  
- Give patient and family contact information for questions or concerns that may arise later. Plan to follow up with the patient. |


### TABLE 35-6  Examples of Clinician Response to Common Questions at the End of Life

| Patient | Clinician | 1 How long do I have?  
Patient: My son is graduating from college in 3 mo and I want to make sure we can all be there for the big occasion.  
Clinician: It is always difficult to say for certain how much time a patient has. I think that there may be a good chance that you will be able to celebrate his graduation. I wish that to be the case; however, it is hard to know for sure. If there are important things that you need to accomplish or people you need to talk or visit, you might want to do it sooner. If you like, we can talk in more detail about how much time you have remaining. Is there any more information that would be helpful to you right now?  
Patient: Thank you, this is enough for now. |
|---|---|---|
| Patient | Clinician | 2 Am I dying?  
Patient: I wish that was not the case, but it is likely in the near future. I am also asking how would you want to spend the remaining time if it were limited? |
| Patient’s wife | Clinician | 3 Does this mean you all have given up on him?  
Patient’s wife: We are stopping treatments that are not helping your husband and rather want to focus on aspects that will help him live comfortably as long as he can. I would like to discuss my plans for managing his pain, nausea, and also discuss home care services, which would help him and the family.  
Clinician: Absolutely not. But can you please explain what you mean by giving up?  
Patient’s wife: Why then are you stopping treatments?  
Clinician: Does this mean you all have given up on him?  
Patient: Thank you, this is enough for now. |

silence in the clinicians’ presence. However, if the silence gets prolonged, this may be an opportunity to explore patients’ values and offer management strategies. A qualitative interview study suggests using statements such as “We know from prior experience (or studies) that most patients express concern about several things. This may be about (1) good pain and symptom control, (2) strengthening relationships with loved ones, (3) relieving burden on family, (4) achieving a sense of control, and (5) avoiding inappropriate prolongation of dying.” Further inquiry should be made if patients have any or all of these concerns.

CONCLUSION

Palliative care involves a multidimensional interdisciplinary care plan to support patients with debilitating and life-limiting illness and their families and is applicable throughout the illness trajectory. It involves skilled assessment and management of pain and other distressing physical, psychological, spiritual, and practical support; assistance with complex medical decision making; and coordination across the continuum of care settings. Effective and empathetic communication is central to the patient–clinician relationship.

References


Rehabilitation in Patients with Cancer

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INTRODUCTION

The objective of rehabilitating patients with cancer is to restore the highest possible level of function and quality of life. This applies to patients at all phases of the cancer continuum including those who are on primary treatment, those with recurrent or stage IV disease, those who are in a palliative state, and those who are considered cured of their disease. It is likely that primary care clinicians will be seeing more patients with cancer and survivors from various cancer types in their offices. Understanding the unique and varied rehabilitation needs of this population will help ensure the highest quality of care for these patients.1

The Rehabilitation Team

Successful rehabilitation of the patient with cancer and/or survivor often depends on an interdisciplinary approach. The primary care clinician should be at the core of this team for most patients. Other team members may include a physical therapist, occupational therapist, nurse, medical oncologist, radiation oncologist, surgeon, nutritionist, speech/language pathologist, psychologist, psychiatrist, clergy, and others as needed. However, when the patient’s rehabilitation needs become more complex, the addition of a rehabilitation medicine physician (preferably one with cancer rehabilitation experience) should be considered. This is analogous to adding a cardiologist to the team when a patient has heart failure that is difficult to control. The cancer rehabilitation physician, or physiatrist, is a specialist trained in the identification, evaluation, and rehabilitation of neuromuscular, musculoskeletal, and functional disorders associated with cancer and its treatment, emphasizing the restoration and maintenance of function and quality of life. In addition to assessing the patient through specialized physical examination and, if necessary, electrodiagnostic skills, they have various procedural tools at their disposal for treating pain, gait dysfunction, spasticity, and other disorders. The physiatrist can also be of tremendous assistance in developing and monitoring a physical or occupational therapy program that is safe and effective. This is of particular benefit in patients with metastatic disease, lymphedema, cancer-related fatigue, radiation fibrosis syndrome (RFS), and other cancer-specific diagnoses.

KEY POINTS

- The goal of cancer rehabilitation is to restore the highest level of function and quality of life to patients with cancer and survivors.
- The primary care clinician will often serve to direct the rehabilitation of the patient with cancer or cancer survivor. In patients with more complex rehabilitation needs, a physiatrist (physical medicine and rehabilitation medicine specialist) should be asked to consult to ensure the highest level of care.
- It is important for the primary care clinician to familiarize himself or herself with the more common function-limiting sequelae that commonly result from cancer and its treatment. Such conditions include, but are not limited to, peripheral polyneuropathy, radiation fibrosis syndrome, lymphedema, trismus, and metastatic bone disease.
- In patients treated with radiation, radiation fibrosis syndrome should always be considered as the cause for atypical symptoms.

COMPLICATIONS OF CANCER AND ITS TREATMENT

Effects of Cancer

The specific impairments that arise directly from cancer are highly variable. The location, size, and degree of involvement of a specific structure such as viscera, bone, nerve, and vascular structures will determine many of the functional impairments faced by the patient. Fatigue and cachexia are also important factors that can limit successful rehabilitation efforts. It is important to have a comprehensive understanding of how cancer is affecting a given patient to conduct a rehabilitation program that is both effective and safe. In addition to the direct effects of cancer, the clinician also needs to be aware that paraneoplastic syndromes can develop in patients with cancer.
This heterogeneous group of disorders is caused by an immune response to an underlying malignancy resulting in neurologic or other side effects that are not the result of a metastasis, nutritional deficit, amyloid deposition, or side effect of treatment.2

Effects of Chemotherapy
Chemotherapy remains a mainstay of cancer treatment. Common functionally limiting disorders that are encountered as a result of chemotherapy administration include anemia, neutropenia, thrombocytopenia, peripheral neuropathy, myopathy, cardiomyopathy, and peripheral edema.3 Clinicians should possess a basic working knowledge of the various complications associated with each specific chemotherapeutic agent before enrolling an individual in a rehabilitation program. If such complications are identified, necessary precautions should be implemented when prescribing therapeutic exercise for rehabilitation purposes.

Effects of Radiation Therapy
Short- and long-term complications related to radiotherapy are a major contributor to physical impairment and disability in the cancer population. This will be discussed more in the “Radiation Fibrosis Syndrome” section.

Effects of Surgery
The postsurgical impairments will depend on the specific cancer type and procedure performed. Scar tissue formation resulting from surgery can often interfere with function and be a major source of pain. Pain from surgery can be localized or radiating and is often neuroathetic in etiology. Pain that persists beyond what is considered the normal postoperative healing period can occur after surgeries of any type including those affecting the extremities in amputation or limb salvage, thoracotomies, breast (lumpectomy, mastectomy, lymph node dissection, and reconstruction), head and neck, or elsewhere on the body. It is important to clarify the source of postsurgical pain and differentiate pain arising as a result of scar formation from pain caused by infection or tumor recurrence. Clinical evaluation combined with imaging is often required to make this determination.

Thromboembolism
Thromboembolism is a clinical entity that deserves specific attention in the rehabilitation setting given its relatively high prevalence in patients with cancer. Previously, some controversy had existed regarding the safety of mobilizing patients with known deep venous thrombosis (DVT) for fear of dislodging an unstable clot, thereby causing a pulmonary embolus (PE). However, with the development of low-molecular-weight heparin (LMWH), activity restrictions in individuals with DVT were reconsidered. Evidence supports early mobilization as both safe and beneficial overall to a patient with DVT.4

NEUROMUSCULAR COMPLICATIONS OF CANCER AND CANCER TREATMENT

Impaired Brain Function
Brain impairment in patients with cancer can be the result of the cancer itself, cancer treatment (radiation, surgery, and chemotherapy), a paraneoplastic process, or other comorbid medical conditions. The focus of most rehabilitation programs for patients with brain tumors or cancer-related brain dysfunction depends on the specific impairments present. Close attention is paid to gait training, bed mobility, transfer training, and use of assistive devices such as wheelchairs and walkers. Cognitive rehabilitation is often required in this population and is focused on memory cues, communication strategies, and executive functioning exercises/training. Speech therapy can be essential in helping to improve or restore fluent and receptive language. A portion of the speech therapy regimen consists of a swallowing evaluation. If swallowing impairment is identified, appropriate treatment should be initiated. Treatment options range from teaching the patient swallowing compensatory techniques that will facilitate the safe passage of food through the oropharynx to placement of a percutaneous endoscopic gastrostomy tube. Two common examples of compensatory swallowing techniques are the chin tuck maneuver and neck rotation technique. In the chin tuck maneuver, patients simply tuck their chin while swallowing to promote laryngeal vestibule closure, thereby allowing gravity to assist in moving an oral food bolus through the oropharynx.
Swallowing is aided using neck rotation technique by turning the head to the weak side, which, in turn, diverts a food bolus to the strong side. This also reduces upper esophageal sphincter (UES) pressure and increases UES relaxation, allowing a bolus to travel more easily into the esophagus.5

Spinal Cord Dysfunction
As with brain dysfunction, spinal cord injury (SCI) in patients with cancer can result directly from tumor growth in or around the cord, a paraneoplastic process, or from cancer treatment.6 Although the prognosis from neoplastic spinal cord compression remains poor, rehabilitation is an essential component of maximizing function and quality of life in affected patients.7 The degree of physical impairment and disability in neoplastic SCI depends on the spinal cord level involved. A higher level and more complete injury will have a greater impact on function. Rehabilitation of individuals with SCI from spinal tumors has shown to improve mobility and independence with activities of daily living.8 The specific rehabilitation program used in this population will be based on the level of injury and resultant physical impairments involved. It is important that the patient with SCI begin rehabilitation as soon as possible to maximize function.9

Peripheral Nervous System Dysfunction
Disorders of the peripheral nervous system include peripheral neuropathy, radiculopathy, and plexopathy.3 Chemotherapy is perhaps the most common source of damage to the peripheral nerve in the cancer setting. Not all chemotherapeutics are neurotoxic, and the toxicity varies greatly in terms of pathophysiology and clinical manifestations by agent. For instance, the vinca alkaloids and taxanes (docetaxel, paclitaxel) cause a predominately length-dependent sensorimotor axonal polyneuropathy. The platinum analogs (cisplatinum, carboplatin) cause a sensory ganglionopathy characterized by dysesthetic pain, sensory loss, and sensory ataxia that can “coast,” that is, progress for several weeks or months following discontinuation of the agent.3 The practitioner should keep in mind that focal neuropathies can result from surgery or procedures such as cryoablation and radiation.3 Paraneoplastic neuropathies generally affect the sensory nerves, are associated with autonomic dysfunction, and are rare.2 In addition, neuropathies seen in the general population, such as diabetic neuropathy, can develop in patients with cancer and survivors.10
Similar to peripheral neuropathy, myopathy, in the setting of cancer, can be the direct result of cancer or its treatment (radiation or chemotherapy induced). Inflammatory myopathy (polymyositis, dermatomyositis) is also encountered. The most common cause for myopathy in the cancer population is glucocorticoid-induced myopathy. Pain is frequently absent in steroid-induced myopathy, and the onset of this condition can be rapid, occurring within 15 days of treatment.

Electrodiagnostic tests consisting of nerve conduction studies and needle electromyography (EMG) can be helpful as an extension of the physical examination when trying to localize a peripheral nerve lesion (radiculopathy vs.plexopathy vs. neuropathy). It is also helpful in determining the severity of nerve injury and often serves as a tool to measure baseline nerve function in individuals who are about to begin cancer treatment. Electrodiagnostic testing should only be performed by physicians who are skilled in these types of examinations. Preconfigured arrays such as those offered by NEUROMetrix are not adequate to differentiate radiculopathy from plexopathy, neuropathy, or myopathy for various reasons (i.e., no needle EMG is performed) and should not be used in these complicated patients.

### MUSCULOSKELETAL COMPLICATIONS OF CANCER AND CANCER TREATMENT

Pain originating from the musculoskeletal system in patients with cancer most commonly occurs from inflammation of soft tissues or is secondary to osseous metastases. This type of pain is of somatic origin wherein pain signals are initiated through the direct stimulation of nociceptors within the structures involved. Pain is often constant and increases with movement. Joints, ligaments, tendons, soft tissue bursae, muscles, and bones can all be affected.

Various chemotherapeutic agents can lead to widespread arthralgias, causing physical impairment. Symptoms usually subside after cessation of treatment but sometimes may persist for several months. Adjuvant hormonal therapies in breast cancer, such as aromatase inhibitors, are well known to cause arthralgias and/or myalgias. This may present a clinical challenge because therapy is often required for several years in breast cancer survivors.

A common cause of musculoskeletal pain and debility in patients with cancer is osseous metastases. The importance of recognizing the presence of bony metastases at risk for fracture in patients undergoing rehabilitation cannot be overstated. In general, patients at risk for pathologic fracture from metastatic tumor infiltration into bone require either surgical or radiotherapeutic intervention to eliminate or reduce this risk. However, there are instances where these interventions do not completely eliminate fracture risk. In such cases, the individuals affected may need to adhere to special precautions during exercise based on their functional goals. Precautions may include toe-touch weight bearing, non-weight bearing, limiting the range of motion at a joint (e.g., no shoulder elevation past 90 degrees), and other specific activity restrictions. Specific precautions should be instituted on a case-by-case basis.

Prediction of pathologic fracture is challenging. In long bones, several risk criteria have been designed. In 1989, Miresl developed a scoring system to quantify the risk of developing a pathologic fracture (Table 36-1). Modern treatments and advances in imaging such as high-resolution computed tomography have changed our approach; however, the basic concept remains. The primary hallmark of an impending fracture is pain, and such lesions should be evaluated by a specialist with experience in determining weight-bearing status.

The Spine Oncology Study Group (SOSG) defines spine instability as “the loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity and/or neural compromise under physiological loads.” The SOSG has validated a standard classification system using radiographic and patient factors to facilitate communication and appropriate referral between oncologists, radiologists, and spine surgeons (Table 36-2).

### RADIATION FIBROSIS SYNDROME

RFS describes the clinical sequelae resulting from progressive tissue sclerosis following radiation treatment. RFS can affect any type of tissue including nerve, blood vessel, muscle, tendon, ligament, or bone. The extent of involvement will largely depend on the amount of tissue radiated and the dose of radiation administered. Signs and symptoms can appear both within the radiation field and distal to it in the distribution of neurovascular and other structures that traverse the field. RFS tends to be particularly common in patients with head and neck cancer (HNC) and Hodgkin lymphoma (HL) survivors but can be seen in most any cancer treated with radiation. The development of RFS is related to not only the intensity of and time since radiation but also to unpredictable factors intrinsic to the patient. It can be seen in various clinical scenarios. When evaluating atypical signs and symptoms in cancer survivors with a radiation history, the clinician should have a low index of suspicion for considering RFS as the primary cause.

Although there are several complications attributable to RFS, space limits discussion and only neck extensor weakness and trismus will be described.

#### Neck Extensor Weakness

Neck extensor weakness or “dropped head syndrome” is common in HL survivors and, to a lesser extent, in patients with HNC treated with radiation. The extensive mantle radiation field formerly used to treat patients with HL causes insidious fibrosis and dysfunction of the neuromuscular structures.
Radiation-Induced Trismus

Radiation-induced trismus can result from ectopic activity in the trigeminal nerve, resulting in spasm of the muscles used for mastication. In addition, direct radiation effects on the surrounding connective tissues such as joints and ligaments ultimately lead to jaw contracture and limited mouth opening. The importance of prevention and early recognition cannot be stressed enough in the management of radiation-induced trismus. It is recommended that the patient be followed closely during their radiation treatments and for 6 months thereafter. A 25% drop in mouth opening from pretreatment baseline should trigger more aggressive observation and intervention. The TheraBite Jaw Motion Rehabilitation System (Atos Medical AB, Hörby, Sweden) (Fig. 36-1) is used to passively maintain or increase mouth opening during the first 6 months because it is relatively inexpensive and easy to use. Patients who are not responding to the TheraBite should be prescribed a Dynasplint Trismus System (Dynasplint Systems Inc., Severna Park, Maryland) (Fig. 36-2). This system employs a low-load prolonged passive stretch mechanism, which is more physiologic and prone to less muscle rebound. In addition, more complicated patients will benefit from a rehabilitation medicine consult and should have physical therapy with a therapist experienced in treating trismus. Such a therapist will instruct the patient on Dynasplint use and conduct a trismus-specific therapy program, which includes deep tissue massage, stretching techniques, neuromuscular retraining exercises, postural muscle, and core strengthening. Finally, a home exercise program will be implemented so that the patient can continue their rehabilitation at home once a formal physical therapy program has ended.

Although physical and/or occupational therapy remain the mainstay of treatment for radiation-induced trismus, the rehabilitation physician may choose to prescribe medications such as oral analgesics, muscle relaxants, nonsteroidal within the field, including the spinal cord, nerve roots, brachial plexus, local peripheral nerves (i.e., dorsal scapular nerve), and muscles. Although generally less common and severe, similar neuromuscular dysfunction can occur in susceptible individual treated with contemporary radiation techniques using lower doses and smaller fields. This has been termed a “myelo-radiculo-plexo-neuro-myopathy.” In addition to neck extensor weakness, clinical manifestations consistent with dysfunction from any segment of the neuromuscular axis can predominate. For instance, patients can be distinctly myelopathic or have severe plexopathy. The primary treatment of neck extensor weakness is physical therapy emphasizing body mechanics, core strengthening, and posture; stretching of the pectoral girdle; restoration of proprioception; and revitalization of lymphatic flow in the upper torso, head, and extremities. Nerve-stabilizing agents such as pregabalin may be useful for relieving cervical pain. A Headmaster Cervical Collar is useful as an energy conservation device to rest overloaded cervicothoracic muscles.
Lymphedema is a progressive pathologic condition of the lymphatic system in which there is interstitial accumulation of protein-rich fluid and subsequent inflammation, adipose tissue hypertrophy, and fibrosis. Risk factors important to patients with cancer and survivors include a history of surgical procedures, particularly nodal dissection, radiation therapy, trauma, infection, as well as local lymph node involvement by cancer. Obesity is also a risk factor for lymphedema. New onset lymphedema should raise suspicion for disease recurrence and/or DVT and should prompt investigation.

 References


Lymphedema often contributes to the development of cellulitis. Proper education should be provided to individuals most at risk to avoid infection. This includes teaching appropriate skin protection precautions. It is essential for the primary care clinician and the rehabilitation specialist to be able to accurately differentiate cellulitis from treatment effect as may occur after radiation therapy.

The cornerstone of lymphedema treatment is the complex decongestive therapy (CDT), which is a combination of manual therapies conducted by a certified lymphedema therapist.

Phase I of CDT consists of manual lymphatic drainage (MLD) combined with compression bandaging. MLD consists of gentle soft tissue massage to augment the flow of stagnant lymphatic fluid through nondisrupted distal to proximal lymphatic pathways. Treatment takes place 5 to 7 days a week. After each MLD session, compression bandages are worn for 21 to 23 hours a day until the next session. Once maximal volume reduction has been achieved, phase II begins. Phase II consists of the implementation of compression garments to maintain the volume reduction gained in phase I; compression bandages are worn at night. In phase II, compression garments sometimes can be substituted for bandages depending on the severity of lymphedema.

Exercise is important in the management of lymphedema. Recent studies have disproven the dogma that resistive exercise is dangerous for breast cancer survivors. Not only did women with lymphedema or those who were at risk not worsen or develop lymphedema but there is also evidence that weight training decreases the risk of developing lymphedema in women who had more than five lymph nodes removed.

CONCLUSION

Rehabilitation is a critical component of restoring the highest possible level of function and quality of life to patients with cancer and survivors. Primary care clinicians are in a unique position to help coordinate multiple aspects of care for their patients, including physical and occupational therapy, but should be quick to adopt a multidisciplinary team approach in more complicated patients to help ensure optimal care.


agents, including small molecule inhibitors and monoclonal antibodies (MoAbs), have been rationally designed to target specific regulatory molecules that affect tumor growth. Tables 37-1, 37-2, and 37-3 list the currently available traditional chemotherapy agents, small molecule inhibitors, and MoAbs, respectively. Cytotoxic chemotherapy combinations are now used for most cancers to overcome tumor resistance because tumors tend to have heterogeneous clones of cells that may or may not be sensitive to individual chemotherapeutic drugs. Modern combination chemotherapy can cure Hodgkin lymphoma, some non-Hodgkin lymphomas, germ cell tumors, Wilms tumor, retinoblastoma, acute leukemias, and early stage breast and colon cancers, among others. Similarly, combinations of chemotherapy and radiation can cure some cancers such as head and neck cancer and nonmetastatic anal cancer.

In anal cancer, chemoradiation has been so successful that it has replaced surgery as the initial preferred treatment intervention.

**Key Points**

- Traditional chemotherapy causes damage to tumor cells and healthy dividing cells in the body.
- Newer chemotherapeutic agents are rationally designed to target specific tumor molecules, thus increasing efficacy and decreasing toxicity.
- Combination of different agents can lead to greater effectiveness of chemotherapy and long-term cures can be achieved with chemotherapy, in multiple tumor types.
- Common side effects of chemotherapy include nausea, vomiting, mucositis, diarrhea, low blood counts, and alopecia.
- Appropriate supportive care can prevent or reduce toxicities of most chemotherapy agents.

The concept of treating cancer using chemotherapy drugs was introduced by Gilman and Philips with the use of nitrogen mustard to treat lymphoma. The primary mechanism of action of traditional chemotherapy drugs is to affect cell division by damaging the cellular nuclear apparatus. Newer chemotherapy agents, including small molecule inhibitors and monoclonal antibodies (MoAbs), have been rationally designed to target specific regulatory molecules that affect tumor growth. The huge range of acute and long-term toxicities associated with chemotherapeutic agents is beyond the range of this section. However, most primary care clinicians (PCCs) will take care of patients receiving anticancer agents and need to be familiar with their common and serious side effects. With modern antiemetic and other supportive care, most chemotherapy can be given safely and is well tolerated.

Although the effects of chemotherapy on tumor cell are desirable, there also have similar effects against normal but rapidly dividing cells in the body including the mucosal surfaces of the gastrointestinal tract, the bone marrow, gonads, skin, and hair follicles. This is the main reason why chemotherapy causes mucositis, diarrhea, low blood counts (leading to anemia, infections, and bleeding), and alopecia. Nausea and vomiting are caused by multiple mechanisms including direct effects of chemotherapy agents on areas of the central nervous system and by certain chemotherapeutic agents. The effects of chemotherapy on the blood cells and the immune system are significant and are monitored carefully. The overall treatment plan is designed to maximize the potential benefit from the chemotherapy while minimizing the unwanted effects.

**Side Effects of Chemotherapy**

The acute and long-term toxicities associated with chemotherapy are significant and can affect many organ systems. The most common acute side effects include nausea and vomiting, mucositis, diarrhea, and alopecia. Nausea and vomiting are due to direct effects on the central nervous system and can be managed with antiemetic medications. Mucositis can be severe and can lead to oral pain and difficulty swallowing. Diarrhea is common and can be managed with anti-diarrheal medications. Alopecia is also common and can be temporary or permanent. The most common long-term side effects include cardiac toxicity, pulmonary toxicity, and secondary malignancies. Cardiac toxicity is common with anthracyclines and can lead to heart failure. Pulmonary toxicity can occur with bleomycin and can lead to fibrosis. Secondary malignancies can occur with alkylating agents and can be a significant risk.

Chemotherapy can also affect the immune system and can increase the risk of infections. Immunosuppressive medications are often used to reduce the risk of infection. Chemotherapy can also affect the reproductive system and can lead to permanent sterility. Chemotherapy can also affect the skin and hair, leading to dry skin, hair loss, and nail changes. The effects of chemotherapy can be minimized by careful monitoring and management of side effects. The patient’s treatment plan is designed to maximize the potential benefit from the chemotherapy while minimizing the unwanted effects.
### TABLE 37-1: Commonly Used Cancer Chemotherapeutic Agents and Their Toxicities

<table>
<thead>
<tr>
<th>Primary Category of Chemotherapy</th>
<th>Chemotherapy Agents Included</th>
<th>Primary Short-term Toxicities</th>
<th>Primary Long-term Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkylating agents</strong></td>
<td>Busulfan, Thiopeta, Melphalan, Chlorambucil, Cyclophosphamide, Ifosfamide, Carmustine, Streptozotocin, Dacarbazine, Temozolomide, Altretamine</td>
<td>Low blood counts, liver toxicity, metabolic abnormalities, nausea and vomiting</td>
<td>Secondary leukemias and myelodysplastic syndrome</td>
</tr>
<tr>
<td><strong>Platinum analogues</strong></td>
<td>Cisplatin, Carboplatin, Oxaliplatin</td>
<td>Renal insufficiency, peripheral neuropathy, low blood counts</td>
<td>Renal insufficiency, hearing loss (cisplatin), peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Antimetabolites</strong></td>
<td>Methotrexate, Pemetrexed, 5-Fluorouracil, Capecitabine, Cytarabine, Gemcitabine, 6-Mercaptopurine, 6-Thioguanine, Pralatrexate, Clofarabine, Fludarabine, Cladribine</td>
<td>Skin rashes (hand/foot), mucositis, diarrhea, mouth sores, low blood counts, liver toxicity, photosensitivity</td>
<td>Secondary leukemias and myelodysplastic syndromes (rare)</td>
</tr>
<tr>
<td><strong>Topoisomerase interacting agents</strong></td>
<td>Irinotecan, Topotecan, Anthracyclines, Doxorubicin (including liposomal), Daunorubicin, Epirubicin, Idarubicin, Mitoxantrone, Etoposide, Teniposide</td>
<td>Gastrointestinal toxicity, diarrhea (irinotecan), low blood counts, liver toxicity, cardiomyopathy (anthracyclines)</td>
<td>Cardiotoxicity and congestive cardiomyopathy, acute leukemia</td>
</tr>
<tr>
<td><strong>Antimicrotubule agents</strong></td>
<td>Paclitaxel, Docetaxel, Cabazitaxel, Vincristine, Vinblastine, Vinorelbine, Estramustine</td>
<td>Low blood counts, neuropathy, hepatotoxicity, blood clots (estramustine)</td>
<td>Neuropathy</td>
</tr>
<tr>
<td><strong>Proteasome inhibitors</strong></td>
<td>Bortezomib, Carfilzomib</td>
<td>Low blood counts, hypotension, neuropathy, herpes zoster reactivation, dyspnea, and heart failure (carfilzomib)</td>
<td>Neuropathy</td>
</tr>
<tr>
<td><strong>Histone deacetylase inhibitors</strong></td>
<td>Vorinostat, Romidepsin</td>
<td>Diarrhea, low blood counts</td>
<td>—</td>
</tr>
<tr>
<td><strong>Immunomodulatory drugs</strong></td>
<td>Thalidomide, Lenalidomide, Pomalidomide</td>
<td>Neuropathy, constipation, bradycardia, birth defects, rash, thrombosis</td>
<td>Neuropathy</td>
</tr>
</tbody>
</table>
Alopecia deserves special mention because it causes significant emotional distress to patients. Cytotoxic chemotherapy damages dividing hair matrix cells and results in thinning of the hair shaft usually 8 to 15 days after initiating chemotherapy leading to break of the hair shaft at the follicular orifice or damage to the hair bulb. As a result, hair loss may occur in a short time when the patient is treated with high-dose chemotherapy or more gradually in the case of lower doses of cyclical chemotherapy regimens. The degree of hair loss depends on the chemotherapy agent, its dose, and schedule of administration. Agents causing complete alopecia include higher doses of cyclophosphamide, daunorubicin, mitomycin, doxorubicin, procarbazine, and irinotecan, whereas less hair loss is seen with 5-fluorouracil, dacarbazine, etoposide, gemcitabine, ifosfamide, melphalan, mitomycin, methotrexate, and vinca alkaloids. Permanent alopecia is rare following chemotherapy because the hair follicle almost always resumes normal cycling within a few weeks following cessation of chemotherapy and generally complete regrowth has taken place within 3 to 6 months. Curling of hair following chemotherapy and generally complete regrowth has taken place within 3 to 6 months. Curling of hair following chemotherapy and generally complete regrowth has taken place within 3 to 6 months. Curling of hair following chemotherapy and generally complete regrowth has taken place within 3 to 6 months. Curling of hair following chemotherapy and generally complete regrowth has taken place within 3 to 6 months. Curling of hair following chemotherapy and generally complete regrowth has taken place within 3 to 6 months.

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---

**TABLE 37-2**

<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Main Targets</th>
<th>FDA-Approved Indication(s)</th>
<th>Main Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imatinib</strong></td>
<td>BCR-ABL, PDGFR</td>
<td>CML, Ph+ ALL, hypereosinophilic syndrome, GIST, dermatofibrosarcoma protuberance</td>
<td>Fluid retention, muscle cramps, liver toxicity, rash, nausea, hypothyroidism, hypophosphatemia, heart failure (rare)</td>
</tr>
<tr>
<td><strong>Dasatinib</strong></td>
<td>BCR-ABL</td>
<td>CML, Ph+ ALL</td>
<td>Pleural effusions, fluid retention, rash, platelet dysfunction and bleeding, liver toxicity, hypothyroidism</td>
</tr>
<tr>
<td><strong>Nilotinib</strong></td>
<td>BCR-ABL</td>
<td>CML, Ph+ ALL</td>
<td>Rash, QTc prolongation, liver toxicity, hypothyroidism, hypophosphatemia</td>
</tr>
<tr>
<td><strong>Bosutinib</strong></td>
<td>SRC, BCR-ABL</td>
<td>CML</td>
<td>Diarrhea, nausea, vomiting, fever, abdominal pain</td>
</tr>
<tr>
<td><strong>Ponatinib</strong></td>
<td>BCR-ABL</td>
<td>CML</td>
<td>MI, stroke, liver toxicity, Hypertension, rash, fatigue</td>
</tr>
<tr>
<td><strong>Gefitinib</strong></td>
<td>EGFR</td>
<td>Non-small cell lung cancer</td>
<td>Acneiform rash, liver function abnormalities, nausea, diarrhea</td>
</tr>
<tr>
<td><strong>Erlotinib</strong></td>
<td>EGFR</td>
<td>Non-small cell lung cancer, pancreas cancer</td>
<td>Acneiform rash, liver function abnormalities, nausea, diarrhea</td>
</tr>
<tr>
<td><strong>Crizotinib</strong></td>
<td>ALK</td>
<td>Non-small cell lung cancer</td>
<td>Vision disorders, nausea, diarrhea</td>
</tr>
<tr>
<td><strong>Sorafenib</strong></td>
<td>VEGFR, RAF, FLT3, PDGFR</td>
<td>Renal cell cancer, hepatocellular carcinoma</td>
<td>Fatigue, hand/foot rash, liver function abnormalities, nausea, diarrhea</td>
</tr>
<tr>
<td><strong>Sunitinib</strong></td>
<td>VEGFR, PDGFR, c-kit</td>
<td>Renal cell cancer, GIST, pancreatic neuroendocrine tumors</td>
<td>Fatigue, hypertension, proteinuria, hand/foot rash, liver function abnormalities, nausea, diarrhea</td>
</tr>
<tr>
<td><strong>Avitinib</strong></td>
<td>VEGFR, PDGFR, c-kit</td>
<td>Renal cell cancer</td>
<td>Fatigue, hand/foot rash, hypertension, nausea, diarrhea, dysphonia</td>
</tr>
<tr>
<td><strong>Pazopanib</strong></td>
<td>VEGFR, PDGFR, c-kit</td>
<td>Renal cell cancer</td>
<td>Hand/foot rash, hypertension, skin hypopigmentation</td>
</tr>
<tr>
<td><strong>Lapatinib</strong></td>
<td>HER2/neu</td>
<td>HER2/neu + breast cancer</td>
<td>Diarrhea, rash, cardiomyopathy</td>
</tr>
<tr>
<td><strong>Vandetanib</strong></td>
<td>VEGFR, RET, EGFR</td>
<td>Medullary thyroid carcinoma</td>
<td>Diarrhea, rash, acniform rash, QTc prolongation, hypertension, liver function abnormalities, hypocalcemia, hypoglycemia</td>
</tr>
<tr>
<td><strong>Cabozaatinib</strong></td>
<td>cMET, VEGFR2</td>
<td>Medullary thyroid carcinoma</td>
<td>Diarrhea, mucositis, hand/foot rash, fatigue</td>
</tr>
<tr>
<td><strong>Everolimus</strong></td>
<td>mTOR</td>
<td>Renal cell cancer, pancreatic neuroendocrine tumors, subependymal giant cell astrocytoma, breast cancer</td>
<td>Rash, acniform rash, mucositis, thyroid dysfunction, hyperglycemia, hyperlipidemia, pneumonitis</td>
</tr>
<tr>
<td><strong>Temsirolimus</strong></td>
<td>mTOR</td>
<td>Renal cell cancer</td>
<td>Rash, acniform rash, mucositis, thyroid dysfunction, hyperglycemia, hyperlipidemia, pneumonitis</td>
</tr>
<tr>
<td><strong>Vemurafenib</strong></td>
<td>B-RAF</td>
<td>Melanoma</td>
<td>Arthralgia, rash, alopecia, fatigue, photosensitivity, nausea, skin cancers</td>
</tr>
</tbody>
</table>

**FDA,** U.S. Food and Drug Administration; **PDGFR,** platelet-derived growth factor receptor; **CML,** chronic myeloid leukemia; **Ph+ ALL,** Philadelphia positive acute lymphocytic leukemia; **GIST,** gastrointestinal stromal tumor; **QTc,** corrected QT interval; **EGFR,** epidermal growth factor receptor; **ALK,** anaplastic lymphoma kinase; **VEGFR,** vascular endothelial growth factor receptor; **RAF,** rapidly accelerated fibrosarcoma; **FLT3,** fms-related tyrosine kinase 3; **RET,** rearranged during transfection; **HER2/neu,** human epidermal growth factor receptor 2; **mTOR,** mammalian target of rapamycin.
Small Molecule Inhibitors

Small molecule inhibitors are low-molecular-weight organic compounds (usually less than 800 Da), which have the capacity to rapidly diffuse across lipid cell membranes and bind with high affinity to a protein, nucleic acid, or a cellular polysaccharide to affect cell signaling in a manner that limits tumor growth. These agents broadly comprise tyrosine kinase inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and proteasome inhibitors. The first highly successful example of targeted therapy and the use of small molecule kinase inhibitors in cancer is imatinib mesylate, a rationally designed inhibitor of the tyrosine kinase Abelson, which is overexpressed in chronic myeloid leukemia. The success of imatinib led to the development of multiple other small molecule inhibitors, and Table 37-2 lists the currently used small molecule inhibitors with their indications and common side effects.

Monoclonal Antibodies

Antibody-based anticancer therapy has increased exponentially in recent years. MoAbs can serve as antitumor agents by several mechanisms including enhancing the bodies’ immune system, altering signal transduction pathways, and/or delivering radiation or toxins directly to tumors. There are currently 13 approved agents for the treatment of cancer (see Table 37-3) and many more in clinical development. MoAbs can be murine based (tositumomab, ibritumomab), human (panitumumab), humanized (trastuzumab, gemtuzumab, alemtuzumab, bevacizumab), or chimeric (rituximab, cetuximab), depending on the percentage fraction of murine and human components in the antibody structure. The suffix in the MoAbs names indicates the composition of the antibody: -momab for murine, -umab for human, -zumab for humanized, or -ximab for chimeric. The common side effects of MoAbs include acute allergic infusion reactions such as fevers, chills, hives and itching, flulike symptoms, diarrhea, nausea, and skin rash. Serious but rare side effects include shock, myocardial infarction and other cardiac complications, bleeding, low blood counts, and death. MoAbs can also be used for the targeted delivery of a toxin, radioisotope, cytokine, or an active drug conjugate.

Side Effects of Targeted Therapy

Tables 37-2 and 37-3 describe the main side effects of the small molecule inhibitors and MoAbs used to treat cancer. Because some patients will be on these treatments for years, it is important that the PCC is aware of their long-term side effects. The majority can cause hypothyroidism, and thus thyroid

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Disease Indication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>B-cell non-Hodgkin lymphoma and CLL</td>
<td>Infusion reactions, infections, leukopenia, thrombocytopenia, hepatitis B reaction</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>CD52</td>
<td>B-cell CLL</td>
<td>Infusion reactions, severe infections</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>CD20</td>
<td>Refractory B-cell CLL</td>
<td>Infusion reactions, leukopenia, infections, rash, hepatitis B reaction</td>
</tr>
<tr>
<td>Tositumomab and 131I-tositumomab</td>
<td>CD20 (radioimmunotherapy)</td>
<td>B-cell non-Hodgkin lymphoma</td>
<td>Infusion reactions, pancytopenia, infections</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan</td>
<td>CD20</td>
<td>B-cell non-Hodgkin lymphoma</td>
<td>Infusion reactions, pancytopenia, infections</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>CD30</td>
<td>Anaplastic large cell lymphoma and Hodgkin lymphoma</td>
<td>Infusion reactions, leukopenia, infections, neuropathy, pulmonary toxicity</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF-A</td>
<td>Glioblastoma multiforme and cancers of the breast, colorectum, lung, kidney, and ovary</td>
<td>Infusion reactions, hypertension, proteinuria, kidney damage, arterial and venous clots, hemorrhage, delay in wound healing, gastrointestinal perforation</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>Colorectal and head and neck cancers</td>
<td>Infusion reactions, acniform rash, hypomagnesemia, diarrhea</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>EGFR</td>
<td>Colorectal cancer</td>
<td>Infusion reactions, acniform rash, hypomagnesemia, diarrhea</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
<td>Infusion reactions, severe autoimmune manifestations including colitis, neuropathy, endocrinopathies, dermatitis, hepatitis</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2/neu</td>
<td>Breast and gastric cancers</td>
<td>Infusion reactions, cardiomyopathy</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>HER2/neu</td>
<td>Breast</td>
<td>Infusion reactions, cardiomyopathy</td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANKL</td>
<td>Bone metastasis from solid tumors, increase bone mass in patients on androgen deprivation therapy or aromatase inhibitors</td>
<td>Asthenia, hypocalcemia, hypophosphatemia, osteonecrosis of jaw</td>
</tr>
</tbody>
</table>

CLL, chronic lymphocytic leukemia; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; CTLA, cytotoxic T-lymphocyte associated protein; HER2/neu, human epidermal growth factor receptor 2; RANKL, receptor activator nuclear factor-κB ligand.
Biotherapy or biologic therapy constitutes the pharmacologic use of compounds naturally occurring in the body to induce anticancer effects through the activation of host defense mechanisms. The main agents currently in use include the interferons and interleukins. Interferons enhance the anticancer response of the immune system, have direct antiproliferative effects, and may induce some tumor cell maturation. They have shown limited efficacy in the treatment of renal cell cancer, metastatic melanoma, hairy cell leukemia, chronic myeloid leukemia, AIDS-related Kaposi sarcoma, and some types of non-Hodgkin lymphoma but have largely been replaced by more effective and less toxic agents. Interleukin 2 (IL-2, aldesleukin) is used for the treatment of metastatic renal cell cancer and melanoma and at high doses can induce complete and durable remissions in a small percentage of patients.

The side effects of interferons and interleukins are dose dependent and include flu-like symptoms (fatigue, fever, chills, nausea, vomiting, and appetite loss), glucose intolerance, liver damage, rash, depression, and suicidal ideation. High-dose IL-2 causes a life-threatening capillary leak syndrome, which is characterized by hypotension, severe edema and third spacing, and cerebral edema. It should be administered only in centers with specialized experience and in highly monitored settings.

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Cancer vaccines have been extensively studied but thus far have had only limited application for the treatment of
cancer. In April 2010, the U.S. Food and Drug Administration (FDA) approved the first cancer treatment vaccine sipuleucel-T (Provenge) for the treatment of early castrate-resistant prostate cancer based on a randomized study showing an approximately 4-month prolongation of survival in treated patients compared with patients who did not receive the vaccine. This vaccine stimulates an immune response to prostate acid phosphatase (PAP), an antigen found on most prostate cells. After obtaining dendritic cells from patients by performing leukapheresis, these antigen-presenting cells are mixed and cultured ex vivo with a fusion protein composed of granulocyte-macrophage colony-stimulating factor fused to PAP. The cultured mixture is reinfused back into the patient and elicits a T-cell immune response against prostate cancer cells.

**ENDOCRINE THERAPY**

**KEY POINTS**

- Endocrine therapy of cancer involves the exogenous administration of hormones to control cancer progression by interfering with the action of endogenous hormones.
- Endocrine therapy is the mainstay of therapy of most advanced breast and prostate cancers.
- The main side effects of tamoxifen include hot flashes, endometrial cancer, venous thromboembolism, and cataracts.
- The main side effects of aromatase inhibitors in women with breast cancer include hot flashes, osteoporosis, and musculoskeletal symptoms.
- The main side effects of androgen deprivation therapy in men include hot flashes, osteoporosis, metabolic syndrome, weight gain, loss of muscle mass, and loss of libido.

Endocrine therapy, also called hormonal therapy, involves the exogenous administration of hormones to control cancer progression. Endocrine therapy works by interfering with the action of endogenous hormones, which are powerful drivers of gene expression and cell growth in cancers of the prostate, breast, ovary, endometrium, thyroid, and adrenal cortex. Endocrine therapy, different from traditional cytotoxic chemotherapy, induces anticancer activity either by binding to specific hormone receptors (e.g., androgen or estrogen receptors) or by inhibiting enzymes that are involved in the biosynthesis and metabolism of sex steroids. The actions and side effects of commonly used anticancer hormonal agents will be reviewed in this section with emphasis on the endocrine management of prostate and breast cancers.

**Hormonal Treatment of Prostate Cancer**

The cornerstone of treatment of advanced prostate cancer is androgen deprivation therapy (ADT), first described by Huggins and Hodges in 1941. Since this pioneering work, the molecular regulation of androgen action has been well elucidated. The arrest of the androgen-dependent growth stimulus can be performed by surgical or medical castration. Medical castration is usually achieved by gonadotropin-releasing hormone (GnRH) analogue implants such as goserelin or leuprolide or by GnRH antagonist implants such as abarelix and degarelix. A reduction in circulating androgens, especially dihydrotestosterone (DHT), induces apoptotic regression of androgen-dependent cancer cells. A decrease in DHT levels to subcastrate levels occur within 72 hours of administration of GnRH antagonists and in 3 to 4 weeks after the administration of GnRH analogues. The initial agonist activity of GnRH analogues can cause a tumor flare from temporarily increased androgen levels, which can be prevented by the concomitant use of a peripheral antiandrogen such as bicalutamide, flutamide, or nilutamide.

ADT is commonly combined with surgery or radiation therapy to treat patients with locally advanced prostate cancer. Its most established use, however, is in metastatic disease, where it controls the cancer for a median of 18 to 30 months before clinical progression occurs because of the emergence of resistant clones. It has recently been shown that even in patients with castrate levels of circulating androgens, the androgen-androgen receptor (AR) axis continues to play an active role in tumor progression. To block the activity of the AR at this castrate-resistant stage, novel hormonal agents that target the testosterone-AR axis have been successfully incorporated into the treatment of advanced prostate cancer. One such drug, abiraterone acetate, is a selective steroidal irreversible inhibitor of CYP17 (17 hydroxylase/C17,20-lyase), which blocks two important enzymatic activities in the synthesis of testosterone resulting in depleted androgen levels in the cancer tissue. As a result, patients with advanced prostate cancer that have progressed through castration and antiandrogen can experience disease control when treated with abiraterone acetate. High-dose ketoconazole functions in a similar fashion, although less effectively.

Enzalutamide (previously named MDV3100) is a second-generation antiandrogen that binds to the AR with an affinity that is severalfold greater than first-generation antiandrogens (bicalutamide, nilutamide, and flutamide). It also lacks the partial agonistic activity associated with the first generation of AR inhibitors. Both enzalutamide and abiraterone acetate have been shown to prolong survival of patients with castrate-resistant prostate cancer who have progressed on chemotherapy. Acute and chronic side effects of ADT administration include hot flashes, loss of sexual libido, loss of muscle mass, weight gain, osteoporosis, fatigue, and the metabolic syndrome. Abiraterone can cause hypokalemia, hypertension, peripheral edema, and headaches from secondary mineralocorticoid excess which can be prevented by combining the drug with oral prednisone. The antiandrogens bicalutamide, flutamide, and nilutamide cause gynecomastia and hepatotoxicity.

**Endocrine Therapy of Breast Cancer**

More than two-thirds of patients with breast cancer have tumors that express estrogen receptors, progesterone receptors, or both. In these women, endocrine therapy is the mainstay of treatment of both localized and metastatic disease (Table 37-5). Among women with newly diagnosed metastatic...
breast cancer, approximately 30% to 40% will have an objective response to endocrine therapy, sometimes lasting for several years, and a substantial number will have a clinically significant period of disease stability. Tamoxifen, a selective estrogen receptor modulator (SERM), was one of the first hormonal agents to be used in breast cancer and continues to be the most important breast cancer treatment worldwide. It is approved by the FDA for the prevention of premenopausal breast cancer,\(^3\) for the treatment of ductal carcinoma in situ,\(^2\) for the treatment of surgically resected premenopausal estrogen receptor (ER)–positive breast cancer,\(^3\) and for the treatment of metastatic disease. Tamoxifen acts by blocking estrogen stimulation of breast cancer cells at the level of the ER, which inhibits both translocation and nuclear binding of the ER. This alters transcriptional and posttranscriptional events mediated by this receptor.\(^3\) Tamoxifen has binding of the ER. This alters transcriptional and posttranslational events mediated by this receptor.\(^3\) Tamoxifen has binding of the ER. This alters transcriptional and posttranslational events mediated by this receptor.\(^3\) Tamoxifen has binding of the ER. This alters transcriptional and posttranslational events mediated by this receptor.\(^3\)

Uncommon side effects of tamoxifen include cataracts and retinal toxicity. Tamoxifen predisposes patients to thromboembolic phenomena, especially when used with concomitant chemotherapy. Depression may also be associated with tamoxifen.

### Additional Hormonal Agents Used for Treating Breast Cancer\(^4\)

**Other SERMs** currently in use include toremifene\(^43,44\) and raloxifene.\(^45,46\) In the Study of Tamoxifen and Raloxifene (STAR), raloxifene was compared with tamoxifen in postmenopausal women at high risk for the development of breast cancer. Tamoxifen was superior to raloxifene in the prevention of invasive and noninvasive breast cancer but was associated with a higher risk of thromboembolic events and endometrial cancer compared with raloxifene.

Fulvestrant is an ER pure antagonist that is given as an intramuscular injection and is FDA approved for the treatment of postmenopausal women with hormone receptor–positive metastatic breast cancer after progression on antiestrogen therapy.\(^49,51\) Its main side effects include injection site reactions, hot flashes, asthenia, headache, and gastrointestinal disturbances.

An important class of hormonal drugs in use for breast cancer targets the aromatase enzyme system. Aromatase is the enzyme complex responsible for the final step in estrogen synthesis in which the androgens androstenedione and testosterone are converted to the estrogens estrone (E\(_1\)) and estradiol (E\(_2\)). Alterations in aromatase expression have been implicated in the pathogenesis of estrogen-dependent diseases including breast cancer, endometrial cancer, and endometriosis. Aminoglutethimide was the first clinically used aromatase inhibitor. When it became available, it was used to cause a medical adrenalectomy. Because of the lack of selectivity for aromatase and the resultant suppression of aldosterone and cortisol, aminoglutethimide is no longer

### TABLE 37-5 Overview of Major Hormonal Agents Used in Breast Cancer

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Individual Drug</th>
<th>Route of Delivery</th>
<th>Frequency of Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective estrogen receptor modulator</td>
<td>Tamoxifen</td>
<td>PO</td>
<td>qd</td>
</tr>
<tr>
<td></td>
<td>Toremifene</td>
<td>PO</td>
<td>qd</td>
</tr>
<tr>
<td></td>
<td>Raloxifene</td>
<td>PO</td>
<td>qd</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>Anastrozole</td>
<td>PO</td>
<td>qd</td>
</tr>
<tr>
<td></td>
<td>Letrozole</td>
<td>PO</td>
<td>qd</td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td>PO</td>
<td>qd</td>
</tr>
<tr>
<td>Estrogen receptor down-regulator</td>
<td>Fulvestrant</td>
<td>IM</td>
<td>Once monthly(^a)</td>
</tr>
<tr>
<td>Luteinizing hormone–releasing hormone agonist</td>
<td>Goserelin</td>
<td>IM</td>
<td>Once monthly(^a)</td>
</tr>
<tr>
<td></td>
<td>Leuprolide</td>
<td>IM/SC</td>
<td>Once monthly(^a)</td>
</tr>
<tr>
<td>Androgen</td>
<td>Fluoxymesterone</td>
<td>PO</td>
<td>bid</td>
</tr>
<tr>
<td>Progestational agents</td>
<td>Megestrol</td>
<td>PO</td>
<td>qd</td>
</tr>
<tr>
<td></td>
<td>Medroxyprogesterone acetate</td>
<td>PO or IM</td>
<td>Varies</td>
</tr>
</tbody>
</table>

\(^a\)Longer acting depot preparations (every 3 months) are available.
\(^b\)Depot formulations are available.
\(^c\)q4, every day; bid, twice a day; tid, three times a day.
recommended for treating metastatic breast cancer. Aromatase inhibitors have been classified in several different ways, including first, second, and third generation; steroidal and nonsteroidal; and reversible (ionic binding) and irreversible (suicide inhibitor, covalent binding). The nonsteroidal aromatase inhibitors include aminoglutethimide (first generation); rogletimide and fadrozole (second generation); and anastrozole, letrozole, and vorozole (third generation). The steroidal aromatase inhibitors include formestane (second generation) and exemestane (third generation). The main side effects associated with aromatase inhibitors include bone loss and musculoskeletal symptoms.

Megestrol is a progestational agent which is effective in treating patients with advanced breast cancer and hormonally responsive metastatic endometrial cancer. It also has limited benefits in the management of prostate cancer. Megestrol at higher doses has been used for the treatment of anorexia-cachexia syndrome related to cancer and at low dosages for the management of hot flashes in women and men. Its main side effects are appetite stimulation and resultant weight gain, suppression of adrenal steroid production, a mild increase in thromboembolic phenomena, and impotence.

Hormonal Therapy for Carcinoid Disease
Octreotide is a somatostatin analogue that is used for the treatment of carcinoid syndrome and other hormonal excess syndromes associated with some pancreatic islet cell cancers and acromegaly. Octreotide can be administered intravenously or subcutaneously. Initial doses of 50 μg are given two to three times on the first day. The dose is titrated upward, with a usual daily dose of 300 to 450 μg per day for most patients. At times, doses up to 1,500 μg per day have been given. A depot preparation is available, allowing doses to be administered at monthly intervals. Octreotide is generally well tolerated but potential side effects include bradycardia, diarrhea, hypoglycemia, hyperglycemia, hypothyroidism, and cholelithiasis.

**PRINCIPLES OF RADIATION ONCOLOGY**

**KEY POINTS**

- Radiation therapy is administered either as brachytherapy or by a machine, which delivers external beams of radiation and rarely using an intense beam of radiation for treating metastasis called stereotactic radiation therapy.
- Acute radiation effects refer to those toxicities that occur within a few weeks to months of radiation therapy.
- Late effects refer to those toxicities that occur months to years after radiotherapy and, although rare, are more commonly permanent.

**Radiation Physics and Biology**

When ionizing radiation encounters biological tissues, ejected electrons interact either directly with the target molecules within the cell or indirectly with water to produce free radicals (such as hydroxyl radicals) that subsequently produce lesions in nearby molecules, the most critical of which is the DNA double-strand break (DSB). A single DSB can kill a cell. Thus, a single large dose of radiation will produce many DSBs and have a high rate of tumor cell killing, but nearly equal killing of the adjacent normal tissue cells limits this approach to specific situations. Normal cells tend to repair DNA DSBs more effectively than cancer cells. Because tumor usually abuts or infiltrates critical normal tissue, a multifraction treatment course gives the best therapeutic effect.

**Administration of Radiation Therapy**

Radiation therapy planning involves three major steps. The first is to determine the region that requires treatment. This is done by a combination of physical exam, plain X-rays, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), as well as knowledge of the patterns of spread and failure patterns. In the second step, optimal patient position is determined to allow a combination of beams to treat the target while minimizing normal tissue dose. Immobilization devices such as custom-made foam cradles or mesh-plastic masks are constructed to allow reproducible patient positioning for daily treatment. A three-dimensional representation of the patient is computer-generated from the CT or MRI. At the end of this session, reference marks are placed on the patient (tattoos) that will be used along with imaging to facilitate precise daily set up. The third step is to determine the beam arrangement. The complexity of this step varies tremendously depending on the clinical setting. In some cases, a single radiation beam may be sufficient to treat the tumor. In other cases, many hours of planning and quality assurance checks are required in a process called intensity-modulated radiation therapy (IMRT) in which the physician defines a set of objectives that are to be met in treating the tumor and avoiding normal tissue and a computer calculates hundreds of potential beam arrangements to optimize therapy.

Radiation therapy can be administered as brachytherapy (permanent or temporary implantation of radioactive sources in or around a tumor) or by a machine (a linear accelerator) with the patient lying on a treatment couch. This latter kind of radiation is typically delivered in daily fractions, from as few as 1 to more than 40 treatments. Treatment typically takes less than 15 to 20 minutes. Most of this time is spent aligning the patient on the machine; the radiation beam is on for only a minute or two. Treatment is similar to undergoing a diagnostic X-ray; the patient will not feel the “beam.” The recent introduction of stereotactic radiation therapy, using many intersecting beams and five or fewer high doses of radiation permits the noninvasive ablation of metastases (see Table 37-6). When critical normal tissues abut the tumor, image-guided radiation therapy (IGRT), which involves the use of imaging techniques on the linear accelerator (such as a form of CT scanning), can permit treatment delivery to attain millimeter accuracy.

Approximately 50% of patients with cancer will receive radiation therapy during the course of their illness, either with curative intent or for palliation. With respect to cure, radiation therapy can be used (1) alone to cure small malignancies, (2) in combination with chemotherapy to cure locally advanced tumors that are either unresectable or resectable only with substantial functional loss (e.g., laryngectomy),
bony metastases. The combination of systemic treatment with narcotics and adjuvant medications (antidepressants, anti-epileptic, and anti-inflammatory) with localized radiation to sites of severe pain can relieve pain in the great majority of patients. Radiation therapy may also be used for palliation of tumors that may obstruct the respiratory, gastrointestinal, or genitourinary tracts. Radiation can also play a role in oncologic emergencies. These include superior vena cava (SVC) syndrome resulting from tumor occlusion of the SVC (most commonly from either lymphoma or lung cancer) and spinal cord compression. In both of these cases, the prompt initiation of radiation therapy may reverse life-threatening or neurologically devastating situations.

and (3) before or after surgery to prevent the recurrence of clinically occult disease (see Table 37-6). The doses used in these setting are typically determined by the tolerance of the surrounding tissue. (Although a site can be re-irradiated if tumor recurs, the risks of toxicity are substantially increased.) The acute and chronic toxicity of radiation is summarized in Table 37-7. It is important to note that there is no evidence that radiation therapy increases the risk of breast cancer in woman treated with lumpectomy and radiation therapy for breast cancer.

Radiation is also important in palliation of symptoms produced by cancers even when cure is not possible. Treatment is highly effective at relieving the pain resulting from

<table>
<thead>
<tr>
<th>Organ site</th>
<th>Curative RT alone</th>
<th>Curative Chemo–RT</th>
<th>Organ Sparing</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1) Metastases to the brain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Malignant brain tumors</td>
<td>—</td>
<td>1) Postoperative (with chemo for malignant tumors)</td>
</tr>
<tr>
<td></td>
<td>2) Benign brain tumors</td>
<td></td>
<td></td>
<td>2) Prophylactic cranial RT for small cell lung cancer</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Small head and neck cancers (particularly larynx)</td>
<td>Advanced head and neck cancers</td>
<td>Locally advanced laryngeal cancer</td>
<td>Postoperative</td>
</tr>
<tr>
<td>Lung</td>
<td>Small metastases to and primary tumors of the lung</td>
<td>Limited stage small cell lung cancer and stage III non–small cell lung cancer</td>
<td>—</td>
<td>Postoperative therapy for positive mediastinal lymph nodes</td>
</tr>
<tr>
<td>Breast</td>
<td>—</td>
<td>—</td>
<td>Breast preservation “postlumpectomy”</td>
<td>Postmastectomy</td>
</tr>
<tr>
<td>Liver</td>
<td>Small metastases and primary tumors of the liver&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>Postoperative</td>
</tr>
<tr>
<td>Pancreas</td>
<td>—</td>
<td>Locally advanced unresectable</td>
<td>—</td>
<td>Postsurgery (with chemo)</td>
</tr>
<tr>
<td>Esophageal</td>
<td>Early stage</td>
<td>Locally advanced</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stomach</td>
<td>—</td>
<td>Locally advanced unresectable</td>
<td>—</td>
<td>Preoperative or postoperative (with chemo)</td>
</tr>
<tr>
<td>Rectum</td>
<td>—</td>
<td>Locally advanced unresectable</td>
<td>—</td>
<td>Preoperative or postoperative</td>
</tr>
<tr>
<td>Anus</td>
<td>Small tumors</td>
<td>Locally advanced</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Endometrium</td>
<td>Locally advanced, nonresectable</td>
<td>—</td>
<td>—</td>
<td>Postoperative for invasive or node-positive disease</td>
</tr>
<tr>
<td>Cervix</td>
<td>Small lesions</td>
<td>Locally advanced</td>
<td>—</td>
<td>Postoperative for positive nodes</td>
</tr>
<tr>
<td>Prostate</td>
<td>Early stage</td>
<td>Locally advanced (with androgen ablation therapy)</td>
<td>—</td>
<td>Preserves potency (compared to surgery)</td>
</tr>
<tr>
<td>Bladder</td>
<td>—</td>
<td>Locally advanced</td>
<td>Bladder preservation</td>
<td>—</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Locally advanced</td>
<td>—</td>
<td>Limb sparing</td>
<td>Preoperative or postoperative</td>
</tr>
<tr>
<td>Skin</td>
<td>Small and large basal and squamous</td>
<td>—</td>
<td>Eyelid, ear, and nose</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>Ocular melanoma, lymphomas (selected)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup>Using stereotactic radiation.
### Toxicity of Radiation Therapy

<table>
<thead>
<tr>
<th>Organ Site</th>
<th>Acute (During and to Up to 1 Month After Treatment)</th>
<th>Late (Greater than 1 Month After Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
<td>Somnolence (whole brain radiation)</td>
<td>Focal high-dose radiation—necrosis (often difficult to distinguish from tumor progression)</td>
</tr>
<tr>
<td></td>
<td>Nausea and vomiting</td>
<td>Whole brain radiation—decreased neurocognitive function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased pituitary function</td>
</tr>
<tr>
<td><strong>Eye and visual apparatus</strong></td>
<td>—</td>
<td>Cataracts (at 10 y)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased tearing (lacrimal glands)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blindness</td>
</tr>
<tr>
<td><strong>Head and neck</strong></td>
<td>Mucositis</td>
<td>Xerostomia</td>
</tr>
<tr>
<td></td>
<td>Xerostomia</td>
<td>Aspiration</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
<td>Decreased thyroid function</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>—</td>
<td>1–6 mo: radiation pneumonitis (fever, cough, and shortness of breath without infection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;6 mo: fibrosis</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td>—</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac dysfunction (rare in the modern era)</td>
</tr>
<tr>
<td><strong>Esophagus</strong></td>
<td>Dysphagia</td>
<td>Stricture</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>Radiation-induced liver disease (veno-occlusive disease)</td>
<td>Liver failure</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td>Nausea and vomiting</td>
<td>Bleeding, perforation</td>
</tr>
<tr>
<td><strong>Intestine</strong></td>
<td>Diarrhea</td>
<td>Bowel obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td><strong>Rectum/anus</strong></td>
<td>Tenesmus</td>
<td>Proctitis</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td>—</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
<td>Dysuria</td>
<td>Contracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ulcer</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td>Dysuria</td>
<td>Ureteral stricture</td>
</tr>
<tr>
<td></td>
<td>Obstruction from edema</td>
<td>Impotence (preprostatic nerves)</td>
</tr>
<tr>
<td><strong>Ovaries/testes</strong></td>
<td>—</td>
<td>Sterility</td>
</tr>
<tr>
<td><strong>Extremities</strong></td>
<td>—</td>
<td>Soft tissue fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased joint function</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Desquamation</td>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Telangiectasias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decrease in wound healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alopecia</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td>Lymphopenia (without clinical significance)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (when combined with chemotherapy)</td>
<td></td>
</tr>
<tr>
<td><strong>All sites</strong></td>
<td>Fatigue</td>
<td>Second cancers (typically sarcoma) in the treated field</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal latency is 3 y; usual is 10–30 y. Particularly important in childhood cancers and young women receiving radiation therapy for Hodgkin disease (breast cancer). Overall risk is approximately 1 patient in 1,000.</td>
</tr>
</tbody>
</table>
Hematopoietic stem cell transplantation (HSCT) (blood or marrow transplantation [BMT]) is increasingly incorporated as a standard treatment for several hematologic and nonhematologic disorders. This procedure involves the process of administering high-dose chemotherapy with or without radiation followed by infusion of stem cells which can be from self (autologous) or a foreign donor (allogeneic). The primary care clinician plays a pivotal role in long-term survivors receiving HSCT. Chronic GVHD is a multisystem alloimmune and autoimmune disorder that occurs after allogeneic HSCT; common organs affected in chronic GVHD are skin, eyes, lungs, liver, and gastrointestinal tract. Preventive measures including the early detection of secondary cancer are important in reducing morbidity and mortality in long-term survivors after HSCT and require a multidisciplinary approach.

Nearly 60,000 allogeneic HSCTs are performed worldwide annually. Similarly, the number of autologous HSCT in the United States has steadily increased since 2000. In this era, a stem cell source can be found for virtually all patients who have an indication to receive HSCT. Advances in HSCT practice and supportive care have led to improved outcomes. It is estimated that by 2020, half a million long-term survivors will exist worldwide. Most patients will be monitored by their PCC.

Indications for Hematopoietic Stem Cell Transplant

Table 37-8 summarizes the list of diseases for which autologous or allogeneic HSCT may be a treatment. The list includes diagnoses for which transplant is a standard treatment as well as diagnoses for which the role of transplant is a somewhat newer option.

Common Indications of Transplantation

Autologous HSCT: The diseases most commonly treated with transplant are multiple myeloma and lymphoma.

Allogeneic HSCT: The diseases most commonly treated with transplant are acute and chronic leukemias, lymphoma, myelodysplastic syndromes (MDS), and aplastic anemia.

Developments over the Past Decade

HSCT is being studied as a potential therapy for several diseases not traditionally treated with transplant. Some of the diseases for which recent clinical studies are showing promising results include renal cell carcinoma and other solid tumors, sickle cell disease, neuroblastoma, β-thalassemia major, and autoimmune disorders (e.g., systemic lupus erythematosus, multiple sclerosis, etc.). The largest growth in HSCT is the increase in use of transplant to treat patients aged 50 years and older. Increased use of nonmyeloablative transplants and other advances in conditioning regimens (nonmyeloablative conditioning regimen cause minimal cytopenia and can be given also without stem cell support) that have led to decreased regimen-related morbidity and mortality have made transplant an option for the elderly (up to age 75 years). The eligibility of these older patients has contributed to an increase in allogeneic and

<table>
<thead>
<tr>
<th>TABLE 37-8</th>
<th>Indications for Hematopoietic Stem Cell Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic Malignancies</strong></td>
<td><strong>Solid Organ Malignancies</strong></td>
</tr>
<tr>
<td>Non-Hodgkin, Hodgkin lymphoma, and other lymphoproliferative disorders</td>
<td>Testicular cancer</td>
</tr>
<tr>
<td>Acute myeloid and lymphoid leukemia</td>
<td>Medulloblastoma</td>
</tr>
<tr>
<td>Myelodysplastic and myeloproliferative disorders: chronic myelomonocytic leukemia, idiopathic myelofibrosis, familial hemophagocytic lymphohistiocytosis, and other histiocytic disorders</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma and other plasma cell disorders</td>
<td></td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td></td>
</tr>
</tbody>
</table>

MPS-HS, Mucopolysaccharidosis-Hurler syndrome.
autologous HSCT for diseases more commonly occurring in older adults such as MDS, acute myelogenous leukemia, and non-Hodgkin lymphomas.

**Timing of Stem Cell Transplantation**

The likelihood of a successful transplant can be improved by taking steps to enable a transplant to be performed at a time that is most beneficial in the course of the patient’s disease. Generally, better outcomes are achieved when transplants, either allogeneic or autologous, are performed; when patients are in remission or have a small tumor burden; and in patients with good performance status and normal organ function. Studies have shown that for many diseases, transplants performed early in the disease process are associated with lower risks of transplant-related mortality and disease recurrence.

**Complications Following Stem Cell Transplantation and Their Management**

There are several early and late effects of high doses of chemotherapy and/or radiation administered as the preparative regimen prior to the stem cell infusion process. Many different chemotherapeutic agents are used as conditioning regimens, each with unique late effects on vital organs of the body. Importantly, the immunologic response of the graft T cells on the host (graft-versus-host disease [GVHD]) may lead to varying degrees of skin, liver, and mucosal toxicities. Early complications are commonly related to the conditioning regimen often involving the gastrointestinal tract such as severe nausea, mucositis, and diarrhea or damage to endothelium inducing small blood vessel occlusion (veno-occlusive disease/sinusoidal obstruction syndrome). In addition, side effects could be from low graft function including infection, bleeding, or from drug reaction such as pneumonitis from chemotherapy. Late complications occur secondary to deregulation of immune system related to donor graft or delayed immune reconstitution. A spectrum of late complications involves organ dysfunction and secondary malignancy that shortens life span (see next section).

**Role of Primary Care Clinician in Posttransplantation Care**

Transplant patients have special health care needs after returning home, and PCCs assuming the care of such patients work together with the transplant center team to develop a treatment and communication plan to ensure that patients receive appropriate long-term treatment and close monitoring. To reduce the incidence of infectious complications, patients who are immuno-suppressed must restrict their activities. The following are typical restrictions, but restrictions can differ because of variations in transplant center protocols and an individual patient’s condition.

Postdischarge restrictions (3 to 6 months): no longer requires a mask; monthly PCC visit, more frequent if patients have GVHD; monitor for chronic GVHD (skin rash, nausea, vomiting, weight loss, oral ulcerations, ocular problems, abnormal liver function tests, etc.); and continue prophylactic cyclosporin, tacrolimus, or other immunosuppressive drug in consultation with transplant center.

Postdischarge restrictions (6 to 12 months): stop immunosuppressive drugs if there is no GVHD in consultation with transplant center, may be able to return to work, monitor for chronic GVHD, still at risk for infection, and monitor for disease status. A few patients may still require prophylactic agents (e.g., antibiotics).

**Guidelines for Long-term Care (>12 Months Post-HSCT)**

For long-term survivors, the prospect of long-term survival is excellent (>85% at 10 years after HSCT). Yet, among long-term survivors, mortality rates are fourfold to ninefold higher than observed in an age-adjusted general population for at least 30 years after HSCT, yielding an estimated 30% lower life expectancy compared with someone who has not been transplanted. The most common causes of excess deaths other than recurrent malignancy are chronic GVHD, infections, second neoplasms, and respiratory and cardiovascular disease.

Recommended screening and preventive practices for transplant recipients have been developed by a consensus panel formed by members of the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Group for Blood and Marrow Transplantation (EBMT), and the American Society for Blood and Marrow Transplantation (ASBMT). These guidelines list recommended tests and procedures for patients’ 6-month, 1-year, and annual posttransplant checkups. The checklist indicates the tests and procedures applicable to autologous or allogeneic recipients only. Most transplant centers recommend a detailed checklist to be followed by the treating physician; however, if not available, it can be found at http://www.marrow.org or http://www.asbmt.org.

**Common Late Effects and Follow-up Guidelines**

1. Thyroid function: Up to 30% of patients with HSCT will develop hypothyroidism. The incidence of secondary thyroid carcinoma also increases in the setting of radiation exposure. Recommend measuring thyroid function at 1-year posttherapy, with subsequent testing based on abnormal thyroid hormone levels or patient symptoms.

2. Monitoring bone loss: All patients should be monitored for bone loss at periodic intervals. Many transplant patients need to be on steroids for chronic GVHD; long-term steroid use significantly reduces the bone mineral density. Bone mineral density measurements are therefore recommended at 1-year post–allogeneic HSCT. Subsequent monitoring depends on abnormal test results or new symptoms. In addition, patient should continue calcium and vitamin D replacement unless with any contraindications. We also recommend checking vitamin D level at 6 to 12 months intervals, and patients with vitamin D deficiency should receive weekly ergocalciferol.

3. Gonadal function: Practically all chemotherapeutic and radiation therapies affect gonadal function in some fashion. Alkylating agents in particular are known to cause gonadal failure. The result is loss of fertility and other symptoms, which impair quality of life to varying degrees. Men are usually more symptomatic with erectile dysfunction and fatigue. Hormone replacement therapy can easily be given to all those who need it. Patients who are subclinically deficient benefit from replacement therapy, and it is therefore recommended that gonadal dysfunction be evaluated both biochemically and symptomatically. For prepubertal patients, we recommend assessment of gonadal function at 6 months following chemotherapy and annually thereafter. For postpubertal men and women, it can be assessed starting at 1-year posttherapy.
4. Cardiovascular function: Young adult survivors are at increased risk of various cardiovascular outcomes such as congestive heart failure, myocardial infarction, and pericardial disease. These adverse effects can be apparent as late as 30 years. This risk appears to be apparent even at lower exposures to anthracycline and/or radiation therapy. Therefore, as the young patient approaches the age in which cardiovascular disease becomes more apparent, diligent monitoring is necessary. Regular lab tests focusing on optimal control of cholesterol and triglycerides are required along with a focus on healthy lifestyle.63

Secondary Malignancies

With greater numbers of patients surviving long term after HSCT, second malignancies have increasingly been recognized. Secondary malignancies following HSCT have traditionally been classified into three groups, that is, leukemia, lymphoma, and solid tumors. However, secondary lymphoma, leukemia/MDS, and solid tumors develop with a typical chronology. Malignant solid tumors are really the only late malignant complication of allogeneic HSCT (secondary leukemia generally occurs within a median elapsed time of 6.7 months after SCT, lymphoma within a median of 2.5 months, whereas the median time to development of solid tumors lies between 5 and 6 years). Those who have received radiation therapy that included the breasts (e.g., total body irradiation [TBI]) will need annual mammograms beginning 8 years after radiation exposure or age 25 years, whichever comes first. Aggressive, annual physical exams and screening for secondary malignancies should include a survey of specific organs especially skin, head and neck, and gynecologic cancers.64

Screening for Chronic Graft-Versus-Host Disease

Chronic GVHD is a multisystem chronic alloimmune and autoimmune disorder that occurs later after allogeneic HSCT (Table 37-9). It is characterized by immunosuppression, immune dysregulation, decreased organ function, significant morbidity, and impaired survival. Approximately 10% to 30% of patients require continued immunosuppressive treatment beyond 5 years from the initial diagnosis of chronic GVHD. Therefore, it is not surprising that corticosteroids and other immunosuppressive therapies are major contributors of late complications after allogeneic HSCT. If not treated adequately and in severe cases, chronic GVHD can result in major disability related to keratoconjunctivitis sicca, pulmonary insufficiency caused by bronchiolitis obliterans, or restrictive lung disease related to scleroderma or fasciitis as well as joint contractures, skin ulcers, esophageal and vaginal stenosis, and many other long-term complications.

Early detection and diagnosis of chronic GVHD is vital to prevent long-term complications. Definitive diagnosis of chronic GVHD requires excluding other diagnoses such as infection, drug effects, malignancies, residual postinflammatory damage, and scarring. Administration of topical and/or systemic treatment with prompt and effective management of infections is crucial. Infection is the leading cause of death in chronic GVHD.

### TABLE 37-9 Post–Stem Cell Transplant Management

<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>Symptoms</th>
<th>Drugs and Management Plans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin/hair</td>
<td>Rash, scleroderma (skin tightening like leather), lichenoid skin changes, dyspigmentation, alopecia</td>
<td>- Topical and or systemic steroids for skin GVHD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Additional IST in consultation with transplant team</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Screening for secondary cancer</td>
</tr>
<tr>
<td>Eyes</td>
<td>Dryness, abnormal Schirmer Test (dryness with poor or no watering from eye), corneal erosions, conjunctivitis</td>
<td>- Topical immunosuppressive agents including steroid and calcineurin inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Need regular follow-up with ophthalmologist</td>
</tr>
<tr>
<td>Mouth</td>
<td>Atrophic changes, lichenoid changes, mucositis, ulcers, xerostomia, dental caries</td>
<td>- Topical steroid (e.g., clobetasol cream/gel)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dexamethasone mouth rinse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Regular follow-up with dentist, screening for secondary cancer</td>
</tr>
<tr>
<td>Lungs</td>
<td>Bronchiolitis obliterans</td>
<td>- Inhaled steroids and bronchodilators</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Azithromycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Systemic IST including steroids in severe cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Serial PFT and follow-up with pulmonologist</td>
</tr>
<tr>
<td>Gastrointestinal (GI) tract</td>
<td>Esophageal involvement, chronic nausea/vomiting, chronic diarrhea, malabsorption, fibrosis, abdominal pain/cramps, weight loss</td>
<td>- Topical steroid in mild/moderate cases (e.g., budesonide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Systemic IST in consultation with transplant center</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- GI team follow-up</td>
</tr>
<tr>
<td>Liver</td>
<td>Abnormal liver function tests</td>
<td>- Ursodiol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Systemic IST in consultation with transplant center for liver GVHD</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Vaginitis, strictures, stenosis, cystitis</td>
<td>- Topical steroid (e.g., clobetasol) and estrogen cream</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Gynecology follow-up and screening for secondary cancer</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthritis, contractures, myositis, myasthenia, fasciitis</td>
<td>- Systemic steroid</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Cytopenia, eosinophilia</td>
<td>- Can occur in patients with chronic GVHD</td>
</tr>
</tbody>
</table>

GVHD, graft-versus-host disease; IST, immunosuppressive therapy; PFT, pulmonary function test.
INTEGRATIVE ONCOLOGY

KEY POINTS

- Primary care clinicians should be aware of common issues in integrative oncology because patients with cancer may seek their advice and counsel on nutrition, the safety of dietary supplements, and methods of stress reduction both during and after their cancer treatment.
- Nonpharmacologic interventions such as massage therapy, acupuncture, and engaging spirituality may be useful for improving the quality of life of patients with cancer and survivors.

Patients and survivors of cancer are increasingly turning to practitioners of integrative oncology to complement their conventional cancer care. The Consortium of Academic Health Centers for Integrative Medicine defines the term as “the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, health care professionals, and disciplines to achieve optimal health and healing.” The term integrative medicine is preferable to “complementary and alternative medicine” or “CAM” because it best describes the intent of the practice. “Alternative” implies that an intervention is being used instead of conventional therapy. Integrative oncology practitioners do not advocate the use of alternative therapies but help to integrate complementary interventions into conventional cancer care. Numerous studies have determined that patients with cancer frequently are uncomfortable sharing their use of complementary therapies with their medical or radiation oncologist for fear that they will be told not to or asked to find another provider. Hence, patients undergoing cancer treatment may be more inclined to discuss their use of complementary therapies with their trusted PCCs. PCCs should be aware of some of the more common issues in integrative oncology about which their patients may seek their advice and counsel.

Nutrition and Physical Activity

Integrative medicine takes into account the whole person including all aspects of lifestyle and makes use of all appropriate therapies. In the realm of lifestyle, nutrition, physical activity, and stress are key areas of concern in integrative oncology that may be overlooked or even dismissed by the conventional oncologist. Although most Americans can recognize tobacco as a cause of avoidable cancer morbidity and mortality, fewer are aware of the equivalent contribution of nutrition. Fortunately, the American Institute for Cancer Research (AICR) and the American Cancer Society are at the forefront of the issue, publishing updated guidelines not only pertaining to cancer risk reduction but also relevant to the person living with cancer. In fact, the 10th and last of the AICR guidelines states that “after treatment, cancer survivors should follow the recommendations for cancer prevention.”

The nutrition and physical activity guidelines are summarized as four main recommendations by the American Cancer Society: (1) achieve and maintain a healthy weight throughout life; (2) adopt a physically active lifestyle; (3) choose a healthy diet with an emphasis on plant foods; and (4) if you drink alcoholic beverages, limit consumption. The AICR estimates that obesity-related excesses of seven cancers—postmenopausal breast, esophagus, pancreas, gallbladder, colorectal, endometrial, and kidney—account for 105,000 preventable deaths a year in the United States alone. Numerous mechanisms have been advanced to suggest how obesity increases the risk of cancer. Fat secretes cytokines that produce inflammation, and an excess in body fat may impair immunity. Obesity leads to insulin resistance, elevating levels of insulin, insulin-like growth factor-1 and other growth factors that promote malignancy. Finally, fat produces estrogen. In addition to increasing the risk of several cancers, obesity is associated with a poorer prognosis in several malignancies, and evidence is accumulating that intentional weight loss after a diagnosis may improve survival.

Physical activity is a key component of the integrative approach. An active lifestyle has been shown to reduce the risk of breast, colon, and prostate cancers. Increasing evidence suggests that in patients with a cancer diagnosis, 3 to 6 hours of vigorous exercise each week may be associated with prolonged survival. Exercise also helps to reduce fatigue and depression by way of endorphin release and may also improve sleep. Some physical activities—yoga, tai chi, and qi gong—have a significant mind-body component that also serves to help reduce stress above and beyond the effect of the exercise itself. These practices are increasingly being associated with improvement in quality of life measures in patients with cancer and survivors.

The expanded version of the nutrition guidelines suggest to eat at least 2.5 cups of fruits and vegetables each day, choose whole grains instead of refined grain products, avoid sugary drinks, and limit consumption of red meats while avoiding processed meats. Clearly, these are recommendations attuned to the ultimate goal of achieving and maintaining a healthy weight that will serve to decrease the risk of cancer as well as diabetes, heart disease, and other degenerative diseases that plague our overweight society. Epidemiologic studies in patients participating in cancer clinical trials have shown that patients with cancer who adhere to these more prudent dietary recommendations as opposed to consuming the standard American diet benefit with regards to more prolonged disease-free and overall survival. A common lament of patients with cancer is that upon asking their oncologist what they should eat, they are told that they should “eat whatever you want because it doesn’t matter,” or it is often related that a radiation oncologist advises only to eat white foods while receiving treatment to avoid antioxidant phytonutrients that may interfere with radiation’s oxidative damage to the tumor cell DNA. PCCs could offer a great deal of benefit to their patients who may not access an integrative oncologist or oncology nutritionist by providing them with correct information. In general, patients should consume a rainbow of colors on their plate to assure a diet rich in antioxidants and phytonutrients. Antioxidant supplements, on the other hand, might be best avoided in active treatment situations.

The optimal diet is rich in cruciferous, orange-yellow and green leafy vegetables as well as heavily pigmented fruits. Seasonings should include ginger, garlic, onions, turmeric, and the Mediterranean spices basil, oregano, thyme, and rosemary. Asian mushrooms—shiitake, maitake, and enoki—and green...
teasome synergistic benefits. Deep, cold-water fish such as salmon, black cod, albacore tuna, herring, mackerel, and sardines provide a source of anti-inflammatory omega-3 fatty acids. Poultry products should be organic to minimize exposure to excessive proinflammatory omega-6 fatty acids. If consumed at all, alcoholic beverages should be limited to two a day for men, one a day for women, and one a week for women at high risk for breast cancer. Red wine, rich in resveratrol, would be the preferred alcoholic beverage.

**Dietary Supplements**

Many of the foods listed earlier contain potent phytonutrients. Indole-3-carbinol from cruciferous vegetables, epigallocatechin gallate (ECGC) from green tea, and resveratrol from red grapes and wine are now also frequently sought after as dietary supplement capsules by patients living with and beyond cancer. Whether the “more is better” adage holds true in the situation of concentrated phytonutrients remains to be proven. For example, ECGC taken on an empty stomach was shown to be associated with hepatotoxicity. One gram of resveratrol contains what would be found in 667 bottles of red wine.

Most conventional medical and radiation oncologists will request that their patients simply avoid all supplements, especially during active radiation or chemotherapy. This recommendation is primarily based on the concern that evidence to support the use of any of these agents is lacking and, as a group, oncologists rely very heavily on evidence before recommending any of the very potent therapies they use against malignant disease. In the absence of convincing data supporting therapeutic benefit, the conventional oncologist takes the path of least resistance and advises to avoid all supplements. Other valid concerns about supplement use are the potential for supplement–drug interactions via a pharmacokinetic or pharmacodynamic pathway and the oxidant–antioxidant issue.

The hepatic cytochrome P450 enzyme system is responsible for the metabolism of many chemotherapeutic agents as well as many botanicals. St. John’s wort, for example, used for the treatment of mild-to-moderate depression, should be avoided in patients receiving chemotherapy because it is a strong inducer of many P450 isoforms and will lead to a decreased concentration and, hence, decreased efficacy of many chemotherapeutic agents administered concurrently. There are some resources available to address theoretical potential botanical supplement–chemotherapy drug interactions but pharmacokinetic interaction studies have clearly not been done to assess all the possible.

Many patients boost their intake of antioxidant supplements to protect their normal tissues from being damaged by the effects of chemotherapy or radiation. Oncologists generally fear that this will serve to protect the tumor as well. Only one trial of vitamin E supplementation in patients receiving radiation therapy for head and neck malignancies demonstrated a potential negative effect on recurrence and survival. A meta-analysis of 18 studies of antioxidants during chemotherapy failed to show any negative effects on tumor response and did suggest that toxicities of therapy were decreased with antioxidant supplement use. More prospective trials are warranted to understand this issue better. In the meantime, if patients are being treated for cure or in an adjuvant setting, it may be best to advise postponing antioxidant supplements until after active therapy has concluded. If the goal is palliation, use during treatment may be considered.

**Stress Management**

The integrative oncologist appreciates that patients with cancer are often very stressed, leading to sympathetic nervous system excess with overproduction of epinephrine and cortisol. A controlled study in mice with breast cancer confined for 3 hours a day to reproduce stress or not showed that after 3 weeks, the stressed cohort had increased size and number of metastatic lesions, whereas the primary lesions were similar to the unstressed group. Evidence now suggests that women with higher stress levels and less social support have ovarian tumors that are more aggressive because of higher expression of vascular endothelial growth factor (VEGF) compared to women with better social support.

Consultation with an integrative oncologist, or an informed primary care provider, who can outline steps that the patient can take themselves—nutrition, exercise, supplements—allows patients to regain some of the sense of control that they feel they have lost once they heard the diagnosis of cancer. This patient empowerment serves to reduce stress and increase a sense of hope.

Massage is another useful way to deal with stress. For many years, there was a concern that massage could lead to cancer spreading. Massage therapists may want to avoid open lesions but rest assured that massage is not likely the means of cancer metastasizing. The broad field of mind–body interventions includes mindfulness-based stress reduction (MBSR), biofeedback, hypnosis, guided imagery, art therapy, music therapy, yoga, tai chi, and other relaxation techniques. These mind–body interventions work by increasing parasympathetic tone, lowering epinephrine and cortisol levels.

**Acupuncture and Traditional Chinese Medicine**

A National Institutes of Health (NIH) consensus panel in 1997 recognized the benefit of acupuncture for the treatment of chemotherapy-induced nausea and vomiting. Since that time, several controlled clinical trials have shown additional benefits in the treatment of cancer or treatment-related symptoms such as xerostomia following radiation therapy for head and neck tumors, musculoskeletal complaints related to aromatase inhibitor therapy, hot flashes in both men and women with hormone ablation therapies, and chemotherapy-induced peripheral neuropathy. Traditional Chinese medicine (TCM) practitioners are valuable members of the integrative oncology team. These practitioners also employ herbs, attention to diet, moxibustion (burning of the herb mugwort over meridians) and qi gong (meditative movement) in their armamentarium of therapies. Again, the TCM practitioner prescribing herbs should be well versed in cancer chemotherapy drugs and communicate with the prescribing oncologist or integrative care provider to protect against potential undesired interactions with prescribed medications.

**Religion and Spirituality**

Integrative oncology addresses the whole person living with or beyond cancer—mind, body, and spirit. Many patients find comfort and support in their long-standing religious beliefs, practices, and community and should be encouraged to continue to do so. Spirituality has different meanings for different people. One can be spiritual without being active in a specific organized religion. Understanding spirituality to be whatever it is that gives life meaning and the means within oneself for a connection to be felt with the larger universe.
the caring clinicians will redirect their patients with cancer wondering “Why me?” to seek solace in their spiritual beliefs rather than trouble over unanswered questions.

The Role of the Primary Care Clinician

Although certainly not exhaustive, this introduction to integrative oncology should resonate with the goals of the PCC. Relationship-based, patient-centered care allows the patient with cancer to feel less alone during what can be a frightening course of treatment. Where the oncology team may dismiss the importance of nutrition and physical activity and forbid the use of dietary supplements, a well-informed PCC could perhaps offer the patient some alternative suggestions. Referrals to practitioners who may assist with relaxation—massage therapists, guided imagery or other mind–body practitioners, or conventional psychological counseling—may decrease the detrimental effects of ongoing stress. The PCC may consider referring the patient undergoing active cancer treatment to an experienced acupuncturist who may be able to alleviate treatment-related side effects, allowing the patient to be able to better tolerate his or her therapy. Remembering to engage the patient in meaningful discussion about his or her beliefs—religious and/or spiritual—helps the patient find meaning and comfort in a time of turmoil. This brief overview may leave the reader with unanswered questions about this emerging field. An increasing number of references are available for primary clinicians interested in learning more about integrative oncology to assist their patients with their journey through cancer treatment into survivorship or, when needed, end-of-life care.66,69

CLINICAL TRIALS

KEY POINTS

• Phase 1 trials are designed to determine the toxicities and appropriate dose and schedule for a new agent or combination of agents.

• Pharmacodynamic studies in phase 1 trials are increasingly important for targeted agents coming into the clinic; increasingly, phase 1 trials will focus on patients selected by screening for specific molecular characteristics.

• Phase 2 trials define activity for a given agent in a well-defined patient population. The typical end point is response rate with a 95% confidence interval. Randomized phase 2 trials give a contemporaneous point of reference.

• Phase 3 trials are the most definitive and are fundamental for evidence-based medicine.

• Primary care clinicians have a key role in encouraging patients to participate in responsible clinical trials and building patient trust with the oncologist.

Preclinical Studies

Before drugs or targeted agents are selected for human testing in the clinic, they normally undergo a substantial number of preclinical evaluations to determine their activity and their promise as an anticancer agent. Although previously, these tended to be natural products and their chemical derivatives, more recently, candidate drugs are discovered by screening large libraries against well-defined target molecules. Alternatively, MoAbs raised against these targets may be developed. Once candidate agents are identified for development, they are then tested against human tumors implanted in nude (immunoincompetent) mice (xenograft model). In addition, combinations of agents may be tested to demonstrate increased activity for combinations of targeted drugs with standard agents. Targeted agents are known to inhibit specific cellular enzyme targets and may be selected for their in vitro inhibitory concentration regarding a specific target (e.g., erlotinib inhibiting epidermal growth factor receptor [EGFR] or imatinib inhibiting translocation of the breakpoint cluster region Abl oncogene [BCR-ABL]). Once an inhibitor of a specific target has been identified, usually by screening large chemical libraries, in vitro testing can determine the appropriate inhibitory activity in cell lines bearing that enzyme activity and pharmacologic potential for human use. Prior to submission of the investigational new drug applications to the FDA, additional tests related to the toxicology of the drug must be performed. The toxicology tests are performed in at least two species of animals, and these should demonstrate the anticipated toxicities in man as well as the starting dose for phase 1 trials.

Phase 1 Trials

Phase 1 trials are generally the first tests in humans involving any drug with the intention of determining the toxicity profile, dose to be administered in future trials, and the most appropriate schedule. In the oncology setting, phase 1 trials include patients who have already received standard therapy and have no other approved or reasonable therapies available because the benefit for human use of a new agent is as yet unknown. With the use of targeted agents, the potential benefit versus risk of phase 1 trials has shifted much more toward potential benefits, especially in selected populations. The phase 1 trial generally involves few patients and uses a dose escalation design. Typically, three patients are treated at each dose level and expanding to six patients at each dose level where significant toxicity is observed. Initial starting dose is generally determined by the toxicology results in the most sensitive species. Subsequent dosing levels are generally multiples of the starting dose in decreasing step size to approach the maximum tolerated dose (MTD) without overshooting.

Phase 1 studies generally involve additional sampling of blood and tissue for pharmacokinetics and pharmacodynamics. The pharmacokinetics studies generally involve rather frequent blood sampling of patients for drug levels to determine the rate of drug metabolism and the area under the curve (AUC) for a given dose. Pharmacodynamic studies generally involve tissue sampling and are especially important with targeted agents because they will attempt to determine if the target of an inhibitor is actually inhibited. Ideally, the inhibition should occur at a nontoxic dose level.

Window of Opportunity Studies

Another more recent type of phase 1 trial involves short courses of a drug prior to surgery or biopsy, which has been called a “window of opportunity” study. In this type of study, the patient receives a targeted agent for 2 to 3 weeks before undergoing the procedure. The purpose is to biopsy a tumor before dosing and then obtain surgical tissue after a short-dosing interval to establish the tissue pharmacodynamic effects of the inhibitor. This is a very important type of study for patient
participation because it is one of the key ways that we can actually determine whether targeted therapy inhibits the proposed targets of these drugs. This is similar to a “phase 0” study, although it involves patients and the preoperative time frame. In a phase 0 study, the agent is given in low doses to a normal volunteer (typically) and a pharmacodynamic end point (target binding if radiolabelled or protein inhibition in a biopsy specimen) is determined.

**Phase 2 Studies**

In the phase 1 study, the appropriate dosing schedule for additional studies and the toxicity profile of the new agent are established. Once this is known, single-agent studies in appropriate disease sites can be performed to determine the activity of the new agent. In the era of broadly active cytotoxic agents, phase 2 trials were done for most tumor types to determine the activity for each particular cancer. With the advent of more targeted therapies, drug development has focused on phase 2 studies on more limited and selected populations where a particular pathway may be particularly important for growth of the molecular phenotype of that particular type of cancer (e.g., a human EGFR 2 [HER2] inhibitor in HER2 overexpressing breast cancer or c-kit inhibitors in gastrointestinal stromal tumors [GIST]).

Phase 2 oncology studies are generally modestly sized to determine whether the drug has a reasonable degree of activity preliminary to more definitive studies. In phase 2 studies, the patient population tends to be defined by the disease type and the number of prior therapies as well as patients who have good performance status and adequate organ function. As targeted therapies are developed that focus more on specific molecular targets, phase 2 trials may cross diagnoses but be open to those patients who have a specific molecular profile. This can be seen in the studies of BRAF inhibitors for patients who have activating BRAF V600E mutations, whether they have melanoma, colon cancer, or other types of cancer. Classically, the goal of the phase 2 study is the response rate (RR) with a 95% confidence interval (CI). The 95% CI is a function of the study sample size. Phase 2 studies may be designed to show a certain level of activity that exceeds a minimal threshold; which is determined by the treatment setting. For example, for most solid tumors, any response rate for untreated patients of 20% or higher would be considered promising, although in patients who have failed prior therapies and for targeted agents’ lower response rates, even a 5% response rate may be considered worthy of future development.

**Randomized Phase 2 Trials**

With the advent of the new biologic therapies, randomized phase 2 trials have become more common. In this setting, a new biologic therapy may be added to a standard cytotoxic regimen versus the cytotoxics alone (e.g., for colon cancer, FOLFOX chemotherapy plus/minus cetuximab). The benefit of the phase 2 trial is that the activity level of the novel agent can be estimated somewhat more precisely given the control arm as a point of reference. It should be understood clearly that a randomized phase 2 trial is not a “poor man’s phase 3 trial,” meaning it is not a phase 3 comparative trial with a smaller sample size. The randomized phase 2 trial should be viewed as one trial with two arms, which are not compared statistically to each other but stand on their own without comparative statistical tests. These trials are generally powered with approximately 50 to 100 patients per arm and do not have the statistical power to show differences but may give the investigators confidence that in fact the novel agent has sufficient promise to be worthy of performing a larger and more definitive phase 3 trial. Therefore, this design, with a modest trial size, gives greater confidence that a new agent may be superior to the reference arm, and a phase 3 trial can be designed with greater knowledge of the expected observable differences.

**Phase 3 Trials**

Prospectively randomized phase 3 trials are the most important tool in oncology clinical trials to determine the actual benefit of a new agent or the addition of newer therapies to standard therapies. The prospectively randomized phase 3 trial is a large trial involving hundreds or even thousands of patients with a particular disease type and have the statistical power to determine whether a new agent or adding a new agent to an older regimen can improve the outcome, be it progression-free survival (PFS) or overall survival (OS) by a clinically meaningful amount. The difference between the two arms is generally expressed as a hazard ratio (HR), and generally speaking, an HR of 0.8 or less would be considered clinically reasonable benefit in OS for a randomized phase 3 trial. The size of the trial is determined by the power calculation, which is based on the response rate of the control regimen and the difference one would anticipate observing between the control regimen and the experimental arm. For example, if a control arm has a response rate of 50%, one wants to show an improvement to 75% (an HR of 0.67), then the trial will not be as large as one would need to show an increase from 50% to 60%. However, if the response rate for the control arm is 90%, showing improvement to 95%, then a much larger sample size would be required. The randomized phase 3 trial in oncology has classically compared new treatments to standard treatment or, in the refractory setting, a new treatment versus a standard of care treatment or best supportive care for the control arm. In general, oncology trials have tended not to use placebos because the end points of these studies tend to be relatively free of observer bias, involving radiologic response rates or overall survival. However, today, with the use of targeted therapies that are pills or additions to complex chemotherapy programs with baseline activity, it is much more common to use a placebo to eliminate all observer bias. In general, studies have historically used response rate (RR) as an end point where response as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria promulgated by the National Cancer Institute, which require a minimum 30% reduction in the sum of linear measurements of the indicator target lesions (corresponding to a 50% reduction in cross section used in older systems). Other typical end points used in randomized phase 3 trials include PFS for adjuvant trials, in other words, time to development of a recurrence; time to progression (TTP) for patients with advanced disease, that is, time on the study until tumor growth is observed according to the RECIST method; or OS time from beginning treatment until the patient dies. Time-based outcomes PFS, TTP, and OS are generally calculated by the method of Kaplan and Meier, which involves the fraction of patients who have not yet had the event divided by the number of patients at risk for the event at each time interval. The benefit of the Kaplan-Meier method is that patients can be started at various times through the study and their time at risk for an event is calculated from the beginning of treatment through the individual follow-up time.

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Overpowered Trials

One problem today with phase 3 trials is that they tend to be very large to ensure “a positive study” with a statistically significant $P$ value for the primary outcome ($P < .05$, meaning that the trial is true 95 out of 100 times, or we would accept 5% false-positive result). But given a large enough study, most end points can be shown to have a statistical significance even though the difference between the two arms may be clinically insignificant. These studies are “overpowered,” allowing investigators to publish a positive study, and presenting regulatory authorities with a positive result for approval. Overpowered studies should however be viewed from the perspective that the benefit shown may not be clinically significant even though it is statistically significant.

Role of the Primary Care Clinician

It is essential that the PCCs encourage their patients with cancer to participate in oncology clinical trials, even though they are being treated by oncologists. Many patients trust their primary care provider more than other physicians based on their long-standing relationship. Advice of the PCC may be particularly sought out when randomization is involved. Phase 3 trials may be sponsored by the pharmaceutical industry or often are sponsored by the National Cancer Institute through the cooperative group mechanism. The various cooperative groups today collaborate nationally to perform large studies designed to answer questions which are of importance for oncology management and to set new standards of care but are not as important for initial drug approval as are industry-sponsored trials. Once a new agent has been approved by the FDA, many unanswered questions still exist, such as understanding how to use such new drugs in other disease types or in comparison to other standard therapies or in comparison to other agents that may target similar pathways (but are manufactured by other companies). These studies are conducted independently by unbiased investigators and tend to set the standard of practice for most oncology therapeutics today. These can only be done with the cooperation of the patients who are willing to undergo randomization and comparison between therapies, which, by definition, has a degree of uncertain benefit. An important role of the PCC is to help the patient understand why they should participate in randomized trials and how that can lead to benefits for both that patient and future patients with cancer.

References


KEY POINTS
- The population of cancer survivors is growing rapidly; many cancer survivors have complex health care needs.
- Risk-based health care of cancer survivors is lifelong care that integrates the cancer and survivorship experience in the overall health care needs of the individual and includes a systematic plan for surveillance and prevention that incorporates risks based on the previous cancer, cancer therapy, genetic factors, lifestyle behaviors, and comorbid health conditions.
- The survivorship care plan is a key component of risk-based health care.
- Many cancer survivors are lost in transition from active therapy to posttreatment health care and have many health care needs that are not addressed.
- The primary care clinician’s role in the care of cancer survivors is critically important.

Long-term cancer survivors represent a significant proportion of the US population. Currently, there are more than 12 million cancer survivors; by 2020, it is estimated that this number will increase to 20 million. As the number of long-term survivors has increased, there has been a growing realization that many will develop health conditions as a direct or an indirect consequence of their cancer therapy. Although some of these conditions occur during therapy and persist well after the therapy has been completed (or become permanent), such as ifosfamide-induced renal dysfunction or steroid-induced osteonecrosis, many outcomes are not evident until 10 to 20 years later such as second cancers and therapy-related heart failure or ischemic coronary artery disease. Collectively, these outcomes are referred to as “late effects.”

Fortunately, the incidence and severity of many late effects of cancer therapy can be substantially reduced with strategies that incorporate prevention and early detection. The Institute of Medicine (IOM) published two seminal reports on survivors of childhood and adult cancer. The latter report, subtitled Lost in Transition, highlighted the fact that the transition of patients from active cancer therapy to posttreatment care is often suboptimal. Through these reports, the concept of risk-based health care for cancer survivors was developed. Risk-based health care (Table 38-1) is an approach to lifelong care that integrates the cancer and survivorship experience in the overall health care needs of the individual and includes a systematic plan for surveillance and prevention that incorporates risks based on the previous cancer, cancer therapy, genetic factors, lifestyle behaviors, and comorbid health conditions. The document that is the cornerstone of this process is the survivorship care plan (SCP), which includes an individualized cancer treatment summary, information on potential late effects, and guidelines for follow-up care. Figure 38-1 provides an example
# Cancer Treatment Summary / Survivorship Care Plan

**Date of preparation:** June 14, 2012

<table>
<thead>
<tr>
<th>Name: Jane Doe</th>
<th>Date of Birth: 7/1/1972</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer Diagnosis:</strong> Hodgkin lymphoma, nodular sclerosing, stage IV B</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment center:** Best Cancer Center, USA

- **Date of diagnosis:** 12/1/1998
- **Age at diagnosis:** 26 y
- **Date of completion of therapy:** 7/29/1999

### Surgery

<table>
<thead>
<tr>
<th>Date</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/1/1998</td>
<td>Left supraclavicular lymph node biopsy</td>
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</tbody>
</table>

### Radiation Therapy

<table>
<thead>
<tr>
<th>Date Start</th>
<th>Date Stop</th>
<th>Field</th>
<th>Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/1/1999</td>
<td>6/24/1999</td>
<td>Modified mantle (cervical, supraclavicular, infraclavicular, mediastinal, and left axillary nodes)</td>
<td>2,100</td>
</tr>
<tr>
<td>7/12/1999</td>
<td>7/29/1999</td>
<td>Spleen and para-aortic lymph nodes</td>
<td>2,100</td>
</tr>
</tbody>
</table>

### Chemotherapy:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dose (units or mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>300 mg/m²</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>100 U/m²</td>
</tr>
<tr>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4 g</td>
</tr>
</tbody>
</table>

### Potential Late Effects

- Cardiovascular problems
- Lung problems
- Thyroid problems
- Fertility problems
- Second cancers
- Musculoskeletal problems
- Psychosocial problems including anxiety or depression

### Screening Recommendations**

- Complete physical exam every year
- Echocardiogram annually
- EKG baseline and as clinically indicated
- Breast MRI/mammogram annually
- DXA baseline and as clinically indicated
- Pulmonary function test baseline and as clinically indicated
- Annual blood work: CBC, BUN, creatinine, fasting lipids, TSH, urinalysis
- Counseling as needed
- Yearly evaluation of skin in radiation field

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**Screening recommendations adapted from the Children’s Oncology Group Long-Term Follow-Up Guidelines [http://www.survivorshipguidelines.org](http://www.survivorshipguidelines.org).**

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**For any questions, please contact:**

Dr. Mary Doe  
Best Cancer Center, Anywhere USA  
1111 Main Street, USA  
Phone: 888-888-8888

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**FIGURE 38-1.** Example of one-page cancer treatment summary/survivorship care plan. EKG, electrocardiogram; MRI, magnetic resonance imaging; DXA, dual energy X-ray absorptiometry; CBC, complete blood count; BUN, blood urea nitrogen; TSH, thyroid-stimulating hormone.

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Low risk for future cancer-related health problems:

All of the following:
- Surgery only or chemotherapy that did not include alkylating agent, anthracycline, bleomycin, or epipodophyllotoxin
- No radiation
- Low risk of recurrence
- Mild or no persistent toxicity of therapy

Moderate risk:

Any of the following:
- Low- or moderate-dose alkylating agent, anthracycline, bleomycin, or epipodophyllotoxin
- Low-to-moderate dose radiation
- Autologous stem cell transplant
- Moderate risk of recurrence
- Moderate persistent toxicity of therapy

High risk:

Any of the following:
- High-dose radiation
- High-dose alkylating agent, anthracycline, bleomycin, or epipodophyllotoxin
- Allogeneic stem cell transplant
- High risk of recurrence
- Multi-organ persistent toxicity of therapy

Communication points with PCC

1. CA DX and planned therapeutic approach, brief overview of chemotherapy, radiation therapy, and/or surgery
2. Survivorship care plan: CA DX, cancer therapy, surveillance recommendations, contact information
3. Periodic update with changes in surveillance recommendations and new information regarding potential late effects
4. Periodic update of survivor’s health for PCC record

**FIGURE 38-2**. Risk-stratified shared care model for cancer survivors. Solid line denotes primary responsibility for cancer-related care; PCC continues care to manage non-cancer comorbidities and routine preventive health maintenance. *Cancer center or oncologist/oncology group practice; if there is not an LTFU/survivor program available, care in the gray box is provided by the primary oncologist. CA, cancer; DX, diagnosis; Off RX, completion of cancer therapy; PCC, primary care clinician; LTFU, long-term follow-up (survivor) program; Onc, oncologist.
of a simple one-page SCP. Despite recommendations from the IOM and numerous other national groups, studies indicate that most survivors do not have an SCP; they are often unsure about the details of their cancer therapies; and most community physicians are unaware of their risks. Thus, most survivors, including those at highest risk, are not engaged in risk-based follow-up care that is aimed on optimizing their health and quality of life.

The following chapters highlight some of the more serious late effects and key aspects of integrating the health care needs of the cancer survivor with his or her routine health care needs. The primary care clinician, with expertise in preventive care and the management of chronic conditions, is critically important in this process. Figure 38-2 presents an approach, stratified by risk, for shared care between the primary care clinician and the cancer specialist(s).

References
Cardiac and pulmonary sequelae are major contributing factors to serious morbidity and premature mortality among survivors of cancer.

- Chest (mediastinal) radiation frequently causes ischemic coronary artery disease. Traditional risk factors increase this risk and therefore should be aggressively managed.
- Anthracycline therapy frequently causes asymptomatic left ventricular dysfunction, which occasionally can progress to overt heart failure.
- Pulmonary disease including pulmonary fibrosis and restrictive and obstructive lung disease can result from radiation to the chest and/or bleomycin and other pulmonary toxic chemotherapeutic agents.

Ischemic Coronary Artery Disease

Radiation fields that include the mediastinum, often used in the therapy of Hodgkin and non-Hodgkin lymphoma, can cause direct injury to the proximal coronary arteries and accelerate atherosclerotic plaque formation leading to CAD (Fig. 39-2) and myocardial infarction (MI).

Following mediastinal radiation:
- By 20 years, the cumulative incidence of symptomatic CAD is 21%.
- By 30 years, the cumulative incidence of MI is 13%.
- A survivor of cancer with an MI has a threefold increased risk of dying compared with a noncancer person with an MI. This is because the proximal coronary arteries, including the left main and left anterior descending arteries, are directly in the field of radiation.

Heart disease risk prediction models are often used in practice to estimate the 10-year risk of a serious cardiac event and then intervene with high-risk individuals by targeting risk factors. Unfortunately, traditional risk prediction models for cardiovascular disease fail to account for cancer treatment–related risk factors. Take, for example, a 52-year-old female with a history of Hodgkin lymphoma diagnosed at the age of 22 years and treated with mediastinal radiation and chemotherapy, including cyclophosphamide, vincristine, procarbazine, and prednisone. She is asymptomatic, does not smoke, has a total cholesterol of 210 mg per dL and a high-density lipoprotein (HDL) of 44 mg per dL, and a systolic blood pressure of 138 mm Hg. Using the cardiovascular risk calculator on the National Heart, Lung, and Blood Institute website based on the Framingham Study, her risk is <1% for having an MI or coronary death in the next 10 years. However,
results in obesity, insulin resistance, decreased levels of physical activity, and ultimately to increased rates of CAD. Cisplatin-based chemotherapy used in the treatment of men with testicular cancer has been associated with an increased risk of CAD and MI. This may be the result of direct endothelial damage caused by cisplatin and/or increasing the risk of developing hypertension and lipid abnormalities.

To date, studies of the use of stress exercise testing, echocardiography, and radionucleotide imaging to screen for obstructive CAD in asymptomatic survivors have been inconclusive. Stress echocardiography appears to be more sensitive and specific than other methods. However, this area of research is still in its infancy, and further studies are needed to determine the best approach for risk assessment in long-term survivors of cancer.

FIGURE 39-1. Factors associated with cardiac sequelae in survivors of cancer.
interval from therapy, and can occur even with low cumulative doses. Although the incidence of overt HF is low with conventional regimens, subclinical echocardiographic abnormalities of LV structure and function have been reported in more than half of patients in the first few years after anthracycline exposure and the abnormalities worsened over time. Importantly, HF can develop a decade or two after completion of the anthracycline therapy. Risk factors for anthracycline-induced HF include young age at therapy, cumulative doxorubicin dose, rate of administration, concurrent mediastinal or chest radiation, female gender, preexisting heart disease, and hypertension. Recent studies have identified modifying genetic factors associated with anthracycline-related cardiomyopathy.

The primary care clinician is an important member of the team for patients who may be treated with anthracycline chemotherapy as well as those who have completed their therapy. Before a patient starts on potentially LV cardiotoxic therapy, risk stratification should be formulated based on treatment-related factors (type of drug, cumulative dose, combination of potentially cardiotoxic treatment) and patient-specific risk factors (age, coexisting cardiovascular conditions, and prior history of cardiotoxic treatment). In high-risk patients, there should be a discussion between the oncologist, the primary care clinician, and a cardiologist assessing the oncologic benefit of treatment and possible adverse cardiac risk, with consideration of cardioprotective measures or alteration of the treatment. Optimization of the cardiovascular status (e.g., management of hypertension) prior to initiation of chemotherapy is recommended with close cardiac monitoring during treatment so that an intervention can be initiated as soon as signs of cardiotoxicity are detected. The American College of Cardiology (ACC)/American Heart Association (AHA) recommend echocardiographic monitoring in patients who are at risk for HF (class I indication).

For children, adolescents, and young adults who have completed anthracycline-based chemotherapy, the Children’s Oncology Group has published evidence-informed recommendations for screening. The frequency of monitoring is based on cumulative anthracycline dose, age at exposure, and whether or not the patient was treated with chest radiation. Guidelines for posttherapy cardiac screening and follow-up in asymptomatic survivors of adult cancer have not been established.

The most common method for monitoring LV function during or after cancer therapy is measurement of LV ejection fraction (LVEF) either by echocardiography or multigated acquisition (MUGA) scan. Other newer methods include cardiac magnetic resonance imaging (MRI) and 3-D echocardiography (Table 39-2). Because a broad range LVEF can be seen in healthy individuals, changes in LVEF indicative of cardiac damage can be identified only when comparison between serial studies and pretreatment study are made. Cardiotoxicity in recent major clinical trials has been defined as reduction of LVEF >5% to <55% with symptoms of HF or an asymptomatic reduction of LVEF of >10% to <55%.

The natural history of anthracycline-induced LV dysfunction and its response to modern HF therapy has not been well established. Mortality rates up to 50% within 2 years of diagnosis have been reported in the past, which is worse than many other forms of cardiomyopathy. Although ACC/AHA has published evidence-based treatment guidelines

**FIGURE 39-2.** A 39-year-old man who was treated for Hodgkin lymphoma 25 years ago with 45 Gy mantle field radiation. The curved reconstruction of coronary computed tomography (CT) angiogram shows two areas of severe stenosis (straight arrows) in left anterior descending coronary artery (LAD) and multiple plaques (arrowhead). More distal LAD has relatively wide diameter and might represent normal vessel or region of ectasia (curved arrow). (From Rademaker J, Schoeder H, Ariaratnam NS, et al. Coronary artery disease after radiation therapy for Hodgkin lymphoma: coronary CT angiography findings and calcium scores in nine asymptomatic patients. AJR Am J Roentgenol. 2008;191:32–37, with permission.)

**Left Ventricular Dysfunction and Heart Failure**

Anthracycline chemotherapy (e.g., doxorubicin, daunorubicin, epirubicin) is an important component in the treatment of several types of cancer including breast, lung, endometrial, and ovarian cancer; lymphoma; leukemia; and sarcoma. In a seminal study, von Hoff et al. reported that anthracycline-induced cardiac injury is characterized by dose-dependent and progressive left ventricular (LV) dysfunction, which can lead to HF, developing within 1 year of treatment in 3% of patients treated with a cumulative dose of 400 mg per m² of doxorubicin, 7% at 550 mg per m², and 18% at 700 mg per m². Subsequent studies have established that anthracycline-induced LV dysfunction is common, risk increases with increasing
TABLE 39-2 Assesment of Cardiac Function

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUGA scan</td>
<td>Reproducible LVEF measurement with low interobserver and intraobserver variability</td>
<td>Radiation exposure; limited information on cardiac structure and diastolic function</td>
</tr>
<tr>
<td>2-D echocardiography</td>
<td>Low cost, easy to perform and widely available; no radiation exposure; comprehensive evaluation of cardiac structure and function</td>
<td>High intraobserver and interobserver variability of LVEF calculation because of dependency on image quality, geometric assumption, and operator expertise. May fail to detect subtle changes in LVEF</td>
</tr>
<tr>
<td>3-D echocardiography</td>
<td>Same as 2-D echo; highly reliable LVEF calculation</td>
<td>Limited data on its use in monitoring cardiotoxicity; not yet incorporated into routine clinical practice</td>
</tr>
<tr>
<td>MRI</td>
<td>Accurate and reliable assessment of LVEF; gold standard in the measurement of LV volume, structure, and systolic function; can detect myocardial fibrosis and scarring when combined with late gadolinium contrast enhancement</td>
<td>High cost and not widely available</td>
</tr>
</tbody>
</table>

MUGA, multigated acquisition scan; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; LV, left ventricular.

for HF in general, the effectiveness of therapy in anthracycline-related HF has not been well established. Given the well-established final common pathway of remodeling and compensation in systolic HF, treatment for chemotherapy-related LV dysfunction based on current HF management guideline is recommended.

Valvular Heart Disease and Arrhythmias

Mediastinal (chest radiation) occasionally causes valvular heart disease, predominantly involving the aortic and mitral valves. About 6% of survivors treated with moderate- to high-dose mediastinal radiation develop clinically significant valvular disease and have an eightfold higher likelihood of valve surgery. Evaluation for and monitoring of valvular heart disease in survivors treated with mediastinal radiation can be accomplished with periodic echocardiography. Importantly, survivors of cancer with valvular heart disease following mediastinal radiation have a higher incidence of perioperative morbidity.

Life-threatening arrhythmias, including complete heart block, are rare outcomes following cancer therapy and are generally attributable to mediastinal radiation. Prolongation of QTc infrequently occurs following anthracycline therapy. As in the general population, the patient should be counseled about the use of medications that may prolong the QT interval such as antifungal agents and metronidazole.

PULMONARY SEQUELAE

Cancer therapy–related pulmonary sequelae include restrictive and obstructive lung disease and pulmonary fibrosis. In addition, patients with cancer treated with a hematopoietic stem cell transplant may develop an array of pulmonary problems, as described in Chapter 46. In contrast to cardiac outcomes, most pulmonary sequelae develop either during therapy or soon thereafter.

Dose-related bleomycin-induced pneumonitis has long been recognized. With contemporary therapy for germ cell tumors in men, this outcome is very uncommon because of limits in the total dose of bleomycin. Other chemotherapeutic agents that are associated with pulmonary disease include busulfan, carmustine, and lomustine. Combination of pulmonary toxic chemotherapy with chest radiation increases the risk of pulmonary disease. Survivors of Hodgkin lymphoma treated with chest radiation in combination with bleomycin frequently have pulmonary problems; fortunately, these are generally mild to moderate in severity.

The natural history of treatment-related pulmonary disease, particularly 10 years or more after therapy, is not well described. Thus, the optimum frequency and duration of monitoring pulmonary function is not known. As previously mentioned, it is imperative that survivors of cancer treated with potentially pulmonary toxic therapy avoid or stop smoking.

References


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Osteoporosis is a systemic disorder of the skeletal system characterized by low bone mass and deterioration in the bone tissue microarchitecture leading to an increased risk of bone fractures. Cancer and cancer treatments often negatively impact bone health, resulting in higher rates of osteoporosis and subsequent fractures among survivors of cancer.

Bone remodeling continues throughout life. Peak bone mass is achieved by 18 to 20 years of age. After the age of 35 years, bone resorption exceeds formation. Adequate bone mineralization is crucial to bone health and is dependent on vitamin D, calcium, magnesium, phosphorus, and other trace elements. Important factors in bone remodeling include the receptor activator for nuclear factor κB (RANK) pathway, which stimulates bone resorption via osteoclast activation, and hormones such as estrogen and growth hormone (GH). Estrogen inhibits osteoclast-driven resorption and promotes bone formation by stimulating osteoblast activity. In males, estrogen is formed by the aromatization of testosterone and is thus dependent on adequate testosterone levels. Adequate levels of GH are essential for bone density acquisition in children and adolescents. Thus, bone remodeling involves a complex network of cells and signals, which, if disrupted, can negatively impact bone health.

Childhood cancer and its treatment coincide with a vital period of bone growth, interfering with the acquisition of maximal bone density and leading to increased bone loss via several mechanisms (Table 40-1). The Children’s Oncology Group (COG) provides updated evidence-based guidelines for screening for early- and late-occurring sequelae following therapy for pediatric cancer, including bone-related morbidity. Table 40-2 provides a synopsis of these recommendations.

Survivors of adult cancer are at increased risk for accelerated bone loss through several mechanisms (Table 40-3). The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend monitoring of bone mineral density (BMD) in men and women who have undergone cancer therapy that negatively impacts bone health. Dual-energy X-ray absorptiometry (DEXA) scans are used to measure BMD; however, there are limitations with this approach in children. Lifestyle modification is recommended for everyone regardless of BMD (Table 40-4). The World Health Organization (WHO) fracture risk algorithm (FRAX) calculates the 10-year probability of hip and major osteoporotic fracture risk. The NCCN Task Force on Bone Health in Cancer Care recommends using the WHO FRAX algorithm to assess baseline fracture risk for all patients with cancer at risk for bone loss. Pharmacotherapy is generally indicated for patients with osteoporosis or a history of fragility fractures (Tables 40-2 and 40-5). As in persons without a history of cancer, bisphosphonates are usually first line to treat bone loss when clinically indicated. Denosumab is a newly U.S. Food and Drug Administration (FDA)–approved monoclonal antibody that interferes with RANK ligand binding and is also approved to treat bone loss. Teriparatide is a recombinant human parathyroid hormone, which can be used to build bone in individuals with severe osteoporosis. It is seldom used in survivors of cancer because of concerns about the risk of subsequent osteosarcoma. Treatment for survivors of childhood cancer with bisphosphonates may be considered, but evaluation with an endocrinologist is recommended.
### TABLE 40-1  Childhood Cancer Therapy Associated with Reduced Bone Mineral Density

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Used for</th>
<th>Mechanism of Bone Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Supportive therapy, chemotherapy (ALL, NHL, HSCT)</td>
<td>Impair osteoblastic function and differentiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interfere with GH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impair calcium absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased risk of bone loss if total prednisone equivalent dose is ≈9 g/m².⁸,⁹</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Ewing sarcoma, Osteosarcoma, NHL, Leukemias (ALL)</td>
<td>Directly toxic to osteoblasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increases osteoclast formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total dose ≈40 g/m² is associated with highest risk for osteopenia.⁹</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>HSCT, Hodgkin lymphoma, Ewing sarcoma, Osteosarcoma, Rhabdomyosarcoma</td>
<td>Confer risk of premature menopause/ovarian failure/Leydig cell dysfunction</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td>Concurrent radiation potentiates gonadal toxicity.¹⁰</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>Cranial radiation Brain tumors, ALL</td>
<td>Doses ≈18 Gy to the HPA associated with GH deficiency.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doses ≈40 Gy to the HPA may cause gonadotropin deficiency.</td>
</tr>
<tr>
<td></td>
<td>Radiation to abdomen &amp; pelvis or TBI</td>
<td>Ovarian failure/estrogen deficiency and Leydig cell dysfunction/androgen deficiency²⁰</td>
</tr>
<tr>
<td></td>
<td>Prepubertal girls ≥10 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pubertal girls ≤5 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Males ≥20 Gy</td>
<td></td>
</tr>
<tr>
<td>Surgical castration</td>
<td>Testicular cancer</td>
<td>Rapid loss of androgens result in loss of estrogen</td>
</tr>
<tr>
<td>Orchiectomy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; HSCT, hematopoietic stem cell transplant; GH, growth hormone; Gy, gray; HPA, hypothalamic-pituitary-adrenal axis; TBI, total body irradiation.

### TABLE 40-2  Evaluation and Management of Bone Health in Childhood Cancer Survivors

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMD testing</strong></td>
</tr>
<tr>
<td>For patients who received therapies that have negative impact on bone health (see Table 40-1)</td>
</tr>
<tr>
<td>For individuals &lt;50 y, use z-scores, which compares measured BMD to BMD of age-, gender-, and ethnicity-matched controls.</td>
</tr>
<tr>
<td><strong>Based on z-score results</strong></td>
</tr>
<tr>
<td>Normal (z-score &gt; −1.0)</td>
</tr>
<tr>
<td>If not at risk for ongoing bone loss, consider stopping until menopause. Consider restarting screening if clinically indicated.</td>
</tr>
<tr>
<td>Osteopenia (−1.0 ≥; z ≥ −2.5)</td>
</tr>
<tr>
<td>Repeat as clinically indicated—usually every 2 y</td>
</tr>
<tr>
<td>Osteoporosis (z ≤ −2.5 or fragility fracture, i.e., a fracture that results from a fall from a standing height or less)</td>
</tr>
<tr>
<td>Refer to endocrinology for consideration of possible contributing factors for severe bone loss. Consider treatments when appropriate. Repeat BMD as clinically indicated (usually every 2 y)</td>
</tr>
</tbody>
</table>

BMD, bone mineral density.
### TABLE 40-3 Adult Cancer Therapy Associated with Reduced Bone Mineral Density

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Used in</th>
<th>Mechanism of Bone Loss</th>
<th>Degree and Site of Bone Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase inhibitors</td>
<td>Hormone sensitive breast cancer</td>
<td>Inhibit peripheral conversion of androgen to estrogen (reduces estrone sulfate, estradiol, estrogen)</td>
<td>↓ 4.1% in LS after 2 y&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Premenopausal hormone sensitive breast cancer</td>
<td>Potentially interferes with estrogen action on bone when used in premenopausal women but not in postmenopausal women</td>
<td>↓ 1.44%/y in LS (unclear if increased fracture risk)&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>GnRH agonists</td>
<td>Prostate cancer; Premenopausal breast cancer</td>
<td>Decrease LH and FSH receptors; Decrease testosterone; Decrease estrogen (via decreased testosterone conversion to estradiol)</td>
<td>↓ 4%–10% in LS the first year, then ↓ 4%–5% per year with sustained use&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antiandrogens</td>
<td>Prostate cancer; Premenopausal breast cancer</td>
<td>Block androgen receptors</td>
<td>↓ 2%–5% in BMD at 12 mo; 40%–50% increase in RR of vertebral and hip fractures&lt;sup&gt;14,15&lt;/sup&gt;</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Supportive therapy, chemotherapy</td>
<td>Impair osteoblastic function and differentiation; Impair calcium absorption; No safe dose; however, risk increased when ≥5 mg/d for 3 mo or if total dose ≥10 g&lt;sup&gt;5&lt;/sup&gt;; Impair calcium absorption</td>
<td>Impact greater on cancellous bone than cortical bone. Fractures typically occur at higher BMD than with natural menopause.</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Ovarian cancer; Breast cancer; Germ cell tumors</td>
<td>Magnesium wasting leads to increased osteoclast activity through activation of the RANK pathway&lt;sup&gt;8&lt;/sup&gt;</td>
<td>No data on degree of bone loss</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Premenopausal breast cancer</td>
<td>Premature menopause; Depletion of estrogen and androgens</td>
<td>Greater loss of BMD than with natural menopause</td>
</tr>
<tr>
<td>High-dose ifosfamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical castration</td>
<td>Prostate cancer; Testicular cancer; Breast cancer; Ovarian cancer</td>
<td>Rapid depletion of sex hormones</td>
<td>Rapid loss of BMD; increased fracture risk</td>
</tr>
</tbody>
</table>

↓, decrease; LS, lumbar spine; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; BMD, bone mineral density; RR, relative risk; RANK, receptor activator of nuclear factor κB

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### TABLE 40-4 Recommendations by NCCN for All Cancer Survivors Regardless of Menopausal Status<sup>a</sup>

<table>
<thead>
<tr>
<th>For All Cancer Survivors</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium from food is best supplement if/when needed (calcium citrate is better absorbed than carbonate)</td>
<td>1,200 mg/d in divided doses</td>
</tr>
<tr>
<td>Vitamin D&lt;sub&gt;3&lt;/sub&gt;</td>
<td>800–1,000 IU/d&lt;br&gt;&lt;i&gt;T&lt;/i&gt; score less than −1.0, check 25-OH vitamin D levels and target to levels ≥ 30 ng/mL&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Encourage</td>
<td>Weight-bearing exercises</td>
</tr>
<tr>
<td>Avoid</td>
<td>Smoking, intake of excess alcohol, caffeine, and carbonated beverages</td>
</tr>
<tr>
<td>Consider</td>
<td>Replacement of GH (for children) and sex steroids (for adults and children) when appropriate</td>
</tr>
</tbody>
</table>

<sup>a</sup>For all cancer survivors regardless of age, calcium and vitamin D recommendations are the equivalent National Osteoporosis Foundation guidelines for individuals aged 50 years and older.

NCCN, National Comprehensive Cancer Network; GH, growth hormone.

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## TABLE 40-5  Evaluation and Management of Bone Health in Adults

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evaluation and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCO, NCCN</strong></td>
<td>Initiate BMD testing for women and men who have undergone treatments that negatively impact bone health (see Table 40-3).</td>
</tr>
<tr>
<td><strong>Recommendations based on t-score results</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Normal (t &gt; -1)</strong></td>
<td>If not at increased risk for ongoing bone loss, consider stopping BMD testing until menopause.</td>
</tr>
<tr>
<td><strong>Osteopenia (-1.0 ≥ t &gt; -2.5), and if all the following apply:</strong></td>
<td>Repeat BMD as clinically indicated, usually every 2 y.</td>
</tr>
<tr>
<td>1) No history of fragility fracture</td>
<td>Check 25-OH vitamin D level and treat to levels ≥30 ng/mL.</td>
</tr>
<tr>
<td>2) FRAX 10-y hip fracture risk &lt;3%</td>
<td>NCCN guidelines—start antiresorptive therapy for t-score &lt; -2.0.</td>
</tr>
<tr>
<td>3) FRAX 10-y osteoporotic fracture risk &lt;20%</td>
<td></td>
</tr>
<tr>
<td><strong>Osteoporosis (t ≤ -2.5) or if any of the following apply:</strong></td>
<td>Antiresorptive therapy</td>
</tr>
<tr>
<td>1) History of fragility fracture</td>
<td>Continue BMD testing (in some individuals, may be appropriate to retest after a year).</td>
</tr>
<tr>
<td>2) FRAX 10-y hip fracture risk &gt;3%</td>
<td>Check 25-OH vitamin D level and target values ≥30 ng/mL.</td>
</tr>
<tr>
<td>3) FRAX 10-y osteoporotic fracture risk &gt;20%</td>
<td></td>
</tr>
</tbody>
</table>

| BM | bone mineral density; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network. |


### References

KEY POINTS

- Many cancer treatments affect fertility.
- Many cancer survivors want to be parents after cancer treatment.
- Most postpubertal patients can preserve fertility before treatment begins if they are informed of the risks and options early during treatment planning.

Before beginning treatment

Postpubertal males can cryopreserve sperm prior to treatment and should be encouraged to bank at least three semen samples. Sperm banking is noninvasive, does not delay treatment, and is relatively inexpensive. Later use of this limited quantity of cryopreserved sperm is most efficient if used in conjunction with in vitro fertilization. Other FP options are available for postpubertal males who are unable to masturbate or who have impaired fertility before treatment begins and for prepubertal males who have not yet initiated spermatogenesis. Women can cryopreserve oocytes or embryos, but this is expensive and takes 2 to 3 weeks. It requires daily hormone injections, monitoring with regular blood tests and ultrasound examinations, and a transvaginal needle aspiration under sedation to retrieve oocytes. Early referrals to reproductive specialists can ensure patients have time to do this without significantly delaying treatment. Other FP options are available for postpubertal and prepubertal females and are summarized in Table 41-3.

FP decisions must be made before treatment begins, because once the patient has received gonadal radiation or systemic chemotherapy, collection of gametes is discouraged because of risk of damage and poor outcomes. Men continually produce new gametes after puberty and may recover spermatogenesis after treatment. Women are born with a finite supply of gametes and they continually deplete with age. This loss is hastened by gonadotoxic therapy, potentially resulting in premature ovarian failure. The difficulty in predicting risk is compounded by the fact that research on fertility risks in females often uses amenorrhea as the outcome; however, fertility declines many years prior to the cessation of menses. Additional effects of cancer treatment on fertility are described in Table 41-2.

After treatment is completed

Evaluating gonadal function after treatment helps individuals understand their fertility potential. In males, a semen analysis will evaluate for the presence of sperm and measure density, motility, and morphology. Some men will be infertile immediately after treatment but will recover spermatogenesis. This occurs most often within 3 years but has been seen to occur even many years after treatment is completed.

Many women will cease menstruation during treatment because of the effects of treatment on developing follicles but...
depending on their age and treatment may resume menses within the first year after treatment is completed. However, as discussed previously, resumption of menses does not guarantee fertility. Measures of ovarian reserve to evaluate fertility include transvaginal ultrasound to count potential follicles in the ovaries, anti-müllerian hormone (AMH) levels, and, in menstruating females, day 3 follicle-stimulating hormone (FSH) levels.

The oncologist should determine when it is safe for the patient to try to start a family—to pass the time interval when he or she is at the greatest risk of an early recurrence, to ensure damaged gametes have been eliminated, and to ensure the patient has recovered from treatment. This time is generally 1 to 3 years.

If semen parameters are normal or ovarian function is present, patients should first try to conceive naturally. If unsuccessful after 3 to 6 months, referral to a reproductive specialist for evaluation and treatment is warranted. Patients may be able to use their own gametes to conceive; others will be interested in pursuing alternative options for building a family. These include use of donor sperm or eggs, gestational carriers (for women who have had a hysterectomy, received high-dose pelvic radiation, or are at risk for recurrence if they were to carry a pregnancy), or adoption. A history of cancer does not preclude adoption, but patients generally have to be cancer free for at least 5 years. These alternative options for building a family are summarized in Table 41-4.

Young women who are not ready to start a family but are at risk for premature ovarian failure can consider fertility preservation with oocyte or embryo cryopreservation after treatment once cleared by their oncologist.

** risk with total body irradiation) High

---

**RESOURCES**

The treating oncologist should have a network of sperm banks and reproductive specialists to whom they can refer patients interested in pursuing one of these options. The process can be complicated, time consuming, costly, and stressful. However, with the support of a multidisciplinary team and the ongoing advances in reproductive technology, the process can be extremely rewarding for your patients. PCCs can encourage their patients to speak with their oncologists about their desires and concerns, provide resources for them to access information at their own pace, and guide them toward resources for financial assistance. Table 41-5 lists resources you can share with your patients.

---

**TABLE 41-1** Risk of Infertility from Chemotherapy

<table>
<thead>
<tr>
<th>Single Agents</th>
<th>Risk of Infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>Meclizine</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Melphalan</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Procarbazine</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td></td>
</tr>
<tr>
<td><strong>Platinum analogues</strong></td>
<td>Antimetabolites</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Cytarabine</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Nitrosoureas</td>
</tr>
<tr>
<td>Oxaplatin</td>
<td>Carmustine</td>
</tr>
<tr>
<td><strong>Anthraclyines</strong></td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Lomustine</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
</tr>
<tr>
<td><strong>Multiagent Regimens</strong></td>
<td>Risk of Infertility</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>Any regimen with cisplatin or carboplatin</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>AC (doxorubicin, cyclophosphamide)</td>
</tr>
<tr>
<td></td>
<td>CMF (cyclophosphamide, methotrexate, fluorouracil)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)</td>
</tr>
<tr>
<td></td>
<td>Any regimen with procarbazine</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td></td>
</tr>
<tr>
<td>CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone)</td>
<td></td>
</tr>
<tr>
<td>VAPEC-B (vincristine, doxorubicin, prednisone, etoposide, cyclophosphamide, and bleomycin)</td>
<td>Low</td>
</tr>
<tr>
<td>VACOP-B (vinblastine, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin)</td>
<td></td>
</tr>
<tr>
<td>MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin)</td>
<td></td>
</tr>
<tr>
<td>VEEP (vincristine, etoposide, epirubicin, and prednisolone)</td>
<td></td>
</tr>
<tr>
<td>Hematopoietic cell transplant</td>
<td>All conditioning regimens (↑ risk with total body irradiation)</td>
</tr>
</tbody>
</table>

Risks of specific agents are dose related, and in females, are age related, with increased risk at increased age.

↑, high/increase.

---

**TABLE 41-2** Potential Fertility Effects of Cancer Treatment

<table>
<thead>
<tr>
<th>Males</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depletion of spermatogonial germ cells with oligosperma or azoosperma (C, RT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leydig cell dysfunction with reduced testosterone production (C, RT, S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury to genitourinary ductal system with impaired transport of sperm during ejaculation (RT, S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury to genitourinary nerves and blood vessels with erectile or ejaculatory dysfunction (RT, S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury to pituitary gland with impaired hormonal regulation of spermatogenesis (RT, S)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Females</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depletion of primordial follicles with decrease in ovarian reserve, premature ovarian failure, infertility, and/or early menopause (C, RT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrotic changes in uterus leading to endometrial damage, vascular insufficiency, and loss of elasticity with inability to support embryo implantation and/or accommodate a growing fetus (RT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of reproductive structures with inability to conceive or carry a pregnancy (S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury to pituitary gland with impaired hormonal regulation of menses (RT, S)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C, chemotherapy; RT, radiation therapy; S, surgery.
<table>
<thead>
<tr>
<th>Options for Fertility Preservation Before Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
</tr>
<tr>
<td><strong>Sperm cryopreservation</strong></td>
</tr>
<tr>
<td><strong>Sperm banking</strong></td>
</tr>
<tr>
<td>For postpubertal males able to obtain a semen sample by masturbation</td>
</tr>
<tr>
<td>• Home collection kits are available if no local sperm bank: Live:On (Fertile Hope), OverNite Male (Reprotech)</td>
</tr>
<tr>
<td><strong>Electroejaculation</strong></td>
</tr>
<tr>
<td>For males unable to masturbate for physical, emotional, religious, or cultural reasons</td>
</tr>
<tr>
<td>• Collected by a reproductive urologist in the OR under anesthesia; ejaculation stimulated by an electrical current from a rectal probe placed over the prostate gland</td>
</tr>
<tr>
<td><strong>Testicular sperm extraction/epididymal aspiration</strong></td>
</tr>
<tr>
<td>For males with obstruction of the vas deferens or impaired spermatogenesis and who are azoospermic on semen analysis</td>
</tr>
<tr>
<td>• Collected by a reproductive urologist in the OR, under anesthesia, through testicular biopsy, microsurgical epididymal aspiration, or percutaneous aspiration</td>
</tr>
</tbody>
</table>

| **Testicular tissue cryopreservation** |
| For prepubertal males |
| • Collected by a reproductive urologist in the OR under anesthesia, through testicular biopsy |
| • Investigational; no live human births from reimplantation of tissue to date. |

| **Testicular shielding** |
| For males getting pelvic radiation |
| • Use of external shields to protect the testes from the effects of radiation |

| **Females** |
| **Embryo cryopreservation** |
| For females with a partner or willing to use donor sperm |
| • Freezing of embryos obtained by ovarian stimulation, egg retrieval, and in vitro fertilization |

| **Oocyte cryopreservation** |
| For females with no partner and unwilling to use donor sperm or patients with ethical concerns about freezing embryos |
| • Freezing of unfertilized eggs obtained by ovarian stimulation and egg retrieval |

| **Ovarian tissue cryopreservation** |
| For prepubertal females or those who cannot delay treatment for ovarian stimulation |
| • Collected in the OR under anesthesia |
| • Investigational; only 18 live human births reported from reimplantation of tissue to date. |

| **Ovarian transposition** |
| For females getting pelvic radiation |
| • Surgical placement of ovaries out of the field of radiation |

| **Ovarian suppression** |
| For females getting chemotherapy |
| • Use of GnRH agonists to suppress ovarian function |
| • Investigational; data on effectiveness is conflicting. |

OR, operating room; GnRH, gonadotropin-releasing hormone.
TABLE 41-4

Alternative Options for Building a Family After Treatment Is Completed

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s frozen sperm</td>
<td>Ovarian stimulation</td>
</tr>
<tr>
<td>• Sperm thawed and used for in vitro fertilization</td>
<td>• For females with decreased ovarian reserve, attempt to achieve pregnancy through ovarian stimulation, egg retrieval, in vitro fertilization, and transfer of embryos into the uterus</td>
</tr>
<tr>
<td>Testicular sperm extraction</td>
<td>Patient’s frozen embryos or oocytes</td>
</tr>
<tr>
<td>• For azoospermic males, search for sperm by a reproductive urologist in the OR, under anesthesia, through testicular biopsy; used for in vitro fertilization</td>
<td>• Transfer of thawed embryos (or embryos created from thawed oocytes) into the uterus</td>
</tr>
<tr>
<td>Donor sperm</td>
<td>Donor oocytes or embryos</td>
</tr>
<tr>
<td>• Obtained from a sperm bank; used for intrauterine insemination</td>
<td>• Oocytes obtained from a younger woman; fertilized with partner or donor sperm and transferred into the uterus</td>
</tr>
<tr>
<td>Gestational carrier</td>
<td>Gestational carrier</td>
</tr>
<tr>
<td>• Arranging for another woman to carry a pregnancy; embryos transferred to her uterus</td>
<td>• Arranging for another woman to carry a pregnancy; embryos transferred to her uterus</td>
</tr>
</tbody>
</table>

**TABLE 41-5**

Resources

- **Cancer and fertility**
  - Fertile Hope/LIVESTRONG (www.fertilehope.org)
  - MyOncofertility (myoncofertility.org)
- **Fertility**
  - American Society of Reproductive Medicine, ReproductiveFacts (www.reproductivefacts.org)
  - InterNational Council on Infertility Information Dissemination (INCIID) (www.inciid.org)
  - RESOLVE: The National Infertility Association (www.resolve.org)
  - Society for Assisted Reproductive Technology (www.sart.org)
- **Financial assistance (for FP before treatment)**
  - Fertile Hope (http://www.fertilehope.org/financial-assistance/index.cfm)
- **Adoption**
  - Adoption.com (www.adoption.com)
  - Adoption.org (www.adoption.org)
  - Adoptive Families (www.adoptivefamilies.com)
  - Adoptive Parents Committee (adoptiveparents.org)
  - Yahoo! Groups: Adoption after Cancer (groups.yahoo.com)

**FP**, fertility preservation.

**References**


CHAPTER 42 Sexual Dysfunction

Shari Goldfarb, MD • Kevin C. Oeffinger, MD • Aarati D. Didwania, MD

KEY POINTS

- Male and female survivors at highest risk for treatment-related sexual dysfunction are those with pelvic tumors, breast cancer, testicular cancer, or those whose treatments affect hormone levels and pathways mediating sexual desire and pleasure.
- Primary care clinicians can help direct care by exploring the extent of sexual dysfunction and basing therapeutic options on the etiology of dysfunction.
- Testosterone effects are complex and use of standard replacement for sexual dysfunction needs further evaluation.
- Women with cancer often experience abrupt or premature menopause from their treatment, which causes them to have greater intensity and duration of symptoms such as hot flashes, vaginal dryness, dyspareunia, decreased libido, and changes in sexual response.
- Treatment options for sexual dysfunction in men depend on etiology of the problem and concomitant medical conditions. Some possible options include phosphodiesterase-5 inhibitors, SSRIs, penile suppositories, penile injections (alprostadil or phentolamine), vacuum pumps, or implantable prostheses.
- Treatment options for sexual dysfunction in women also depend on etiology of the problem and concomitant medical conditions. Some possible options include lubricants, moisturizers, counseling/sex therapy, altering contributing medications, physical therapy for pelvic floor disorders, mechanical devices/vibrators, and local intravaginal estrogens.

Quality of life issues are exceedingly important in caring for cancer survivors, and sexual dysfunction is one of the significant challenges faced by this population. Effectively addressing sexual dysfunction can be difficult given the varied etiologies, multifactorial nature of the disorder, and the comfort level of the clinician in addressing it. It is important for primary care providers to address this topic with cancer survivors to improve their quality of life. The National Health and Social Life Survey (NHLS) defines sexual dysfunction as symptoms or problems associated with (1) desire for sex, (2) arousal difficulties, (3) inability to achieve climax or ejaculation, (4) anxiety about sexual performance, (5) climaxing or ejaculating too rapidly, (6) physical pain during intercourse, and (7) not finding sex pleasurable. Both cancer and its treatment can impact sexual function. Survivors at highest risk for treatment-related sexual dysfunction are those with pelvic tumors and those whose treatment affects the hormonal systems mediating sexual desire and pleasure. Emotional distress, relationship conflict, and having a partner with sexual dysfunction can also increase the risk of sexual dysfunction in survivors.

Specific cancer types are associated with higher rates of sexual dysfunction. Men treated for prostate or testicular cancer have an increased risk of sexual dysfunction. Erectile dysfunction (ED) rates among these survivors can be related to extent of surgery, increased doses of external beam radiation, and need for hormonal therapy. Studies attempting to modify surgery or radiation therapy for prostate cancer to spare sexual function suggest that 75% to 85% of men treated for localized disease still have long-term problems with ED. In addressing survivorship care, primary care clinicians can help direct care by exploring the extent of sexual dysfunction and basing therapeutic options on etiology of dysfunction if this can be determined. Factors correlated with better outcome include having more counseling sessions, younger age, absence of depression, and absence of marital conflict. The role of hormonal assessment and treatment for male cancer survivors is not clear. Low normal to low levels of testosterone are common in young men treated with high-dose alkylating agent chemotherapy (e.g., Hodgkin and non-Hodgkin lymphoma). Male cancer survivors with androgen deficiency report impairment in sexual functioning, but studies of replacement have not consistently demonstrated improvement. Testosterone effects are complex, and use of standard replacement for sexual dysfunction needs further evaluation. Determining primary tumor type, treatment dose, and common side effects of specific treatment modalities can help guide evaluation and management. To date, most of the efforts in improving sexual dysfunction in male survivors focus on mechanically restoring erectile rigidity. A few studies of outcome in impotence clinics where men were not selected for health or etiology of ED demonstrated that only 30% to 40% of men were sexually active and considered their problem resolved up to 5 years after evaluation despite trying a mean of two treatments.
In women, treatment of cancers that affect the sexual organs such as breast, endometrial, ovarian, cervical, fallopian tube, and vulva directly impacts sexual function. However, even cancers that do not directly involve sexual organs can impact sexual health through side effects of the multimodality treatment. Surgery, chemotherapy, endocrine therapy, and radiation therapy all can cause body image concerns including decreased feelings of attractiveness and femininity, alopecia, scars, and weight changes.\textsuperscript{10,11} Cancer and its treatment can also lead to fatigue, neuropathy, decreased libido, change in physical capacity for sex, hormonal changes, anxiety, stress, depression, infertility, transient or permanent amenorrhea, and premature menopause.

Menopause in the patient with cancer is different than natural menopause.\textsuperscript{12} Estrogen depletion from transient or permanent ovarian suppression leads to instability of the hypothalamic thermoregulatory set point and allows changes in body temperatures and hot flushing sensations. Women with cancer often experience abrupt or premature menopause from their treatment, which causes them to have greater intensity and duration of symptoms such as hot flashes, vaginal dryness, dyspareunia, decreased libido, and changes in sexual response.\textsuperscript{10,11} These symptoms have been shown to negatively impact quality of life. Even in women already in menopause, treatment can have significant sexual health effects.\textsuperscript{13}

Changes in sexual health often cause distress. When distress is high, libido often declines. A decreased libido may cause confusion and embarrassment. Many women and men are not cognizant that their sexual problems are related to their treatment. Available treatments should be discussed with patients, and, for women, some possibilities are lubricants, moisturizers, counseling/sex therapy, altering contributing medications, physical therapy for pelvic floor disorders, mechanical devices/vibrators, and local intravaginal estrogens (Tables 42-1 and 42-2).\textsuperscript{14-17} There are currently no U.S. Food and Drug Administration (FDA)–approved medications for decreased libido, arousal, or orgasmic difficulties in women. However, these are areas of active drug development by pharmaceutical companies. Men experiencing sexual dysfunction have a few options for treatment depending on etiology and concomitant medical conditions (Table 42-3).\textsuperscript{18-19} Exploration of sexual dysfunction and referral to appropriate specialists for treatment can improve quality of life for survivors.

Sexuality in patients with cancer is understudied, and a better understanding of the impact of specific treatments on sexual function is needed to appropriately counsel patients about the relative morbidity of cancer treatment strategies. Additional research is warranted to improve prevention, diagnosis, and treatment of sexual concerns throughout cancer treatment and survivorship. Safe and effective interventions to ameliorate sexual dysfunction in survivors are needed to improve quality of life. Because primary care clinicians are often the first level of interaction with the medical community, it is important that they address this topic with survivors.

<table>
<thead>
<tr>
<th>TABLE 42-1</th>
<th>Vaginal Health Products to Address Sexual Side Effects in Patients Treated for Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Over-the-Counter Products</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Water-based lubricants** | • Improve dryness  
• Increase comfort with sexual activity and decrease pain with intercourse  
• Safe to use with latex condoms  
• Apply to both partners during sexual activity  
• Examples: K-Y Jelly, Astroglide, vitamin E, Eros for Women, almond oil, and Liquid Silk |
| **Silicone-based lubricants** | • Longer lasting than water-based lubricants  
• Increase comfort with sexual activity and decrease pain with intercourse  
• Safe to use with latex condoms  
• Apply to both partners during sexual activity  
• Cannot be used with silicone sex toys  
• Examples: K-Y Intrigue, Eros Body Glide, Wet Platinum Silver |
| **Vaginal moisturizers** | • Suppositories that hydrate vaginal tissue  
• Improve dryness, pruritus, elasticity, and irritation  
• Not uncommon for patients with cancer to use three to five times per week  
• Take 2 mo to realize full benefit  
• May cause watery discharge  
• Examples: Replens, K-Y Aquabeads, vitamin E vaginally |
| **Prescription Products** | |
| **Intravaginal estrogens** | • Reestrogenize vaginal epithelium  
• Effective in improving vaginal dryness and comfort  
• May cause transient estradiol elevation  
• Controversial in women with breast cancer or hormone receptor-positive cancers; safety unclear  
• Examples: Vagifem, Estring, Estrace, and Premarin |

<table>
<thead>
<tr>
<th>TABLE 42-2</th>
<th>Sexual Health Strategies to Address Pain and Promote Pelvic Floor Health in Women Treated for Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic Approach</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Dilator therapy** | • Mechanically stretches vaginal tissue  
• Use to decrease pain with intercourse or gynecologic exams  
• Use to prevent or treat vaginal stenosis/adhesions  
• Dilators usually come in a set of increasing size  
• Use for 5–10 min several times per week |
| **Pelvic floor exercises** | • Stretch and relax pelvic floor muscles  
• Improve control and strength of pelvic muscles  
• Use to decrease pain with intercourse or gynecologic exams  
• May promote circulation and pelvic blood flow  
• Daily use recommended |
| **Increase blood flow to pelvic floor** | • May promote circulation and arousal response  
• May have rehabilitative effects by drawing oxygenated blood  
• Methods include pelvic floor exercises, vibrators, and self-stimulation |
## Treatment Options for Male Sexual Dysfunction

### Therapeutic Approach

#### Phosphodiesterase-5 inhibitors
- **Sildenafil, vardenafil, tadalafil**
- Allows accumulation of cyclic GMP within the penis
- 100 mg dose effective in 75% of men
- Contraindicated if patient is also using nitrates
- Taken 1 h before sexual activity and effective for up to 4 h

#### SSRI
- Inhibits serotonin reuptake by neurons
- May help patients with premature ejaculation
- Effective dose is dependent on specific drug.

#### Penile suppository
- Alprostadil is prostaglandin E₁
- Causes smooth muscle relaxation in corpus cavernosum
- Delivered in gel formulation into meatus of penis
- Can be used twice daily
- Inserted up to 10 min prior to sexual activity and effective for 1 h

#### Penile injection (alprostadil)
- Prostaglandin E₁ injected into base of penis
- Effective in 50%–85% of patients
- Priapism is an uncommon side effect.
- Injected 10–20 min prior to sexual activity and effective for up to 1 h

### Penile implant

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflatable penile implants</td>
<td>Offered to patients unresponsive to medical therapy</td>
</tr>
<tr>
<td>Noninflatable penile implants</td>
<td>Semirigid surgically implanted rod</td>
</tr>
</tbody>
</table>

### Penile injection (phentolamine)
- Causes relaxation of penile vascular smooth muscle
- Injected 10–20 min before sexual activity
- Requires stimulation to have erection

### Vacuum pump
- Draws blood into penile cavernosa
- Tourniquet at base holds blood in penis.
- Inflated before sexual activity and effective until elastic ring at base is removed
- Erection not to be maintained more than 1 h

**GMP**: guanosine monophosphate; **SSRI**: selective serotonin reuptake inhibitor.

### References

KEY POINTS
- Survivors of cancer are at risk for the development of a wide range of endocrine health conditions as a result of prior cancer therapies, particularly radiation therapy or high-dose alkylating agents.
- Hypothalamic–pituitary dysfunction is a dose- and time-dependent specific late effect following cranial irradiation.
- Continued lifelong surveillance is required in both children and adults for the development of endocrine dysfunction.
- Referral to an endocrinologist is recommended for management of hormonal issues.

INTRODUCTION
With improvements in cancer detection and treatment, the population of survivors of cancer in the United States is growing. Unfortunately, exposure to cancer therapies including surgery, chemotherapy, and radiation can lead to persistent or late-occurring health outcomes collectively termed “late effects.” Although endocrine disorders among survivors of childhood cancers have been well described, the adult survivorship literature in this area is limited. Nonetheless, it is important for the adult primary care clinician to have a basic understanding of common endocrine complications among survivors. In this chapter, we will touch briefly on three common cancer treatment–related endocrinopathies: disorders of the gonads, thyroid, and hypothalamic–pituitary axis (HPA) as well as the metabolic syndrome. Table 43-1 outlines common cancer treatments and their endocrine-related late effects. For detailed clinical guidelines pertaining to survivors of childhood cancer, the reader is directed to the Children’s Oncology Group (COG) recommendations regarding cancer-related exposures and potential late effects, which are publically available at www.survivorshipguidelines.org.

GONADAL DYSFUNCTION
Gonadal dysfunction is likely to be the most common late effect of cancer therapy. A functioning gonadal system requires intact hypothalamus, pituitary, and gonads. Therefore, damage to any part of the system may result in dysfunction. Among males, primary Leydig or germ cell dysfunction can result from alkylating agent chemotherapy or radiotherapy to the testes. Although Leydig cell dysfunction may require testosterone replacement, germ cell dysfunction will result in oligoazoospermia. Among females, the ovaries of prepubertal girls are more resistant to chemotherapy than the ovaries of older women, but high-dose alkylating agents or radiation to the ovaries can cause ovarian failure even in younger subjects.

Finally, it should be noted that premature menopause is a common side effect of chemotherapy among women older than the age of 40 years. Thyroid gland disorders following cancer treatment are extremely common; a study of 5-year survivors of Hodgkin lymphoma found a cumulative incidence of thyroid chronic conditions exceeding 50% by 30 years from diagnosis (Fig. 43-1). Radiation therapy to the thyroid gland itself, including craniospinal irradiation (doses ≥15 Gy), may not only lead to central or primary hypothyroidism but can also cause hyperthyroidism (doses ≥35 Gy), thyroiditis, or multinodular goiter. Primary hypothyroidism can also be caused by cytokine treatment or interleukin-based immunotherapy. Tyrosine kinase inhibitors, such as sunitinib and sorafenib, have also been frequently associated with primary hypothyroidism. Thyroid neoplasms, both benign and malignant, are frequently seen following radiation to the gland. Children treated prior to the age of 10 years and doses of 20 to 29 Gy to the thyroid gland are the highest risk groups for these tumors.

HYPOTHALAMIC–PITUITARY DISORDERS
Exposure to high doses of radiation therapy or surgery in the vicinity of HPA places survivors of cancer at risk for multiple hormone deficiencies, including thyroid-stimulating hormone (TSH), growth hormone (GH), adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), and gonadotropin (luteinizing hormone [LH]/follicle-stimulating hormone [FSH]) deficiencies. Patients treated with cranial irradiation are at risk for other endocrinopathies such as hyperprolactinemia and central precocious puberty as well.

Growth Hormone Deficiency
GH deficiency (GHD) is the most common endocrinopathy seen in survivors of cancer following cranial irradiation,
TABLE 43-1. Cancer Therapies and Potential Endocrine Late Effects

<table>
<thead>
<tr>
<th>Potential Late Effect</th>
<th>Cancer Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonadal dysfunction</td>
<td>- Alkylating agents</td>
</tr>
<tr>
<td></td>
<td>- Nitrosoureas</td>
</tr>
<tr>
<td></td>
<td>- Cisplatin</td>
</tr>
<tr>
<td></td>
<td>- Tamoxifen (transient)</td>
</tr>
<tr>
<td></td>
<td>- Radiation to the gonads</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>- Radiation to the hypothalamic–pituitary axis (≥10 Gy)</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>- Radiation to the hypothalamic–pituitary axis (≥18 Gy)</td>
</tr>
<tr>
<td></td>
<td>- Surgery</td>
</tr>
<tr>
<td>Skeletal dysplasia</td>
<td>- Radiotherapy to the spine</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>- Methotrexate</td>
</tr>
<tr>
<td></td>
<td>- Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>- Cranial radiotherapy</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>- Cranial radiotherapy</td>
</tr>
<tr>
<td></td>
<td>- Abdominal irradiation and total body irradiation</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>- Radiotherapy to neck or scatter</td>
</tr>
<tr>
<td></td>
<td>- Total body irradiation</td>
</tr>
<tr>
<td></td>
<td>- Cytokines and immune therapy</td>
</tr>
<tr>
<td></td>
<td>- Tyrosine kinase inhibitors</td>
</tr>
<tr>
<td>LH/FSH deficiency</td>
<td>- Radiation to the hypothalamic–pituitary axis (≥30 Gy)</td>
</tr>
<tr>
<td>TSH deficiency</td>
<td>- Cranial radiotherapy (≥30 Gy)</td>
</tr>
<tr>
<td>ACTH deficiency</td>
<td>- Cranial radiotherapy (≥30 Gy)</td>
</tr>
<tr>
<td></td>
<td>- Injury to the adrenals (surgery, tumoral expansion)</td>
</tr>
<tr>
<td></td>
<td>- Glucocorticoids (transient)</td>
</tr>
<tr>
<td>SIADH (transient)</td>
<td>- Cisplatin</td>
</tr>
<tr>
<td></td>
<td>- Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>- Melphalan</td>
</tr>
<tr>
<td></td>
<td>- Vinca alkaloids</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>- Cranial radiotherapy (≥40–50 Gy)</td>
</tr>
</tbody>
</table>

LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; ACTH, corticotropin; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

activation of the hypothalamic-pituitary-gonadal axis, puberty with accelerated progression, and delayed or arrested puberty because of complete or partial gonadotropin deficiency resulting in hypogonadotropic hypogonadism.10 Gonadotropin deficiency in adults is associated with infertility and sexual dysfunction. Estrogen and testosterone deficiencies may be treated with hormone replacement preparations.

Thyrotropin Deficiency
Radiation therapy to the HPA (typically in doses ≥30 Gy may result in TSH deficiency). Although TSH deficiency is easily treated with thyroid hormone replacement, clinicians must be careful to follow free thyroxine (T4) levels, not TSH.

Other Hormonal Derangements
Adrenal insufficiency resulting from loss of ACTH secretion is a relatively rare occurrence in survivors of cancer, but it may be seen in patients treated with surgery in the region of the HPA or high-dose radiation (HPA doses ≥30 Gy).11 Clinical manifestations include fatigue, weakness, nausea, vomiting, diarrhea, hypotension, and temperature instability. Treatment is with lifelong glucocorticoid replacement therapy. Patients who receive very high doses of cranial radiation with HPA doses >40 to 50 Gy may experience elevated levels of prolactin (PRL). Radiation-induced hyperprolactinemia is often clinically silent, but it can cause pubertal delay in children, galactorrhea or amenorrhea in women, and decreased libido and impotence in men.12 Treatment is with dopamine agonists, which lead to inhibition of PRL secretion and synthesis.

METABOLIC SYNDROME
The metabolic syndrome is a cluster of cardiovascular risk factors including hypertension, dyslipidemia, and central or visceral adiposity associated with an increased risk for the development of type 2 diabetes and atherosclerotic disease.
In studies of survivors of childhood cancer, increased prevalence of the metabolic syndrome has been observed in survivors of hematologic malignancies treated with cranial or total body irradiation,13 patients with brain tumor treated with cranial radiotherapy, and those with GHD.14 Higher prevalence of the metabolic syndrome has also been reported in patients with adult-onset hematologic malignancies as well as prostate and testicular cancers. Treatment primarily consists of lifestyle changes such as smoking cessation, increased physical activity, and dietary modification as well as drug therapy when indicated.

**CONCLUSION**

Endocrinopathies remain a well-recognized and frequently encountered complication of cancer therapies affecting the thyroid, gonads, hypothalamus, pituitary, and pancreas. Although certain late effects may develop early after treatment, others may not become apparent for many years, thus warranting lifelong careful surveillance. Awareness of the potential endocrine sequelae of cancer therapies allows for the timely recognition and treatment in those at risk, thereby reducing morbidity and improving quality of life in all survivors of cancer.

**References**

Neurocognitive dysfunction associated with cancer and cancer treatment is commonly described as “chemo brain” by patients who experience a subjective perception of cognitive impairment during and after cancer treatment. This colloquialism is a misnomer, however, because studies have demonstrated objective cognitive impairment in patients both prior to treatment and following cancer treatments that did not include chemotherapy (e.g., endocrine therapy for breast cancer and hormone ablation therapy for prostate cancer, radiation of central nervous system disease). Studies have only begun to characterize and measure this phenomenon, and the current state of the research in this area is nascent; however, patients who present in the primary care setting benefit from a careful evaluation and management of their cognitive concerns.

INCIDENCE AND NATURAL HISTORY

Cancer-associated cognitive change has been reported in 17% to 75% of patients in various studies. This variation in prevalence rates reflects differences in study design and methodology and heterogeneity of cancer and cancer treatments. Using even very conservative approximations of prevalence of cognitive impairment would lead one to estimate that more than a million cancer survivors are currently living with cognitive impairment related to cancer treatment. Longitudinal studies, undertaken primarily among populations with breast cancer, demonstrate that the prevalence of cognitive impairment is highest during and immediately following treatment. Wefel et al. suggest that about half of patients who experience acute cognitive changes will recover function by 1 year after completion of cancer therapy. However, impairments may not emerge until after the completion of treatment, suggesting a late neurotoxicity that results in a delayed cognitive dysfunction. Although negative results have been reported, the predominance of evidence supports the assertion that cognitive change is experienced by a substantial proportion of patients treated for cancer. Population-based studies confirm that impairments for some individuals persist long into survivorship, impact functional abilities, and quality of life. Studies elucidating risk factors for persistent cognitive dysfunction are needed.

THE PATIENT EXPERIENCE

Common cognitive changes described include challenges with slowed thinking, short-term memory, word finding, multitasking, decision making, completion of tasks, and...
It is essential to screen for depression as an underlying factor in complaints of cognitive impairments. The use of a screening tool, such as the Patient Health Questionnaire (PHQ), can improve clinician sensitivity to depression and monitor improvement with interventions. Clinicians should weigh factors such as disease type and stage in considering imaging studies. In brain cancer survivors, cognitive concerns may be the first sign of recurrence. For cancers that frequently metastasize to brain (e.g., lung cancer), cognitive concerns may warrant brain imaging. The more common situation, however, is a patient with early-stage breast cancer who presents fairly shortly after the completion of treatment where imaging studies contribute little to the evaluation of a complaint of cognitive dysfunction in the absence of focal neurologic findings or persistent headache.

Neuropsychological testing can clarify the diagnosis of neurocognitive dysfunction associated with cancer. Many patients find the testing validating, although it may be necessary to explain that the testing is “normed” against population-based means so that a result of “normal” does not mean that they are not experiencing impairment, especially if they were “above average” prior to exposure. Neuropsychiatric evaluation provides focused assessment of deficits within specific cognitive domains. The pattern of deficits that emerges will allow the physician, working collaboratively with the neuropsychologist, to discriminate cancer-associated neurocognitive dysfunction from progressive dementing illnesses in older patients. Neuropsychological evaluation also provides an assessment of patients’ ability to resume their previous employment or need for workplace accommodations and can be very helpful in instances where patients are unable to resume employment in their previous occupation. Formal testing also guides rehabilitative and coping approaches by helping patients and their physicians gain insight into the activities that are most likely to be problematic and to develop management strategies. Figure 44-1 presents an algorithm to guide the evaluation of a patient presenting with cognitive complaints associated with cancer therapy.

A sudden acute confusion or decline in cognitive function is not consistent with cancer-associated neurocognitive dysfunction. Patients presenting with acute confusion should be appropriately evaluated, including chemistries and imaging studies.

CONSIDERATION OF OTHER FACTORS THAT CONTRIBUTE TO COGNITIVE ISSUES

Several factors may contribute to the cognitive dysfunction experienced by chemotherapy-treated patients with cancer. Evaluation for potentially reversible contributing factors is important. Depression is known to impact cognitive function in older adults and can be effectively managed with medication, talk therapy, or a combination. Screening for factors such as substance abuse, long-standing alcohol use, vitamin deficiency, and thyroid dysfunction helps to rule out reversible factors. The current literature also indicates that comorbidities such as diabetes, vascular disease, and epilepsy have a significant impact on cognitive function, particularly among older patients. The use of medications to manage comorbidities or symptoms may contribute to symptoms of cognitive impairment.
survivors, there is robust evidence for enhanced quality of life and reduction of all-cause mortality rates. Structured cognitive behavioral therapy interventions also demonstrate promise, with a recent small study by Ferguson et al. showing improvement in verbal memory, quality of life, and high patient satisfaction measures.

- Pharmacologic strategies—Psychostimulants, including methylphenidate and modafinil, have been used in the context of cancer-associated cognitive change. The use of psychostimulant medications for this indication is off label but may be helpful for some individuals, particularly those who experience significant symptoms related to attention or fatigue (Table 44-3).

- Recommendations for management strategies should be individualized and balance the risk of benefit versus harm in the context of the patient’s personal situation and goals.

**TABLE 44-2** Patient Education Points: Cancer-Associated Cognitive Change

- “Chemo brain” is a real phenomenon demonstrated in clinical studies of varied populations with cancer.
- A subset of patients experience this, but science doesn’t understand which people are at greatest risk or why it happens.
- It is not like Alzheimer disease—it won’t get progressively worse. It is more accurate to think of this like a mild brain injury.
- Like other brain injuries, both rehabilitation and learning to cope with changes are important components to improve function.

**TABLE 44-3** Psychostimulants Used for Cancer-Associated Cognitive Dysfunction (Off Label)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Relative Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>5–20 mg dosed morning and noon</td>
<td>$</td>
</tr>
<tr>
<td>Modafinil</td>
<td>100–200 mg daily</td>
<td>$$$</td>
</tr>
</tbody>
</table>

FIGURE 44-1. Algorithm for evaluation of cognitive concerns in cancer survivors. Onc/neurosurg, oncology/neurosurgery; QOL, quality of life.

**MANAGEMENT OF NEUROCOGNITIVE DYSFUNCTION ASSOCIATED WITH CANCER**

- Patient education—In many cases, patients are substantially reassured to have their symptoms validated and to learn that this condition is not progressive. Table 44-2 summarizes helpful patient education points.
- Behavioral strategies—Behavioral approaches to the management of cognitive dysfunction should include exercise in patients for whom that recommendation is appropriate. Although there is limited evidence that physical exercise will directly improve cognitive functioning among cancer survivors, there is robust evidence for enhanced quality of life and reduction of all-cause mortality rates. Structured cognitive behavioral therapy interventions also demonstrate promise, with a recent small study by Ferguson et al. showing improvement in verbal memory, quality of life, and high patient satisfaction measures.
- Pharmacologic strategies—Psychostimulants, including methylphenidate and modafinil, have been used in the context of cancer-associated cognitive change. The use of psychostimulant medications for this indication is off label but may be helpful for some individuals, particularly those who experience significant symptoms related to attention or fatigue (Table 44-3).
- Recommendations for management strategies should be individualized and balance the risk of benefit versus harm in the context of the patient’s personal situation and goals.
References


The past decades have seen tremendous scientific gains resulting in improved survival after childhood cancer. Currently, more than 300,000 survivors of childhood cancer are living in the United States. Unfortunately, this population is at increased risk for many serious and life-threatening late effects. Of those treated in the 1970s, 1980s, and 1990s, about 75% will develop a chronic health condition by 40 years of age; the condition will be severe or life threatening in more than 40% (Fig. 45-1).3

In that setting, it is imperative that adult primary care clinicians are aware of this high-risk population and have some knowledge of treatments and late effects. For more detailed clinical guidelines, the reader is directed to the Children’s Oncology Group (COG) recommendations regarding cancer-related exposures and potential late effects, which are publicly available at www.survivorshipguidelines.org.

CHEMOTHERAPY

Chemotherapy is the backbone of treatment for most pediatric cancers because of both the attempt to avoid radiation therapy (RT) in growing children and the fact that many pediatric cancers spread rapidly and therefore require systemic treatment. Here, we will review general categories of chemotherapy and common late effects (Table 45-1).

RADIATION

RT is necessary for the cure of many pediatric cancers. Unfortunately, the developing and growing organs and tissues of children are often sensitive to the effects of RT. Late effects following RT may be apparent very early after treatment (e.g., cognitive dysfunction) or years or decades later (e.g., second malignant neoplasms [SMN] or coronary artery disease [CAD]). The incidence and severity of RT-induced late effects are influenced by the organs and tissues involved in the radiation field, type of radiation administered, daily fractional and cumulative radiation dose, and age at treatment. Table 45-2 lists some of the more common or important late effects associated with brain, neck, chest, and abdomen or pelvis RT.

Important surveillance recommendations for second malignancies include initiation of early breast cancer surveillance in women exposed to chest RT. The risk in these women is significantly elevated (15% to 20% of women will develop breast cancer by the age of 45 years). Early detection of breast cancer in these women is imperative because early stage is strongly associated with improved survival, and therapeutic options are limited given prior radiation and chemotherapy treatments. Thus, the COG and other groups recommend surveillance with annual mammography and breast magnetic resonance imaging (MRI) starting at the age of 25 years or 8 years after the radiation, whichever occurs last. Likewise, for elevated risk of colorectal cancer in survivors exposed to 30 Gy abdominal or pelvic radiation or more, the COG recommends colonoscopy starting at the age of 35 years or 10 years after radiation, whichever occurs last.

SURGERY

The following sections review the complications associated with a few select surgeries used in the management of childhood cancers.

Amputation/Limb-Sparing Surgeries

Amputation/limb-sparing surgeries are used to prevent local recurrences of bone tumors by removal of all gross and
Chemotherapy Class Potential Late Effect(s)
Alkylating agent (e.g., cyclophosphamide)
- Gonadal dysfunction
- Acute myeloid leukemia (AML)
- Pulmonary fibrosis and restrictive lung disease
- Bladder and genitourinary disease
- Renal tubular damage (Fanconi syndrome)

Anthracycline (e.g., doxorubicin)
- Cardiomyopathy

Antimetabolite (e.g., methotrexate)
- Osteopenia and osteoporosis

Bleomycin
- Pneumonitis, pulmonary fibrosis, and acute respiratory distress syndrome (ARDS)

Corticosteroid
- Osteonecrosis, osteopenia, and osteoporosis

Heavy metal (e.g., cisplatin)
- Hearing loss and sensory neuropathy
- Chronic kidney disease and tubular dysfunction

Epipodophyllotoxin (e.g., etoposide)
- Treatment-related acute myeloid leukemia (t-AML)

Any radiation
- Skin, bone, soft tissue malignancies

Brain, eyes, and ears
- Cognitive dysfunction
- Growth hormone deficiency
- Obesity and the metabolic syndrome
- Central gonadotropic deficiency (RT doses ≥40 Gy)
- Central adrenal deficiency (RT doses ≥40 Gy)
- Cerebrovascular accidents
- Meningiomas and glial tumors
- Cataracts
- Hearing loss (RT doses ≥30 Gy)
- Dental abnormalities

Neck
- Thyroid nodules and cancer
- Hyperthyroidism or hypothyroidism
- Carotid and subclavian disease (RT doses ≥40 Gy)

Chest, mantle, or mediastinal
- Breast cancer
- Cardiovascular heart disease (i.e., coronary heart disease, valvular disease, arrhythmias)
- Pulmonary disease (especially if combined with bleomycin or nitrosourea chemotherapy)
- Esophageal cancer

Abdomen and pelvis
- Colorectal or gastric cancer (RT doses ≥30 Gy)
- Renal insufficiency
- Hypertension (especially if combined with nephrotoxic chemotherapy)
- Acute ovarian failure or premature menopause
- Oligospermia or azoospermia and Leydig cell dysfunction
- Delayed puberty
- Functional asplenia (RT doses ≥40 Gy)

RT, radiation therapy.

Nephrectomy
Nephrectomy is a mainstay component of treatment for renal tumors (including Wilms tumor). Complications include renal insufficiency, hyperfiltration injury, hypertension, and hydrocele. Compensatory hypertrophy of the remaining kidney often occurs after nephrectomy, likely to adapt to increase in glomerular filtration capacity. Clinicians should be
be screened with a one-time ferritin level after treatment has ended; iron chelation may be warranted.

**PSYCHOSOCIAL ASPECTS OF SURVIVORSHIP**

Although many cancer survivors report positive psychosocial gain, such as enhanced self-concept, most survivors are at risk for psychiatric outcomes, including major depression, anxiety, and posttraumatic stress disorder (PTSD). Isolation is frequently seen, both during and after treatment, and many adult survivors are unemployed or underemployed. Survivors of acute lymphoblastic leukemia (ALL) and brain tumors appear to be at highest risk, but no diagnostic group is immune. Furthermore, lack of insurance coverage can keep this population from the care they need. Ideally, survivors and their families would benefit from ongoing psychosocial support.

**SUMMARY**

Late effects of therapy for childhood cancer are common and serious. Fortunately, many late effects are modifiable. Anticipatory risk-based care can reduce the frequency and severity of treatment-related morbidities. The primary care clinician is crucial to providing this risk-based care to survivors. A cancer treatment summary and care plan provided to the primary care clinician together with continued communication between the primary care clinician and the cancer center is imperative for optimal care of this high-risk population.

**References**

Hematopoietic cell transplantation (HCT) is an established therapeutic option for several hematologic malignancies. With advances in transplantation strategies, more than 70% of those who survive the first 2 years after HCT are expected to become long-term survivors. However, HCT survivors are at increased risk for developing long-term complications such as endocrinopathies, musculoskeletal disorders, cardiopulmonary compromise, and subsequent malignancies. The cumulative incidence of a chronic health condition among HCT survivors is 59% at 10 years after HCT. There is a need to understand the key long-term chronic health conditions that are likely to be encountered in HCT survivors to identify those at highest risk and screen the survivors for these complications with the goal of early detection and reduction in morbidity.

KEY POINTS

- Hematopoietic cell transplantation is an established therapeutic option for several hematologic malignancies.
- More than 70% of those who survive the first 2 years after HCT are expected to become long-term survivors.
- HCT survivors are at increased risk for developing long-term complications such as endocrinopathies, musculoskeletal disorders, cardiopulmonary compromise, and subsequent malignancies.
- The cumulative incidence of a chronic health condition among HCT survivors is 59% at 10 years after HCT.
- There is a need to understand the key long-term chronic health conditions that are likely to be encountered in HCT survivors to identify those at highest risk and screen the survivors for these complications with the goal of early detection and reduction in morbidity.

Cardiac Complications

HCT survivors are at risk for late cardiotoxicity, including cardiomyopathy, congestive heart failure (CHF), valvular dysfunction, arrhythmia, and pericarditis. Anthracyclines are the main cause of cardiomyopathy and damage the heart in a dose-dependent fashion. Female gender, anthracycline dose exceeding 250 mg per m² alone or with chest radiation, and presence of multiple cardiovascular risk factors increase the risk of CHF after HCT. Mediastinal radiation can produce inflammation and fibrosis resulting in restrictive cardiomyopathy and valvular defects. Fibrosis can also affect the electrical conduction pathways causing arrhythmias. Cerebrovascular disease and coronary artery disease are prevalent after HCT and often occur earlier than would be expected in the general population. Presence of multiple cardiovascular risk factors (obesity, dyslipidemia, hypertension, and diabetes) after HCT increases the risk of cardiovascular disease (CVD). HCT survivors are at increased risk for developing de novo cardiovascular risk factors such as diabetes and hypertension because of exposure to total body irradiation (TBI) and prolonged immunosuppressive therapy after allogeneic HCT; this increased prevalence of cardiovascular risk factors potentially contributes to the risk of cardiovascular disease (CVD).

Pulmonary Complications

Noninfectious pulmonary complications are frequent after HCT. These include bronchiolitis obliterans (BO) and BO with organizing pneumonia (BOOP).
Bronchiolitis Obliterans

BO is characterized by a nonspecific inflammatory injury affecting the small airways. The presentation of BO is insidious, with a median latency of 1 year after HCT. Manifesting as an obstructive defect in the initial stages, it progresses to peribronchiolar fibrosis, with emergence of restrictive changes. Patients present with a dry cough, progressive dyspnea, and wheezing. A characteristic mosaic image on high-resolution computed tomography of the chest is highly suggestive of BO. Criteria used to make a clinical diagnosis of BO include (1) forced expiratory volume in the first second of expiration (FEV1)/forced vital capacity (FVC) <0.7 and FEV1 <75% of predicted value, (2) evidence of air trapping or small airway thickening or bronchiectasis on high-resolution computed tomography, and (3) absence of respiratory infection.

Bronchiolitis Obliterans with Organizing Pneumonia

BOOP is a clinicopathologic syndrome involving bronchioles, alveolar ducts, and alveoli. BOOP usually presents as an interstitial pneumonia and occurs usually within the first 12 months after HCT, with a cumulative incidence of less than 2%. The clinical presentation is acute, with sudden onset of dry cough, dyspnea, and fever. The chest X-ray presents peripheral patchy consolidation, ground glass attenuation, and nodular opacities. The pulmonary function tests demonstrate a restrictive pattern. Definitive diagnosis necessitates histologic confirmation.

BO and BOOP are caused by an alloimmune response of donor hematopoietic cells against host lung antigens. These patients are typically treated with immunosuppressive agents; however, there is no strong evidence that any specific therapy is effective in improving long-term outcomes.

Endocrine Complications

Endocrine complications are among the most common chronic health conditions encountered after HCT and include thyroid dysfunction, osteoporosis, metabolic syndrome, growth impairment, and gonadal dysfunction.

Thyroid Abnormalities

Thyroid abnormalities primarily include subclinical and overt hypothyroidism. The incidence of compensated hypothyroidism ranges from 25% to 30%, with median latency of 2 years. The incidence of overt hypothyroidism ranges from 3.4% to 9.0% with a latency of 2.7 years. Hypothyroidism is directly related to radiation to the thyroid gland (as part of neck/mediastinal radiation or TBI). Younger age increases the risk.

Osteopenia and Osteoporosis

The decreased bone mineral density is caused by the use of steroids in the treatment of graft-vs-host disease (GVHD). The known association of HCT with growth hormone deficiency and hypogonadism, physical inactivity, and a diet low in calcium. The incidence of osteopenia in adults is reported to approach 50% at 4 to 6 years after HCT, whereas the incidence of osteoporosis approaches 20% at 2 years.

Metabolic Syndrome

Metabolic syndrome is a cluster of central obesity, dyslipidemia, hyperglycemia, and hypertension and conveys an increased risk of type 2 diabetes mellitus and cardiovascular disease. Disturbances of the hypothalamic–pituitary axis resulting in growth hormone deficiency and hypogonadism play a role in the development of metabolic syndrome. Chemotherapy and radiation can have direct impact on vascular endothelium. Dyslipidemia, glucose intolerance, and arterial hypertension can result as a consequence of prolonged immunosuppression with cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil (MMF), and corticosteroids. Prevalence data indicate that 34% to 49% of adult survivors of HCT have one or more components of metabolic syndrome.

Survivors of allogeneic HCT are 3.7 times more likely to report diabetes mellitus and 2.1 times more likely to report hypertension than their siblings.

Growth Impairment

Growth impairment occurs frequently in children after HCT, primarily because of growth hormone deficiency after cranial radiation or TBI. Patient’s age at HCT is a significant factor in predicting adult height. Children younger than 10 years of age at HCT are at greatest risk for short stature.

Gonadal Failure

Gonadal failure is a frequent endocrine complication after HCT. Pubertal disturbances after HCT are caused by radiation-related perturbations of the hypothalamic–pituitary axis and/or by chemoradiotherapy-related damage to the gonads. The risk of gonadal failure increases with cumulative doses of gonadotoxic therapies. Recovery of spermatogenesis occurs more frequently in patients receiving lower doses of cyclophosphamide (120 mg per kg) than in those treated with higher doses (200 mg per kg). Ovaries are more vulnerable to irradiation and chemotherapy than the testes. Approximately 50% of prepubertal girls given fractionated TBI enter puberty spontaneously and achieve menarche at a normal age, whereas almost all female patients who are more than 12 years old at HCT have ovarian failure, probably because of a decreased reserve of primordial follicles. High-dose busulfan is a major cause of ovarian failure even when given in the prepubertal period. Irreversibility of ovarian function after HCT in most patients highlights the necessity of timely hormonal replacement therapy to prevent osteoporosis and other complications.

Musculoskeletal Complications

Osteonecrosis

Osteonecrosis (ON) is a painful and debilitating condition that develops when the blood supply to the bone is disrupted, usually in areas with terminal circulation. The cumulative incidence of ON is 15% at 10 years after unrelated donor HCT. Among allogeneic HCT recipients, male sex; presence of chronic GVHD; and exposure to cyclosporine, macrolide immunosuppressants, prednisone, and MMF render patients at increased risk.
### Solid Tumors

The risk of solid tumors increases with time from HCT and, for those who survive 10 or more years after HCT, is reported to be eightfold that of the general population. Radiation is the single most important risk factor. These radiogenic cancers have a long latent period, and the risk is frequently high among patients undergoing irradiation at a young age. Immunologic alterations predispose patients to squamous cell carcinoma of the buccal cavity, particularly in view of the association with chronic GVHD. Types of solid tumors reported in excess among HCT recipients include melanoma, cancers of the oral cavity and salivary glands, brain, liver, uterine cervix, thyroid, breast, bone, and connective tissue.

### Late Infections

Late infections with bacteria, viruses, fungi, and other organisms because of persistent immunodeficiency are most common in patients with chronic GVHD, in cord blood and T-cell depleted allogeneic HCT recipients, and following CD34-selected autologous transplants. It is standard practice to administer prophylaxis for infections caused by varicella zoster virus (VZV), Pneumocystis jiroveci, and encapsulated bacteria (Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae) within the first year after HCT, or even later, in patients with chronic GVHD. In addition, vaccinations are recommended in long-term survivors (Table 46-1).

### Bacterial Infections

The most significant risk factor for late bacterial infections with encapsulated bacteria is chronic GVHD because of impaired production of opsonizing antibodies. Late infections may also be caused by other organisms such as Staphylococcus species and gram-negative aerobic bacteria. Patients with chronic GVHD should have antibiotic prophylaxis targeting encapsulated organisms given for as long as immunosuppressive therapy is administered. Administration of prophylactic antibiotics for oral procedures should follow the American Heart Association guidelines for endocarditis prophylaxis. All HCT recipients should receive Pneumocystis jiroveci pneumonia (PCP) prophylaxis for 6 months or as long as immunosuppressive therapy is given for treatment/prevention of chronic GVHD. Because of the high mortality associated with infections with these organisms, prompt administration of antibiotics with broad-spectrum coverage is imperative when infections are first suspected, with appropriate modifications upon identification of the infectious organism.

### Viral Infections

VZV disease is the most common late viral infection after HCT. It is common practice to recommend oral acyclovir prophylaxis to all allogeneic recipients for the first year after HCT and for longer in patients with ongoing chronic GVHD. Most late cytomegalovirus (CMV) disease occurs during the first year after HCT but in some cases may occur up to 3 years after HCT. Gastroenteritis and pneumonia are the most common late manifestations of CMV disease. Late CMV pneumonia is associated with the highest mortality.

### Subsequent Malignant Neoplasms

An important and potentially devastating complication of HCT is the occurrence of subsequent malignant neoplasms (SMNs). The magnitude of risk of SMNs after HCT ranges from twofold to 11-fold that of the general population. Risk factors include age at HCT, exposure to chemotherapy and radiation prior to HCT, use of TBI and high-dose chemotherapy for myeloablative treatment, with infectious agents such as Epstein-Barr virus (EBV) and hepatitis B and C viruses (HBV and HCV), immunodeficiency after HCT aggravated by the use of immunosuppressive drugs for prophylaxis and treatment of GVHD, type of transplantation (autologous vs. allogeneic), source of hematopoietic stem cell, and primary malignancy. SMNs are classified into three distinct groups:

1. Therapy-related myelodysplasia (t-MDS) and therapy-related acute myeloid leukemia (t-AML),
2. Lymphoma and other lymphoproliferative disorders, and
3. Solid tumors. Although secondary leukemia and lymphoma develop relatively early in the posttransplantation period, secondary solid tumors have a longer latency.

### Myelodysplasia and Acute Myeloid Leukemia

The t-MDS/t-AML are the major cause of nonrelapse mortality in patients undergoing autologous HCT for Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The cumulative probability of t-MDS/t-AML ranges from 1.1% at 20 months to 24.3% at 43 months after autologous HCT, with a median latency of 12 to 24 months after HCT. Two types of t-MDS/t-AML are recognized in the World Health Organization (WHO) classification, depending on the causative therapeutic exposure: alkylating agent/radiation and topoisomerase II inhibitor.

In patients exposed to alkylating agents, t-MDS/t-AML usually appears 4 to 7 years after exposure. There is a high prevalence of abnormalities involving chromosomes 5 (-5/del[5q]) and 7 (-7/del[7q]). The t-AML secondary to topoisomerase II inhibitors presents as overt leukemia without a preceding myelodysplastic phase. The latency is brief, ranging from 6 months to 5 years, and is associated with balanced translocations involving chromosome bands 11q23 or 21q22.

The risk of t-MDS/t-AML increases with older age at HCT, pretransplantation therapy with alkylating agents, topoisomerase II inhibitors (such as etoposide), and radiation therapy; use of peripheral blood hematopoietic cells; stem cell mobilization with etoposide; difficult stem cell harvests; conditioning with TBI; number of cluster of differentiation (CD) 34+ cells infused; and a history of multiple transplants.
Continued monitoring and preemptive therapy is useful in patients at risk for late CMV disease. Patients with chronic GVHD are also at risk for acquisition of respiratory virus infections such as respiratory syncytial virus and influenza and parainfluenza viruses. Seasonal vaccination of close contacts with the inactivated vaccine is recommended (see Table 46-1). Finally, HBV and HCV may result in chronic hepatitis and cirrhosis.

**Fungal Infections**
Late invasive aspergillosis is most commonly seen in patients with chronic GVHD and preceding CMV or respiratory virus infections. The outcome of both mold and candidal infections in the setting of chronic immunosuppression remains poor. Some experts recommend antifungal prophylaxis in patients receiving chronic or high-dose corticosteroids for chronic GVHD. Sensitive diagnostic tests (Aspergillus galactomannan assay and polymerase chain reaction) may help in establishing an early diagnosis.

**Recommended Vaccinations**
HCT recipients have declining levels of antibodies to vaccine-preventable diseases in the first few years after HCT, and hence lose protective immunity if they are not revaccinated. The response of the HCT recipients to vaccination depends on the timing of the vaccine after HCT, the immunogenicity of the vaccine, and the immune status of the recipients at the time of the vaccinations. Inactivated or subunit vaccines are generally safe in HCT patients, but all live vaccines are contraindicated in the first 2 years after HCT.

### Table 46-1: A Suggested Immunization Schedule for Hematopoietic Cell Transplantation (HCT) Recipients

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>12 Month Post-HCT</th>
<th>14 Month Post-HCT</th>
<th>18 Month Post-HCT</th>
<th>24 Month Post-HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria/tetanus toxoid (Td) or DTaP/Tdap</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Inactivated poliovirus (IPV)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae (HiB)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>X</td>
<td>X</td>
<td>(skip this dose if using single hep A)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Total three doses PCV (1 mo interval) the fourth dose with PPSV 7 mo later</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seasonal influenza (inactivated)</td>
<td>Seasonal; lifelong administration; start before HCT then resuming ≥6 mo after HCT</td>
<td>Seasonal; lifelong administration; start before HCT then resuming ≥6 mo after HCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seasonal influenza (live, nasal)</td>
<td>Contraindicated in all stem cell transplant recipients</td>
<td>Contraindicated in all stem cell transplant recipients</td>
<td>Seasonal; lifelong administration; start before HCT then resuming ≥6 mo after HCT</td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella (MMR)</td>
<td>Contraindicated in stem cell transplant recipients with chronic GVHD or on immunosuppressants</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Varicella</td>
<td>Limited data, optional in pediatric HCT recipients; not for adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td>Contraindicated in all HCT recipients</td>
<td>Contraindicated in all HCT recipients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients who are immunocompetent (off all immunosuppressive medication) and do not have chronic GVHD should be immunized according to the schedule outlined previously.

* Post-hematopoietic cell transplantation (HCT) patients should be viewed as never vaccinated and receive full doses of toxoids; their diphtheria/tetanus toxoid (DT) vaccine should include full dose acellular pertussis toxoid if possible. Diphtheria, tetanus, and pertussis (DTaP) vaccine should be administered to children <7 years of age. Tetanus, diphtheria, and pertussis (Tdap) is recommended for patients >7 years of age. Tdap should replace a single dose of Td as booster for adults ≥19 years for those who have not received a dose of Tdap for ≥10 years. Then boost with Td every 10 years.

* Oral polio vaccine is no longer recommended for routine immunization in the United States.

* Hepatitis A: Give with hepatitis B in a combination vaccine hep A/B at hepatitis B schedule in ≥18 years. For people 1 to 18 years old, single antigen hepatitis A vaccine formulations should be administered in a two-dose schedule at 12 and 24 months post-HCT.

* HPV is recommended in all females at ages 11 to 12 years (range 9 to 26 years) who have not completed the series.

* Pneumococcal: all ages; PCV (pneumococcal conjugated vaccine) total three doses 1 month apart; A fourth dose with PPSV (pneumococcal polysaccharide) 7 months after the last PCV may be given to broaden immune response. In patients with chronic GVHD who may have poor response to PPSV; fourth dose with PCV may be considered instead. Lifelong prophylactic penicillin is recommended for splenectomized patients. For patients with penicillin allergies, erythromycin or clarithromycin may be used.

* Meningococcal: indicated in anatomic or functional asplenia, terminal component deficiencies, travel to endemic areas, and all college students living in dorm rooms who have not been previously immunized.

* Influenza: It is strongly recommended that all household members of an HCT recipient receive the influenza vaccine on an annual basis. HCT recipients themselves should also receive this vaccination on an annual basis beginning before HCT and then resuming at least 6 months post-HCT. For children <9 years, first year post-HCT, two doses are recommended to be administered 1 month apart and then one dose annually thereafter.

* MMRI: Contraindicated for patients ≤24 months post-HCT, with chronic GVHD, or on immunosuppressants. Not generally recommended for all transplant recipients, although should generally be administered to children.

* Varicella vaccine: Not for adults. Limited data on safety and efficacy. May be considered optional in pediatric patients and only if ≥24 months post-HCT, no active GVHD, and not on steroids or immunosuppressants.

* GVHD, graft versus host disease.
HCT or in patients with chronic GVHD. Table 46-1 details a suggested immunization schedule for HCT recipients drawn from the Centers for Disease Control and Prevention (CDC) guidelines. However, there is no data indicating the efficacy of these vaccinations in preventing infection, and it cannot be assumed that the development of antibody titers after vaccination necessarily correlates with protective immunity in the HCT recipient.

RECOMMENDED SCREENING

Two major groups have developed guidelines for the follow-up of HCT survivors. The Center for International Blood and Marrow Transplantation Research (CIBMTR), European Group for Blood and Marrow Transplantation (EBMT), and American Society for Blood and Marrow Transplantation (ASBMT) has developed guidelines for survivors starting 6 months after therapy completion. Recommendations for monitoring and preventive measures are organized by the organ system of potential late effects. The Children’s Oncology Group has developed guidelines using therapeutic exposures as the organizational basis for follow-up recommendations that are aimed at physicians providing care to survivors 2 or more years after therapy is completed. Table 46-2 summarizes the most commonly observed adverse outcomes after HCT, the therapeutic exposures that are associated with these complications, and recommendations distilled from the two sources cited previously in terms of the recommended evaluations and counseling for HCT survivors.

---

### TABLE 46-2  Periodic Evaluation of Long-term Survivors of Hematopoietic Cell Transplantation (HCT)

<table>
<thead>
<tr>
<th>Potential Adverse Outcomes</th>
<th>Therapeutic Exposures Associated with Increased Risk</th>
<th>Periodic Evaluation and Counseling of Increased Risk Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy/congestive heart failure</td>
<td>Pre-HCT anthracyclines</td>
<td>Echocardiographic evaluation every 1–5 y depending on anthracycline dose; cardiovascular risk factor assessment and counseling; monitor pregnant women closely</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Pre-HCT radiation to chest</td>
<td>Cardiovascular risk factor assessment and counseling</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>Pre-HCT bleomycin, carmustine, radiation to chest, TBI</td>
<td>CXR and PFT at baseline and as clinically indicated; assess for symptoms such as chronic cough and dyspnea; influenza and pneumococcal vaccines; counsel on risk of smoking and secondhand smoke</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Pre-HCT radiation to neck or mediastinum, TBI</td>
<td>TSH and free thyroxine annually</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Pre-HCT radiation to pelvis, lumbar–sacral spine, and brain; alkylating agents</td>
<td>Males: age-appropriate history and Tanner staging; measure LH, FSH, and testosterone at the age of 14 y or if delay of puberty is suspected. Females: history and Tanner staging; measure FSH, LH, and estradiol at the age of 13 y, if delay of puberty is suspected, or for irregular menses or amenorrhea.</td>
</tr>
<tr>
<td>Short stature</td>
<td>Pre-HCT cranial irradiation, TBI, corticosteroids</td>
<td>Growth and growth velocity should be measured every 6 mo during childhood.</td>
</tr>
<tr>
<td>Osteopenia/osteoporosis</td>
<td>Pre-HCT cranial irradiation, TBI, gonadal radiation, corticosteroids</td>
<td>Baseline dual-emission X-ray absorptiometry or quantitative CT scan with repeat as clinically indicated; use of calcium supplements, bisphosphonates, or hormone replacement (in patients with gonadal failure) as clinically indicated</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>Corticosteroids, high-dose radiation to any bone, calcineurin inhibitors</td>
<td>Musculoskeletal exam annually; history for joint pain, swelling, immobility, and limited range of motion annually</td>
</tr>
<tr>
<td>Cataracts</td>
<td>TBI or cranial irradiation, steroids</td>
<td>Annual funduscopic exam and visual acuity</td>
</tr>
<tr>
<td>Myelodysplasia, acute myeloid leukemia</td>
<td>Autologous HCT, alkylating agents, topoisomerase II inhibitors, anthracyclines, radiation</td>
<td>History (fatigue, bleeding, easy bruising); dermatologic exam and CBC/differential annually for up to 10 y posttransplant</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>All survivors</td>
<td>Physical exam for lymphadenopathy and splenomegaly annually</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Pre-HCT radiation and chemotherapies</td>
<td>Physical exam for benign or malignant neoplasms annually</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Females with radiation ≥20 Gy to mantle, mediastinum, lung, or axillary fields</td>
<td>Annual clinical breast exam from puberty to the age of 25 y, then every 6 mo; annual mammogram and MRI 8 y after radiation therapy or at the age of 25 y (whichever is later)</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>Radiation ≥30 Gy to abdomen, pelvis, or spine</td>
<td>Colonoscopy every 5 y beginning at the age of 35 y or 10 y after radiation therapy (whichever is later)</td>
</tr>
</tbody>
</table>

TBI, total body irradiation; CXR, chest X-ray; PFT, pulmonary function test; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; CT, computed tomography; CBC, complete blood count; MRI, magnetic resonance imaging.

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References


KEY POINTS

- Cancer survivors of adult onset cancer can experience long-term and late psychosocial sequelae due to cancer and its treatment.
- Currently, many of these psychosocial problems are not being addressed.
- Simple evidence-based screening and interventions can take place during an extended office visit.
- There are several resources available to assist primary care providers and cancer survivors in the management of psychosocial sequelae.

WHAT ARE THE PSYCHOSOCIAL SEQUELAE OF CANCER TREATMENT?

Most cancer patients recover following treatment despite its toxic nature. However, a large subset of patients with adult-onset cancer experiences several psychosocial problems following treatment. The primary care clinician is in an ideal position to evaluate these problems, manage them in the office, or, when justified, refer the patient to an appropriate resource. This chapter provides guidance in addressing these problems. In cancer survivors, who are defined in this chapter as being post-primary cancer treatment, psychosocial challenges can range from emotional and functional problems because of pain to low mood to difficulty managing work and family. Although over time, these symptoms tend to decline in severity, they can persist for many years and impact health, levels of function, and a sense of well-being.

There is a need to proactively evaluate and manage the psychosocial sequelae of cancer survivors. Surveys indicate that there are many unmet psychosocial needs reported by survivors of post-cancer treatment. In recent years, cancer patients are living longer and have been included in the category of those living with a chronic illness. However, cancer survivors report higher levels of distress than those with other chronic illnesses. Some of the problems contributing to this distress can include cognitive limitations, depressive symptoms, anxiety, pain, fatigue, sleep problems, and sexual dysfunction. Cancer survivors may also have the expectation that recovery will only require a few months, but in reality, symptoms and changes in function can persist for a lifetime. Fortunately, there are tools available that can assist primary care clinicians identify and manage this distress in cancer survivors. Also, it is important to realize that triage to behavioral health providers is not the only option when managing heightened levels of distress in cancer survivors. Other providers offer a range of approaches for distress and the many problems that can trigger it.

HOW TO IDENTIFY WHO NEEDS HELP

Cancer survivors report that psychosocial concerns are not adequately addressed in office visits with their physician providers. Although asking questions about psychosocial problems does add time to an office visit, there are a few simple procedures that one can follow. A discussion with the patient and the use of a brief patient report measure of level and sources of distress can help identify options to manage these psychosocial concerns. Primary care clinicians can either use this information to directly assist the patient further identify problem areas and solutions or to play a role in facilitating necessary referrals to others.

Brief Psychosocial Probe

What questions might be helpful to ask? Prior to asking questions in this sensitive area, it can be helpful to normalize the types of psychosocial problems (e.g., fears, mood changes, feeling of loss of control) that cancer survivors experience...
to reduce perceived stigma. For instance, it can be helpful to mention the following:

It is a normal reaction when a cancer survivor experiences feeling sad or tired or has problems with memory after cancer treatment is over. This experience can be very distressing and the problems you are telling me about are very normal reactions. It’s like soldiers coming back from the battlefield or the emotional reactions found in those who were involved with a major car accident.

Give them time to react. Then continue, “I would like to ask you a few questions so we can work out a plan to help with these problems.”

Curtiss et al.\(^6\) constructed a list of questions to measure problems with fatigue, sleep, self-perception, sexual function, cognition, as well as other symptoms in cancer survivors. Questions include: “Do you have enough energy?”; “What is your stress level?”, “How are you coping (or getting along)?”; and “Do you have problems with memory loss or changes in thinking?” Additional questions can be found in their article on caring for cancer survivors.\(^6\) Based on a cancer survivor’s answer, it is also helpful to obtain a sense of the severity of the survivor’s level of overall distress. This information can help determine whether a referral is warranted or whether some of these problems can be addressed in a few office visits. Table 47-1 provides a brief summary of the various approaches discussed in this chapter.

Distress

One efficient way to determine the severity of distress is through the use of the Distress Thermometer. The National Comprehensive Cancer Network (NCCN) uses the term distress to avoid the stigma associated with “psychiatric,” “psychosocial,” or “emotional” problems.\(^7\) NCCN recommends the use of the Distress Thermometer, a single-item measure of psychological distress, as a brief screen for cancer patients during active treatment for cancer.\(^8\) This self-report measure assesses distress experienced in the past week on a visual analogue scale, which is anchored by “no distress” (0) and “extreme distress” (10).

The Distress Thermometer’s problem list can help identify specific sources of distress. Cancer survivors are instructed to check the causes of their distress as it relates to practical (e.g., housing, insurance), family (e.g., partner, children), emotional (e.g., worry, sadness), spiritual/religious (e.g., loss of faith, relating to God), and physical (e.g., pain, fatigue) problems.\(^9\) A score of 4 or more on the Distress Thermometer merits a referral to mental health services (e.g., psychologist, psychiatrist, advanced practice clinicians), social work and counseling services, or chaplaincy services.\(^7\) Cancer survivors can contact the American Psychosocial Oncology Society’s (APOS) toll-free helpline (1-866-276-7443) to receive a referral to a mental health provider who specializes in cancer distress. Physicians should also consider those patients who score below 4 on the Distress Thermometer. The physician may find it helpful to examine and attend to the problems identified on the Distress Thermometer’s problem list if the patient appears distressed or talks to you about a problem that does not resolve on its own. Follow-up can either be addressed in the office visit or with a referral to a support group or with reliable sources of educational information. The Distress Thermometer can be easily downloaded with the NCCN Distress Management Clinical Practice Guidelines at no cost (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp) and used in practice. Free online lectures on the use of the Distress Thermometer (www.apos-society.org) are available.

### MANAGEMENT OF PSYCHOSOCIAL SEQUELAE IN PRACTICE

Although the detection of a clinically significant problem may necessitate a referral, there are also brief interventions that can take place within an extended office visit.

**Motivational Interviewing**

Motivational interviewing\(^10\) is an evidence-based intervention used with several chronic diseases, long-term health problems, and for the promotion of health behaviors. It is defined as “a client-centered, directive method for enhancing

<table>
<thead>
<tr>
<th>Table 47-1</th>
<th>Brief Evaluation and Intervention Approaches for Primary Care Clinicians</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tool</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Distress Thermometer</td>
<td>A single-item measure of psychological distress. An associated problem list examines sources of distress.</td>
</tr>
<tr>
<td>Brief psychosocial problem solving</td>
<td>Short discussion between patient and provider to identify potential problems a cancer survivor may have.</td>
</tr>
<tr>
<td>Problem solving</td>
<td>A self-management skill where the patient identifies a problem, the source of the problem, and potential solutions of which he or she tries one of them.</td>
</tr>
<tr>
<td>Motivational interviewing</td>
<td>Motivational interviewing increases a patient’s desire to and belief in his or her ability to change. In a non-challenging manner, the provider works with the patient to explore concerns regarding behavior change.</td>
</tr>
</tbody>
</table>
intrinsic motivation to change by exploring and resolving ambivalence. Motivational interviewing can be helpful in a primary care setting and for cancer survivors. Although initially developed for substance abuse, it has been applied to dietary changes, exercise, medication adherence, general anxiety, as well as other problems.

Motivational interviewing includes five components: expressing empathy (i.e., warmth, acceptance, non-judgmental stance), developing discrepancy (i.e., between patient’s current behavior and future goals), avoiding argumentation (i.e., an understanding that it is the patient’s choice to change), rolling with resistance (i.e., acknowledging the ambivalence and avoiding confrontation), and supporting self-efficacy (i.e., patient’s belief in his or her capability in a task). Nurses can assist with motivational interviewing initially in the office visit followed by phone calls to the patient. Motivational interviewing is a skill that requires some training. Additional information about training can be found at http://www motivationalinterviewing.org/quick_links/mitraining.html. Podcasts on motivational interviewing in health care are available (e.g., http://www.podcast.tv/video-episodes/what-are-the-guiding-principles-of-motivational-interviewing-11998915.html).

### Problem Solving

Another simple intervention that can be conducted during an office visit is a self-management skill referred to as problem solving. Often, because of the transition from cancer patient to cancer survivor, or even years following primary treatment, cancer survivors experience difficulties that may simply require generating an action plan to address a given problem. The primary care clinician can allocate 5 minutes as a non-judgmental coach to help teach the effective problem-solving process. This approach is designed to help the patient define the problem and factors influencing it, generate solutions, choose a potential solution, and determine whether the potential solution was helpful. This problem-solving method can empower patients to solve certain psychosocial problems on their own. The following link provides specific examples and podcasts of the problem-solving approach with cancer survivors: http://www.canceradvocacy.org/health-care/toolbox/solving-problems.html.

### Clinical Practice Guidelines for Distress

The NCCN Distress Management Panel has published standards for psychosocial care and distress management in cancer. The guidelines outline how to evaluate, treat, and follow patients with cancer and survivors with dementia, mood disorder, adjustment disorder, anxiety disorder, substance abuse/dependence, personality disorder, existential issues (e.g., grief, concerns of death, loss of faith, questions about the meaning of life), and other psychosocial issues. NCCN has separate clinical practice guidelines for fatigue and pain. Providers may access the full clinical practice guidelines at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

### Managing Unexplained Symptoms

At times, cancer survivors may present with symptoms that have no known etiology and that are unrelated to a cancer recurrence or a new cancer. However, cancer survivors may be concerned that these symptoms (e.g., fatigue, pain) are a sign of cancer recurrence or new malignancy. When symptoms impact function (e.g., endurance, work ability, strength), appropriate options may include referral to physical medicine and rehabilitation, nutrition counseling, physical therapy, occupational therapy, complementary and alternative medicine, vocational counseling, or physical exercise. When the symptoms have a more direct impact on well-being (e.g., fear of recurrence, depression, stress, family problems), appropriate interventions include support groups, self-management, or targeted medication.

### AVAILABLE RESOURCES

#### Multimedia

Cancer survivors express a need for cancer-related information after the completion of primary treatment. Many cancer survivors use the Internet to learn about cancer-related information. However, these cancer survivors are concerned about whether the information they find is reputable. They also express a need for additional information but have difficulty finding it. Providers can supply a list of quality websites such as Mayo Clinic (www.mayoclinic.com), American Cancer Society (www.cancer.org), and the LIVESTRONG Foundation (www.livestrong.org). There are also applications for smartphones that can be used for monitoring symptoms and for cancer-specific assistance (e.g., CancerSupportSource and Cancer.Net Mobile by American Society of Clinical Oncology). The book The Cancer Survivor’s Guide: The Essential Handbook to Life After Cancer, written by one of the authors of this chapter, provides specific examples and exercises to help cancer survivors manage the many challenges that they may encounter.

#### Support Groups

Support groups may be a useful resource for cancer survivors, especially during the transition from cancer patient to cancer survivor. Cancer survivors express that participation in support groups is beneficial. On the other hand, for short-term (i.e., less than 8 months post-intervention) reduction in a specific problem area such as depression or anxiety, cognitive behavioral interventions, which is a more structured form of behavior change compared to generic support groups, might be warranted. Quality of life was also rated as higher in the cognitive behavioral intervention studies than the generic group over the longer term (i.e., >8 months post-intervention).

### SUMMARY

Cancer survivors with no evidence of disease may still experience psychosocial problems. The primary care clinician can screen these problems by asking a few questions and using a simple measure of distress. Elevated scores on the Distress Thermometer indicate a high level of suspicion that “not all is okay.” Depending on the complexity of these problems, many can be managed in everyday practice. However, some may require mental health providers or referrals to other resources (e.g., support groups, complementary and alternative approaches, exercise, etc.). The primary care clinician can play a critical role in the identification and management of psychosocial sequelae.
References


Cancers of Individual Sites
CHAPTER 48

Head and Neck Cancer

Shrujal S. Baxi, MD, MPH • David G. Pfister, MD

KEY POINTS

• Tobacco and alcohol remain the leading risk factors for head and neck cancer.
• There is a rising incidence of HPV-related head and neck cancer, which can occur in never smokers/never drinkers.
• Head and neck cancer treatment is complex and requires careful consideration of oncologic and functional factors, taking into account patient preferences. The decision regarding the best approach should be made in consultation with a multidisciplinary team of providers.
• Survivors of head and neck cancer remain at risk for recurrent and subsequent cancers as well as other medical problems and need close surveillance following treatment.

HEAD AND NECK CARCINOMA

Many different primary sites of cancer occur in the head and neck. However, head and neck carcinoma (HNC) generally refers to a heterogeneous group of tumors arising from the lining of the upper aerodigestive tract. The oral cavity, pharynx, and the larynx are the most common primary sites. There were 52,610 cases of HNC expected in the United States in 2012, representing 3% of the total new cancer cases. HNC is approximately threefold more common in men; the median age at diagnosis is 62 years.

Squamous cell carcinoma or a variant is the predominant histologic subtype seen in more than 90% of HNC cases and will be the focus of this chapter (i.e., head and neck squamous cell carcinoma [HNSCC]). Treatment decisions in HNC are based on primary tumor site and stage according to the American Joint Commission on Cancer (AJCC) Version 7 staging system, which incorporates tumor characteristics (size, local invasion, and extension), nodal status (size, number, and location), and the presence or absence of distant metastatic disease. Approximately 20%, 70%, and 10% of patients present with early-stage disease (stage I or II), locally or regionally advanced disease (stage III, IVA, or IVB), and distant metastatic disease (stage IVC), respectively (Table 48-1).

Risk Factors

The predominant risk factors for HNSCC are tobacco and alcohol. Smoking is associated with a sixfold increased risk of HNSCC compared to never smoking; alcohol is associated with a dose-dependent risk of disease, but the combination of the two can have a synergistic effect. Chewing tobacco, snuff, and betel quid are major risk factors for oral cavity cancer. Smoking during or after treatment for head and neck cancer is associated with poorer oncologic prognosis, worse quality of life, and a significant risk of second primary tumors.

Some HNSCCs are associated with chronic viral infections. High-risk subtypes of human papillomavirus (HPV), most commonly subtype 16, are a risk factor for the development of HNSCC in the oropharynx. Patients with HPV-related HNSCC are younger, healthier, and less commonly have a history of exposure to the traditional HNSCC risk factors. The prevalence of oral HPV infection in the general population is estimated at 6.9%, with an increased risk associated with male sex, certain age groups, number of sexual partners, and the number of cigarettes smoked per day. Nasopharynx cancer is another site with a viral association (Epstein-Barr virus).

Pathogenesis

There are stepwise genetic alterations that transform normal head and neck mucosa into invasive cancer, which varies depending on the etiology. For example, half of tobacco- and alcohol-related tumors contain mutations of p53, an essential tumor suppressor gene, whereas in HPV-related cancers, p53 is more commonly inactivated by viral proteins rather than mutated. The entire epithelial surface of the head and neck undergoes a “field effect” because of a shared carcinogenic exposure rendering patients at risk for synchronous and metachronous second primary tumors, a particular concern in patients with a significant tobacco and alcohol history. Although there has been a great interest in chemoprevention of HNSCC, particularly with the use of vitamin A analogues, there is currently no proven agent for this indication.

Clinical Manifestations

Patients with HNSCC can present with a spectrum of signs and symptoms. The primary tumor is usually seen as a surface...
### TABLE 48-1  Staging and SEER 5-Year Survival by Tumor Site

#### Carcinoma of the Oral Cavity (Includes Lip, Oral Tongue, Hard Palate, Floor of the Mouth, and Gum)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-Year Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor 2 cm or less in greatest dimension, no lymph nodes</td>
<td>71%–96%</td>
</tr>
<tr>
<td>II</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension, no lymph nodes</td>
<td>59%–83%</td>
</tr>
<tr>
<td>III</td>
<td>Tumor more than 4 cm with or without single ipsilateral lymph node (3 cm or less) or any tumor up to 4 cm with single ipsilateral lymph node (3 cm or less)</td>
<td>36%–57%</td>
</tr>
<tr>
<td>IV</td>
<td>Moderately advanced primary tumor or any primary tumor with one lymph node greater than 3 up to 6 cm or multiple lymph nodes all up to 6 cm (IVa) Very advanced primary tumor or any primary tumor with lymph node greater than 6 cm (IVb) Distant metastasis (IVc)</td>
<td>30%–48%</td>
</tr>
</tbody>
</table>

#### Carcinoma of the Nasopharyx

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor without parapharyngeal extension, no lymph nodes</td>
<td>78%</td>
</tr>
<tr>
<td>II</td>
<td>Tumor without parapharyngeal extension with single ipsilateral lymph node (6 cm or less) or tumor with parapharyngeal extension with or without a single ipsilateral lymph node (6 cm or less)</td>
<td>64%</td>
</tr>
<tr>
<td>III</td>
<td>Tumor with no more than parapharyngeal extension with bilateral lymph nodes (6 cm or less) or any tumor that involves bony structures of skull base or paranasal sinuses with no lymph node greater than 6 cm or extending to the supraclavicular fossa</td>
<td>60%</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor with intracranial extension, cranial nerve involvement, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space with lymph nodes up to 6 cm (IVA) Any primary tumor with a lymph node greater than 6 cm in size or extending to the supraclavicular fossa (IVb) Distant metastasis (IVc)</td>
<td>47%</td>
</tr>
</tbody>
</table>

#### Carcinoma of the Oropharynx (Includes Tonsils, Soft Palate, Base of Tongue)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-Year Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor 2 cm or less in greatest dimension, no lymph nodes</td>
<td>75%</td>
</tr>
<tr>
<td>II</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension, no lymph nodes</td>
<td>65%</td>
</tr>
<tr>
<td>III</td>
<td>Tumor more than 4 cm or extension to epiglottis with or without single ipsilateral lymph node (3 cm or less) or any tumor up to 4 cm with single ipsilateral lymph node (3 cm or less)</td>
<td>45%</td>
</tr>
<tr>
<td>IV</td>
<td>Moderately advanced resectable primary tumor or any primary tumor with one lymph node greater than 3 up to 6 cm or multiple lymph nodes up to 6 cm (IVA) Very advanced primary tumor or any primary tumor with a lymph node greater than 6 cm in size (IVb) Distant metastasis (IVc)</td>
<td>30%</td>
</tr>
</tbody>
</table>

#### Carcinoma of the Hypopharynx

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor 2 cm or less in greatest dimension or limited to one subsite, no lymph nodes</td>
<td>49%</td>
</tr>
<tr>
<td>II</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension or invades more than one subsite of hypopharynx, no fixation of hemilarynx, no lymph nodes</td>
<td>39%</td>
</tr>
<tr>
<td>III</td>
<td>Tumor more than 4 cm or with fixation of the hemilarynx or extension to esophagus with or without single ipsilateral lymph node (3 cm or less) or less advanced primary tumor with single ipsilateral lymph node (3 cm or less)</td>
<td>34%</td>
</tr>
<tr>
<td>IV</td>
<td>Advanced resectable primary tumor or any primary tumor with one lymph node between 3–6 cm in size or multiple lymph nodes all less than 6 cm in size (IVA) Any unresectable primary tumor or any primary tumor with a lymph node greater than 6 cm in size (IVb) Distant metastasis (IVc)</td>
<td>23%</td>
</tr>
</tbody>
</table>

#### Carcinoma of the Larynx (Includes Supraglottis, Glottis, and Subglottis)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-Year Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to one subsite (supraglottis, glottis, or subglottis), no lymph node involvement</td>
<td>59%–90%</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends to adjacent subsite of larynx, no vocal cord fixation, no lymph node involvement</td>
<td>56%–74%</td>
</tr>
<tr>
<td>III</td>
<td>Tumor causing vocal cord fixation, tumor with more local extension including postcricoid area, preepiglottic space, paraglottic space, or inner cortex of thyroid cartilage with or without single ipsilateral lymph node (3 cm or less) or less advanced primary tumor with single ipsilateral lymph node (3 cm or less)</td>
<td>47%–56%</td>
</tr>
</tbody>
</table>
lesion but can also grow in an endophytic manner below the visible mucosa and so only initially apparent on palpation. Some patients present with asymptomatic, enlarged cervical lymph nodes, whereas others have signs and symptoms that are directly related to the primary tumor. Patients with HNSCC frequently present with vague symptoms, often delaying diagnosis (Table 48-2). Although the presence of high-risk health behaviors such as tobacco and alcohol abuse may increase the suspicion for a malignancy, it is important to note that many head and neck cancers arise in patients without traditional risk factors.

**Diagnosis**

Initial evaluation should include a comprehensive history and physical exam with a thorough head and neck examination noting the location of the primary tumor along with possibly enlarged cervical lymph nodes. Direct visualization of the mucosal surface at risk is important and facilitated through the use of mirrors, fiberoptic scopes, and exam under anesthesia as indicated. Cross-sectional imaging of the primary and neck assists in delineating the extent of disease; routine brain imaging is not recommended as brain metastases are uncommon in HNSCC. Biopsy of the primary site should be completed after imaging when possible to avoid confounding subsequent imaging interpretation. Fine needle aspiration (FNA) of a lymph node can expeditiously establish the initial diagnosis and should be considered if lymph node status is unclear given the importance of nodal status on staging and treatment in HNSCC (see Table 48-2).

**Prognosis**

In patients with nonmetastatic disease, negative prognostic factors associated with a worse outcome include stage, older age, functional status, and number of pack-years of smoking. In stage III or IV oropharynx cancer, patients with HPV-positive disease have a 3-year overall survival of 82% compared to 57% in patients with HPV-negative disease but this benefit declines with a history of smoking. Prognosis in HNSCC is dependent on site and stage of disease (see Table 48-1).13-15

**Treatment**

Surgery and radiation are the curative backbone of treatment in HNSCC. Chemotherapy is not curative as a single modality but plays an important role as part of combined modality treatment, particularly as a radiation sensitizer when given concurrently with radiation and as palliative therapy. Patients with early-stage disease are generally treated with single modality therapy (surgery or radiation depending on anticipated functional outcomes and available expertise), whereas patients with locally or regionally advanced disease are treated with a multimodality approach. Patients presenting with distant metastatic disease are typically treated with palliative intent. Treatment-related decision making requires careful consideration of oncologic and functional factors, taking into account patient preferences. The decision regarding the best approach should be made in consultation with a multidisciplinary team of providers.

A primary surgical approach involves complete resection of the tumor with or without a neck dissection depending on primary site and stage. Often, postoperative radiation-based therapy is indicated based on pathologic findings. In patients treated

---

**TABLE 48-1** Staging and SEER 5-Year Survival by Tumor Site (cont.)

<p>| Carcinoma of the Larynx (Includes Supraglottis, Glottis, and Subglottis) |</p>
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-Year Survival*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa</td>
<td>Moderately advanced primary tumor or any primary tumor with one lymph node greater than 3 up to 6 cm in size or multiple lymph nodes up to 6 cm</td>
<td>32%–44%</td>
</tr>
<tr>
<td>VBb</td>
<td>Very advanced primary tumor or any primary lesion with a lymph node greater than 6 cm</td>
<td></td>
</tr>
<tr>
<td>Vc</td>
<td>Distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

*Wide variation in 5-year survival reflects variable prognosis based on multiple anatomic sites included in the category.

**TABLE 48-2** Signs and Symptoms at Presentation Based on Site

<table>
<thead>
<tr>
<th>Location of Tumor</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Cavity (lips, front two-thirds of tongue, gums, mucosa of mouth, hard palate)</td>
<td>Pain, Unusual bleeding in the mouth, Change in fit of dentures, Change in articulation</td>
<td>White or red patch, Swelling of jaw, Nonhealing ulcer, Trismus, Halitosis</td>
</tr>
<tr>
<td>Nasopharynx (part of pharynx behind nose)</td>
<td>Epistaxis, Nasal congestion, Otalgia/ear fullness, Difficulty hearing, Tinnitus, Diplopia, Headaches, Nasal voice quality</td>
<td>Otitis media, Mass in neck</td>
</tr>
<tr>
<td>Oropharynx (middle pharynx, soft palate, base of tongue, and tonsils)</td>
<td>Persistent sore throat, Odynophagia, Dysphagia, Voice changes</td>
<td>Mass in neck, Recurrent tonsillitis (opharynx), Unintentional weight loss, Halitosis</td>
</tr>
<tr>
<td>Hypopharynx (lower part pharynx)</td>
<td>Otalgia, Hemoptysis, Breathing problems, Hoarseness</td>
<td>Lump in back of throat, Stridor (larynx)</td>
</tr>
<tr>
<td>Larynx (vocal cords, epiglottis)</td>
<td>Obstructive symptoms, Stridor (larynx)</td>
<td></td>
</tr>
</tbody>
</table>
with a primary radiation-based approach, surgery is reserved for a salvage treatment to resect residual disease or for elective management of neck nodes felt at risk for persistent disease. The acute and chronic sequelae of a surgical approach reflect the site and extent of the procedure and whether postoperative radiation treatment is given. Neck pain and shoulder weakness are potential sequelae of neck dissection, and postoperative radiation may increase the chances for fibrosis and neck stiffness.

Intensity-modulated radiation therapy (IMRT) is a technique of external beam radiation delivery that uses conformal dose distribution to optimize dosing while sparing adjacent normal tissue and is often applied in HNSCC. Radiation can be a primary treatment alone, combined with chemotherapy for more advanced disease that is unresectable or when organ preservation in hopes of a better functional outcome is desired (e.g., avoiding total laryngectomy), or used in the adjuvant setting alone or with chemotherapy for poor prognostic features at surgery. Patients who receive radiation to the head and neck may experience dermatitis, mucositis, xerostomia, thickened saliva, dysphagia, odynophagia, changes in taste, trismus, fibrosis, neck stiffness, anorexia, or weight loss. Some of the acute toxicities of treatment can become chronic problems, and radiation may also potentially cause late effects including hypothyroidism, osteoradionecrosis of the mandible, cervical myelopathy, and enhanced atherosclerosis of the carotid arteries.

Studies have shown that chemotherapy concurrent with radiation improves locoregional control and overall survival compared to radiation alone in patients with advanced HNSCC. The best studied agent in this setting is cisplatin given during weeks 1, 4, and 7 of definitive or adjuvant radiation treatment, although other agents and schedules have been studied and used. The added benefit of concurrent chemotherapy comes with a potential worsening of radiation-related toxicities along with the additional side effects of the chemotherapy itself.

In the recurrent or metastatic disease setting, surgery or radiation are applied with curative intent in selected patients. If surgery or radiation is not feasible, the median survival with the best available chemotherapy is less than 1 year. A platinum-based doublet combined with cetuximab improved overall survival compared to a platinum doublet alone in this poor prognostic population. Although a platinum-based doublet combination can provide better initial tumor response compared to treatment with a single agent, there is no improvement in overall survival compared to single agents given sequentially and the toxicity may be higher. The efficacy of individual cytotoxic agents is often dependent on prior treatment exposure.

**TABLE 48-3**

<table>
<thead>
<tr>
<th>Disease Evaluation</th>
<th>Pretreatment Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All tumors</strong></td>
<td></td>
</tr>
<tr>
<td>History and physical exam</td>
<td>Dental evaluation</td>
</tr>
<tr>
<td>- Complete exam of head and neck</td>
<td>Nutritional consult</td>
</tr>
<tr>
<td>- Mirror or fiberoptic exam, exam under anesthesia of head and neck mucosa as indicated</td>
<td>Speech and swallow evaluation</td>
</tr>
<tr>
<td>Biopsy of lesion/FNA of cervical lymph nodes</td>
<td>Audiogram as indicated</td>
</tr>
<tr>
<td>- Chest X-ray or chest CT to rule out lung lesions</td>
<td>Blood work (CBC, comprehensive metabolic panel, thyroid function tests)</td>
</tr>
<tr>
<td>- Consider PET scan or other assessment for distant metastases in patients with stage III or IV disease</td>
<td>Multidisciplinary consultation as indicated</td>
</tr>
<tr>
<td><strong>Oral cavity</strong></td>
<td></td>
</tr>
<tr>
<td>CT with contrast and/or MRI with gadolinium of primary and neck</td>
<td>Prosthodontics evaluation in selected cases</td>
</tr>
<tr>
<td>Jaw imaging as indicated</td>
<td></td>
</tr>
<tr>
<td><strong>Nasopharynx</strong></td>
<td></td>
</tr>
<tr>
<td>MRI with gadolinium of nasopharynx from base of skull to clavicles and CT (as indicated) with contrast</td>
<td>Imaging for distant metastases in patients with N2/3 disease</td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td></td>
</tr>
<tr>
<td>CT with contrast and/or MRI with gadolinium of primary and neck</td>
<td>Panorex as indicated</td>
</tr>
<tr>
<td>HPV testing of tumor</td>
<td></td>
</tr>
<tr>
<td>Exam under anesthesia with endoscopy as indicated</td>
<td></td>
</tr>
<tr>
<td><strong>Hypopharynx</strong></td>
<td></td>
</tr>
<tr>
<td>CT with contrast and/or MRI with gadolinium of primary and neck</td>
<td>Videostrobe in selected cases</td>
</tr>
<tr>
<td>Exam under anesthesia with endoscopy</td>
<td></td>
</tr>
<tr>
<td><strong>Larynx</strong></td>
<td></td>
</tr>
<tr>
<td>CT with contrast and thin cuts through larynx and/or MRI with gadolinium of primary and neck</td>
<td>Videostrobe in selected cases</td>
</tr>
<tr>
<td>Exam under anesthesia with endoscopy</td>
<td></td>
</tr>
<tr>
<td><strong>Unknown primary (diagnosed as squamous cell carcinoma on a lymph node biopsy)</strong></td>
<td>Special attention to oropharynx sites</td>
</tr>
<tr>
<td>CT with contrast or MRI with gadolinium of skull base to thoracic inlet; PET scan if primary not found</td>
<td></td>
</tr>
<tr>
<td>Complete skin exam</td>
<td></td>
</tr>
<tr>
<td>Exam under anesthesia with biopsy of high-risk sites</td>
<td></td>
</tr>
<tr>
<td>EBV and HPV testing on lymph node biopsy</td>
<td></td>
</tr>
</tbody>
</table>

There is an increased use of reirradiation often in combination with chemotherapy in patients with locally recurrent disease, but it carries the potential for significant toxicity.

**Unknown Primary Carcinoma**

With advancements in imaging, the rates of unknown primary cancer arising in the head and neck have declined. Determining the primary site of disease in HNSCC is important because it allows for optimal treatment planning. Most initially unknown primary cancers are ultimately found to have originated in the oropharynx (Table 48-3).

**Surveillance**

Careful follow-up is recommended following curative treatment for HNSCC given the risk of local recurrence and a 3% to 5% annual rate of second primary malignancies (SPM). Unlike recurrences, which occur mostly in the first 3 years following treatment, the risk of SPM persists for many years to come. In addition to second head and neck primaries, HNSCC survivors also face an increased risk of other tobacco- and alcohol-related tumors, specifically lung cancer. Tobacco cessation should be an ongoing discussion with HNSCC survivors (Table 48-4).

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**TABLE 48-4** Surveillance of Patients in Remission

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Frequency</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical exam</td>
<td>Year 1, every 1–3 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year 2, every 2–6 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Years 3–5, every 4–8 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year 6+, every 6–12 mo</td>
<td></td>
</tr>
<tr>
<td>Local imaging</td>
<td>Posttreatment baseline within 6 mo of treatment</td>
<td>Routine asymptomatic imaging not recommended</td>
</tr>
<tr>
<td>Chest imaging</td>
<td>As clinically indicated</td>
<td>Smoking history considered</td>
</tr>
<tr>
<td>Thyroid function studies</td>
<td>Every 6–12 mo</td>
<td></td>
</tr>
<tr>
<td>Speech/hearing follow-up</td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>Dental evaluation</td>
<td>Routine evaluation</td>
<td>Recommended for oral cavity but only as clinically indicated for other sites</td>
</tr>
</tbody>
</table>


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**References**

CHAPTER 49

Lung Cancer, Mesothelioma, Thymoma

Scott Nicholas Gettinger, MD

KEY POINTS

- Lung cancer continues to be the leading cause of cancer-related death in the United States and worldwide. This is primarily because of the advanced stage at diagnosis; however, with increased interest in CT screening for high-risk patients, relatively more early-stage lung cancers are expected to be diagnosed.
- Non–small cell lung cancer is increasingly being recognized as a heterogeneous group of disorders characterized by distinct histologic and molecular features that can guide systemic therapy.
- Prophylactic cranial irradiation is now considered standard of care for patients with small cell lung cancer responding to either curative intent chemoradiation or palliative chemotherapy, resulting in decreased incidence of brain metastases and improved survival.
- The role of surgery for mesothelioma continues to be controversial, with growing interest in pleurectomy/decortication over extrapleural pneumonectomy in those with potentially resectable disease. In such cases, preoperative chemotherapy is often considered, followed by thoracic radiation after surgery.
- Thymoma is a rare neoplasm, often associated with myasthenia gravis, which is characterized by slow local progression. Work up and management of thymomas should be undertaken at specialty centers that have experience with this uncommon disease.

Lung cancer is the leading cause of cancer mortality in the United States and worldwide. An estimated 160,000 patients in the United States will succumb to lung cancer in 2012, more than those dying from breast cancer, prostate cancer, and colon cancer combined. This is largely because of advanced disease at the time of diagnosis, with more than 50% of patients presenting with metastatic disease. Although lung cancer is primarily a disease of smokers, 10% to 15% of patients have no smoking history. This is a relatively sizable population, with more patients with lung cancer without a smoking history than those with multiple myeloma; acute leukemia; sarcoma; or cancers of the brain, esophagus, or stomach.

Mesothelioma and thymic malignancies are rarer diseases, with an estimated 3,300 cases of mesothelioma and less than 500 cases of thymic malignancy annually in the United States. Mesothelioma and thymomas tend to present locally and can have indolent courses. Most patients with mesothelioma have a history of asbestos exposure, the predominant cause of this disease. Most thymic neoplasms are thymomas, with less than 10% being thymic carcinoma. There are no clear risk factors for the development of thymic malignancies.

LUNG CANCER

Lung cancer can be subdivided into non–small cell and small cell carcinoma. Non–small cell lung cancer (NSCLC) accounts for roughly 85% of lung cancers and can be further divided into adenocarcinoma, squamous cell, and large cell carcinoma. In the United States, adenocarcinoma is the most common NSCLC histology and includes the indolent pure lepidic growth carcinoma (formerly termed bronchoalveolar carcinoma) as well as clearly invasive adenocarcinoma. Large cell neuroendocrine carcinoma is a rare subset of large cell carcinoma and is generally treated like a small cell lung cancer. An estimated 226,000 cases of lung cancer will be diagnosed this year in the United States.

Unfortunately, most patients with lung cancer present with metastatic disease (~56%) or local disease with regional lymph node involvement (~22%). Symptoms can arise from local disease, including cough, hemoptysis, hoarseness (recurrent laryngeal nerve compromise), and dyspnea; distant disease (e.g., bone pain/fracture from bone metastases; headache, nausea, and neurological compromise from brain metastases; and abdominal pain from liver metastases); and paraneoplastic
processes (Table 49-1). Constitutional symptoms including weight loss, anorexia, and fatigue are also common.

Non–Small Cell Lung Cancer

Staging of NSCLC takes into account size and location of primary tumor, location of lymph nodes, and presence of pulmonary and distant metastases (Table 49-2). For treatment purposes, NSCLC can be divided into three broad categories: early-stage disease, where there is no mediastinal/subcarinal, supraclavicular, or distant disease (stage I and stage II); locally advanced disease, generally characterized by mediastinal/subcarinal involvement (stage III); and advanced disease with pleural/pericardial or distant metastases (stage IV) (Table 49-3). Staging evaluation includes computed tomography (CT) chest/abdomen, positron emission tomography (PET) scan if there is not clear evidence of distant metastatic disease on CT, magnetic resonance imaging (MRI) of the brain, and mediastinal sampling to either confirm suspicion of mediastinal involvement in cases where no distant disease is demonstrated on PET or to evaluate a radiographically negative mediastinum with high-risk primary tumors (central location or large size) (Fig. 49-1). Mediastinoscopy continues to be the gold standard for mediastinal sampling; however, endobronchial and endoscopic ultrasound (EBUS and EUS, respectively)–guided sampling are other options, particularly in cases with radiographic suggestion of mediastinal/subcarinal involvement. All of these procedures are done in the outpatient setting.

Early-Stage Non–Small Cell Lung Cancer: American Joint Committee on Cancer Seventh Edition: T1–3, N0/1, M0; Stage I–IIIA

Surgery remains the cornerstone of curative intent treatment for early-stage NSCLC. If possible, this is accomplished with video-assisted thoracic surgery (VATS), which is associated with less morbidity and shorter hospital stays than open thoracotomy. Studies to date suggest no compromise of survival with VATS versus open thoracotomy. The role of sublobar resection for small primary tumors is still unclear, and lobectomy or pneumonectomy continues to be considered the optimal surgery. When surgery is not an option secondary to comorbidities or patient refusal, definitive options include stereotactic body radiation therapy (SBRT) (focused high-dose radiation generally administered in 3–5 daily fractions) and conventional external beam irradiation (over 6–7 weeks). Based on encouraging early-phase clinical trials evaluating SBRT, ongoing studies are currently comparing this to standard surgery in stage I NSCLC.

The role of postoperative (also known as adjuvant) chemotherapy is clearly established in node-positive (N1) early-stage NSCLC (stage II), with absolute improvement in 5-year survival rate between 5% and 15%, respectively. Subset analyses of two recent positive randomized adjuvant clinical trials reported 5-year survival rates of 59% versus 44% (n = 263, hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.5 to 0.92, p = 0.01) and 52% versus 39% (n = 203, HR 0.71, not statistically significant), respectively with the addition of cisplatin-based doublet chemotherapy. Chemotherapy is generally initiated 4–6 weeks after surgery and spans 3 months. The benefit of adjuvant chemotherapy in node-negative early-stage NSCLC is less clear, with some suggestion that patients with large primary tumors (≥4 cm) may benefit. In patients found to have unexpected mediastinal lymph node involvement after surgery (“incidental N2 disease”), adjuvant chemotherapy as mentioned earlier is recommended.

Postoperative thoracic irradiation has not been found to be beneficial in patients with stage I or stage II NSCLC and may be detrimental. However, irradiation is indicated for positive margins on pathologic review (given over 6–7 weeks). This is generally administered before adjuvant chemotherapy. The role of mediastinal irradiation in patients with incidental N2 disease at surgery is less clear; however, a subset analysis from one of the recent positive adjuvant chemotherapy trials and a Surveillance Epidemiology and End Results (SEER) database review suggest benefit. If given, consolidative mediastinal irradiation (over 5–6 weeks) is generally administered after completion of adjuvant chemotherapy.

**TABLE 49-1**

<table>
<thead>
<tr>
<th>Local Disease</th>
<th>Distant Disease</th>
<th>Select Paraneoplastic Phenomena</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Bone metastases</td>
<td>- Hypercalcinemia (bone metastases)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>- Extremity/back pain</td>
<td>- Hematologic manifestations: anemia/euocytosis/thrombocytosis/thrombosis</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>- Fracture</td>
<td>- Hypertrophic osteoarthropathy—digital clubbing and symmetrical painful arthropathy (primarily NSCLC)</td>
</tr>
<tr>
<td>Chest pain (if chest wall involved)</td>
<td>- Brain metastases</td>
<td>- Hypercalcemia with PTH-related protein secretion (squamous NSCLC)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>- Headache</td>
<td>- SIAH (SCLC)</td>
</tr>
<tr>
<td>Superior vena cava syndrome (head fullness and dyspnea)</td>
<td>- Nausea</td>
<td>- Neurologic syndromes including Lambert-Eaton myasthenic syndrome (SCLC)</td>
</tr>
<tr>
<td>Pancoast syndrome (pain in shoulder, Horner syndrome)</td>
<td>- Neurologic compromise</td>
<td>- Cushing syndrome (SCLC)</td>
</tr>
<tr>
<td></td>
<td>Liver metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Abdominal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Weight loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Anorexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Fatigue</td>
<td></td>
</tr>
</tbody>
</table>

CNS, central nervous system; NSCLC, non–small cell lung cancer; PTH, parathyroid; SIAH, syndrome of inappropriate secretion of antidiuretic hormone; SCLC, small cell lung cancer.
### TABLE 49-2: American Joint Committee on Cancer, Seventh Edition, TNM Lung Cancer Staging/Prognosis

#### T (Primary Tumor)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Clinical Stage</th>
<th>Pathologic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor (\leq 3) cm (in greatest dimension), surrounded by lung or visceral pleura, not proximal than the lobar bronchus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>- Tumor (\leq 2) cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>- Tumor &gt;2 but (\leq 3) cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor (&gt;3) but (\leq 7) cm or tumor with any of the following: invades visceral pleura, involves main bronchus (\geq 2) cm distal to the carina, atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung (T2 tumors with these features are classified as T2a if (\leq 5) cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>- Tumor (&gt;3) but (\leq 5) cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>- Tumor &gt;5 but (\leq 7) cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;7 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- or tumor in the main bronchus (&lt;2) cm distal to the carina</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- or atelectasis/obstructive pneumonitis of entire lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- or separate tumor nodule(s) in the same lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor nodule(s) in a different ipsilateral lobe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### N (Regional Lymph Nodes)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Clinical Stage</th>
<th>Pathologic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ipsilateral peribronchial and/or hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### M (Distant Metastasis)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Clinical Stage</th>
<th>Pathologic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodule(s) in a contralateral lobe; or tumor with pleural nodules or malignant pleural dissemination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Clinical Stage</th>
<th>Pathologic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>T1a,b</td>
<td>N0 M0</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>T2a</td>
<td>N0 M0</td>
<td></td>
</tr>
<tr>
<td>Ila</td>
<td>T1a,b</td>
<td>N1 M0</td>
<td></td>
</tr>
<tr>
<td>Iib</td>
<td>T2a</td>
<td>N1 M0</td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>T2a</td>
<td>N0 M0</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>T2b</td>
<td>N1 M0</td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>T3</td>
<td>N0 M0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>T1–3</td>
<td>N2 M0</td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>T3</td>
<td>N1 M0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>N0,1 M0</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N2 M0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>T any</td>
<td>N any M1a,b</td>
<td></td>
</tr>
</tbody>
</table>

#### 5-Year Survival Rate (%)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Clinical Stage</th>
<th>Pathologic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>T1a,b</td>
<td>N0 M0</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>T2a</td>
<td>N0 M0</td>
<td></td>
</tr>
<tr>
<td>Ila</td>
<td>T1a,b</td>
<td>N1 M0</td>
<td></td>
</tr>
<tr>
<td>Iib</td>
<td>T2a</td>
<td>N1 M0</td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>T2a</td>
<td>N0 M0</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>T2b</td>
<td>N1 M0</td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>T3</td>
<td>N0 M0</td>
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<tr>
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<td>T3</td>
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<tr>
<td>III</td>
<td>T4</td>
<td>N0,1 M0</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N2 M0</td>
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</tr>
<tr>
<td>IV</td>
<td>T any</td>
<td>N any M1a,b</td>
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</tbody>
</table>

*MS, median survival.*


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TABLE 49-3  Simplified Lung Cancer Staging/Prognosis with Aggressive Treatment

<table>
<thead>
<tr>
<th>NSCLC</th>
<th>SCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stage: disease limited to resectable lung lesion with no involved lymph nodes (LN) outside the lung/hilum (size of tumor and LN status are prognostic)</td>
<td>Limited stage: disease confined to a tolerable definitive radiation port</td>
</tr>
<tr>
<td>AJCC Seventh Edition: T1–3, N0/1, M0; Stage I–IIIA</td>
<td>Extensive stage: not meeting criteria for limited stage disease</td>
</tr>
<tr>
<td>5-y survival rate:</td>
<td>Median survival: 8–12 mo</td>
</tr>
<tr>
<td>- No LN involvement: 60%–80%</td>
<td>1-y survival rate: 35%–50%</td>
</tr>
<tr>
<td>- LN involvement: 35%–45%</td>
<td>2-y survival rate: 10%–20%</td>
</tr>
<tr>
<td>(with chemotherapy: 45%–55%)</td>
<td>(untreated median survival: 4–6 mo)</td>
</tr>
<tr>
<td>Locally advanced: involvement of locoregional lymph nodes outside the lung/hilum and/or invasion of lung lesion into unresectable tissue</td>
<td></td>
</tr>
<tr>
<td>AJCC Seventh Edition: T1/2/3/4, N2/3, M0; Stage IIIA/B</td>
<td></td>
</tr>
<tr>
<td>5-y survival rate: 15%–25%</td>
<td></td>
</tr>
<tr>
<td>Metastatic disease</td>
<td></td>
</tr>
<tr>
<td>AJCC Seventh Edition: Tany, Nany, M1; Stage IV</td>
<td></td>
</tr>
<tr>
<td>Median survival: 8–12 mo</td>
<td>1-y survival rate: 35%–50%</td>
</tr>
<tr>
<td>1-y survival rate: 35%–50%</td>
<td>2-y survival rate: 10%–20%</td>
</tr>
<tr>
<td>(untreated median survival: 4–6 mo)</td>
<td>(untreated median survival: 2–4 mo)</td>
</tr>
</tbody>
</table>

Rough estimates of prognosis for simplified lung cancer staging.5–13

NSCLC, non–small cell lung cancer; AJCC, American Joint Committee on Cancer; SCLC, small cell lung cancer.

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**FIGURE 49-1.** Staging workup algorithm for lung cancer. **a**Solitary site of possible metastasis should be biopsied to confirm stage IV disease. If oligometastatic disease is appreciated, work up should include positron emission tomography (PET)/magnetic resonance imaging (MRI) of the brain and mediastinal sampling (if no other sites of distant disease are identified on imaging) because definitive management can be considered for oligometastatic disease with an uninvolved mediastinum. **b**Peripheral lesion—within outer third of lung (vs. central lesion). CBC, complete blood count; CT, computed tomography; FDG, fluorine 18-fluorodeoxyglucose; PFTs, pulmonary function tests.
Locally Advanced Non–Small Cell Lung Cancer: American Joint Committee on Cancer Seventh Edition: T1/2/3/4, N2/3, M0; Stage IIIA/B

Locally advanced NSCLC is often divided into potentially resectable and unresectable disease; however, randomized clinical trial data do not clearly support a role for surgery to date. Despite this, it is not unusual for a patient with low-bulk N2 disease to receive chemoradiation or chemotherapy followed by surgery. Currently, concurrent chemoradiation remains the standard of care for patients with locally advanced NSCLC.

Curative intent concurrent chemoradiation for locally advanced NSCLC is administered over 6 to 7 weeks with daily irradiation (except on the weekends). Interruptions in radiation dosing are avoided as much as possible because delays between dosing can compromise effectiveness of radiation. The role of consolidation chemotherapy after curative intent chemoradiation is unclear, with one randomized trial finding no benefit with monotherapy.11 Despite this, two additional 3-week cycles of platinum-based doublet therapy are recommended in some cases where patients have tolerated concurrent therapy well. Five-year survival rates in patients with locally advanced NSCLC treated with definitive concurrent chemoradiation are on the order of 15% to 20%.

The primary acute toxicities from concurrent chemoradiation are fatigue and esophagitis with odynophagia and dysphagia. Although a gastrostomy tube is rarely needed, many patients have difficulty tolerating solids by the end of radiation. This generally resolves within a few weeks of completing radiation. Potential late toxicities include radiation pneumonitis (developing up to 3 months after radiation), esophageal stricture, and rarely, tracheoesophageal fistula. Early identification of radiation pneumonitis is of particular importance because initiation of steroids may limit the amount of subsequent pulmonary fibrosis. Development of dry cough and/or new dyspnea in the 3 months following completion of irradiation should be evaluated with CT chest imaging, and if suggestive of radiation pneumonitis, high-dose steroids should be initiated (e.g., prednisone 60 mg daily) with long taper. Serial pulmonary function tests with diffusing capacity of the lung for carbon monoxide (DLCO) may be helpful in monitoring pneumonitis/fibrosis. In patients with persistent dysphagia, esophagram, and esophagogastroduodenoscopy should be considered to evaluate possibility of stricture. This is often effectively managed with esophageal dilation, which may need to be repeated several times, with occasional need for esophageal stent placement.

Metastatic Non–Small Cell Lung Cancer (American Joint Committee on Cancers Seventh Edition: T any, M any, M1; Stage IV)

The last decade has seen significant advances in the treatment of metastatic NSCLC. With the addition of bevacizumab (Avastin) to standard first-line platinum-based doublet chemotherapy, median survival has surpassed the 1-year mark (12.6 months), with 1- and 2-year survival rates of 51% and 23%, respectively.12 Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF), an important mediator of angiogenesis required for tumor growth. For second- or third-line therapy, use of oral daily erlotinib (Tarceva), a small molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), resulted in improved survival compared to placebo and is U.S. Food and Drug Administration (FDA) approved in this setting. Pemetrexed (Alimta) is a newer antifolate chemotherapy that is currently approved in the first line, second line, and as maintenance therapy for patients with metastatic NSCLC. Pemetrexed is tolerated well and, unlike other approved chemotherapies for lung cancer, it can be given for prolonged periods with minimal toxicity.

There has clearly been a paradigm shift in the way we approach patients with metastatic NSCLC. Such patients are no longer considered as part of a homogenous population treated in the same way. Rather, NSCLC histology, clinical characteristics, and an expanding array of molecular markers are increasingly being used to individualize therapy. Currently, histology and two molecular markers, anaplastic lymphoma kinase (ALK) and EGFR, have established roles in directing therapy in the clinic as reflected in FDA indications and national guidelines. Histology is used to select therapy based on both efficacy and toxicity. Pemetrexed and bevacizumab are FDA approved only for treatment in patients with non–squamous NSCLC because pemetrexed does not appear to be effective against squamous NSCLC and bevacizumab is associated with higher risk of fatal hemoptysis in such patients. Activating EGFR mutations and ALK rearrangements, which are generally mutually exclusive, are more potent biomarkers predicting high response rates to erlotinib and crizotinib, a small molecule ALK TKI, respectively, in tumors that harbor these events. EGFR mutations can be identified in approximately 10% to 15% of patients with adenocarcinoma of the lung and 50% of patients with no smoking history (accounting for approximately 20,000 patients annually in the United States). ALK rearrangements are found in approximately 5% of adenocarcinomas of the lung and are also more common in never smokers. Additional driver mutations have been identified, including KRAS, BRAF, HER2, PI3K, ROS, and RET, and clinical trials are currently evaluating agents targeting these events. It is estimated that approximately 40% to 50% of adenocarcinomas of the lung will be driven by such mutations. Other molecular markers are additionally being evaluated in hopes of predicting benefit from established chemotherapy and targeted therapies.

In addition to specific anticancer therapy, vigilant supportive care is paramount to the treatment of patients with cancer. One key NSCLC study presented in 2010 demonstrated the importance of early initiation of such palliative care.23 One hundred fifty-one patients with newly diagnosed metastatic NSCLC were randomized to standard oncologic care versus the same with additional management by a palliative care team who evaluated the patient at least monthly until death. Based on serial well-established questionnaires assessing quality of life, specific lung cancer symptoms, and mood, patients receiving additional care by a palliative care team had consistently improved quality of life and less depressive symptoms. Furthermore, despite less aggressive anticancer therapy at the end of life in patients randomized to the early palliative care arm, median survival in such patients was longer (11.6 months vs. 8.9 months, p = .02).

Oligometastatic Disease

Rarely, patients with NSCLC can present with a solitary site of metastasis, most commonly in the brain or adrenal. Aggressive management of both sites is often considered if there is no mediastinal involvement, with long-term survival in 10% to 25% of patients.24–26 There is some literature suggesting better prognosis with metachronous presentation compared to identification of oligometastatic disease at presentation. All such patients should have PET imaging and a mediastinoscopy before proceeding. Both brain and adrenal lesions can be...
Small Cell Lung Cancer

SCLC is characterized by rapid growth, early dissemination, and high response rates to chemotherapy and radiation. Unfortunately, responses to chemotherapy are generally short lived, with subsequent relative resistance to further systemic therapy. Incidence has decreased over the last decade, with SCLC cancer currently accounting for approximately 14% of the lung cancer cases in the United States. This is likely related to changes in smoking patterns because SCLC occurs almost exclusively in those with a significant smoking history.

Most medical oncologists continue to stage SCLC with the Veterans Administration (VA) staging system; however, the same TNM staging used for NSCLC is gaining favor and is more informative. The VA staging system divides patients with SCLC into those with limited-stage disease, defined by disease encompassable within a tolerable curative intent radiation field and extensive stage disease, which includes all patients not making criteria for limited-stage disease. Staging workup includes PET/CT and MRI of the brain. Unlike NSCLC, mediastinoscopy is generally not done to evaluate the mediastinum, with treatment choices directed by PET/CT findings. However, in the rare situation when PET/CT does not suggest involvement in the mediastinum or at distant sites, and the patient has potentially resectable disease, mediastinoscopy is recommended.

Limited-Stage Small Cell Lung Cancer

Limited-stage SCLC often presents with a small primary lung mass and bulky hilar/mediastinal adenopathy. Symptoms can include cough, dyspnea, and hoarseness from recurrent laryngeal nerve compromise. Treatment is curative and consists of concurrent chemoradiation with etoposide and cisplatin or carboplatin chemotherapy. On conclusion of such therapy, prophylactic cranial irradiation (PCI) is recommended because this has been found to not only decrease the risk of developing brain metastases but also improve survival without clear detrimental effect on neurocognitive functioning. With aggressive therapy for limited-stage SCLC, 5-year survival rates are on the order of 15% to 25%.

Extensive Stage Small Cell Lung Cancer

Patients with metastatic SCLC can present with symptoms seen in limited-stage disease but are likely to have constitutional symptoms as well, including weight loss, anorexia, and fatigue. Paraneoplastic syndromes are more commonly seen in SCLC than NSCLC (see Table 49-1), particularly the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). There has been little change in the management of extensive stage SCLC over the last decade, with first-line therapy continuing to consist of etoposide combined with a platinum agent. Median survival with such therapy is between 8 and 13 months. Oral topotecan was approved as second-line therapy in 2007 based on a statistically significant improvement in median survival compared to best supportive care alone (25.9 weeks vs. 13.9 weeks, \( p = .01 \)).

The most significant development in the treatment of extensive stage SCLC in the last decade has been the routine recommendation of PCI in all responders to chemotherapy. This is based on the results of a phase III European trial randomizing 286 patients with response to 4 to 6 cycles of chemotherapy to PCI or observation. Not only did PCI decrease the risk of developing brain metastases but it also led to improvement in survival (median survival 6.7 months vs. 5.4 months from time of randomization, \( p = .003 \), with 1-year survival rate of 27% vs. 13%).

Surveillance

Surveillance strategies after curative-intent treatment of NSCLC and SCLC include routine interview and physical exam, CT imaging, and chest X-ray. There is no clear consensus among medical oncologists, surgeons, and pulmonologists concerning particular imaging study and frequency; however, there are a handful of established guidelines. Most medical oncologists follow the guideline provided by the National Comprehensive Cancer Network (NCCN), which is accepted by most health insurers. This recommends history and physical exam and CT chest with or without contrast every 6 to 12 months for 2 years after definitive treatment for NSCLC followed by history and physical exam and noncontrast CT chest annually. Recommendations for SCLC include follow-up visits every 3 to 4 months for 2 years, every 6 months for the following 3 years, then annually thereafter. At each follow-up visit, chest imaging is recommended but not clearly defined (e.g., chest X-ray vs. CT). Most oncologists choose to follow with CT imaging.

MESOTHELIOMA

Mesothelioma is a rare neoplasm that typically arises from the mesothelial surfaces of the pleural cavity; however, it can originate from the peritoneal surface and rarely from the pericardium or tunica vaginalis. Inhalation exposure to asbestos is the predominant cause of mesothelioma, with a latent period of 30 to 40 years between exposure and development of mesothelioma. Approximately 3,300 cases are diagnosed yearly in the United States, with expected continued decline secondary to more stringent national and local control of exposure to asbestos.

Pleural mesothelioma typically presents in the fifth to seventh decade of life, although it is occasionally seen at younger ages in patients exposed to asbestos as children. Common symptoms include dyspnea and chest pain. Imaging generally shows pleural thickening, often with effusion. Metastatic disease is uncommon at presentation, with disease generally progressing locally with increasing pleural involvement leading to a thick rind of tumor; invasion of the chest wall/pericardium, and diaphragm; and spread to hilar and mediastinal lymph nodes. Pathologic diagnosis can be difficult to render from cytology, and video-assisted thoracoscopic sampling is often required. There are three major histologic subtypes of mesothelioma: epithelioid, accounting for approximately 60% of cases; sarcomatoid; and biphasic with mixed epithelioid/sarcomatoid features. The latter two are associated with worse prognosis. Overall, median survival is on the order of 6 to 18 months.

Treatment of localized mesothelioma is controversial, with an unclear role of surgery and radiation. Some centers advocate extrapleural pneumonectomy (removal of ipsilateral lung, parietal pleura, pericardium, and most of the hemidiaphragm), which is associated with significant morbidity; however, there has been a recent trend toward radical pleurectomy and decortication. In either case, chemotherapy (either before or after surgery) is generally recommended, with
consideration of consolidation radiation after surgery. Such an aggressive approach should be reserved for only the most fit patients with limited disease and epithelioid histology. Before proceeding, patients need to be made aware of the risk of significant morbidity and mortality, without a clear survival benefit demonstrated to date with surgery with or without thoracic irradiation in randomized trials.

Most patients who present with mesothelioma are approached palliatively. Recurrent pleural effusions are often controlled with pleurodesis, which can be achieved through a chest tube or video thoracoscopy. Chemotherapy has a clear role in both amelioration/delay of symptoms and prolongation of survival. This was demonstrated in the landmark EMPHASIS trial, which randomized 456 patients to cisplatin chemotherapy combined with either placebo or pemetrexed.32 With the addition of pemetrexed, median survival was prolonged by approximately 3 months (9.3 to 12.1 months), with improvement in symptoms and quality of life. Radiation is also occasionally used to palliate pain from chest wall involvement with mesothelioma.

## THYMOMA AND THYMIC CARCINOMA

Thymoma and thymic carcinoma are rare neoplasms arising from the thymus that generally present in the fifth to sixth decade of life. Estimated incidence of thymoma in the United States is only 0.13 per 100,000 person-years.3 Thymic carcinomas are exceedingly rare, accounting for less than 10% of thymic malignancies and are associated with more aggressive behavior and worse prognosis. Thymomas tend to grow locally over years and are often found incidentally on chest X-ray or CT imaging obtained for unrelated processes. MRI may help differentiate a thymoma from a benign lesion. Potential signs and symptoms include those from local disease (e.g., chest pain, dyspnea, cough, phrenic nerve palsy, superior vena cava syndrome) or from paraneoplastic syndromes such as myasthenia gravis (diplopia, ptosis, dysphagia, facial/neck/limb weakness), which is found in up to 50% of thymoma but is rare in thymic carcinomas. Symptoms of myasthenia gravis may improve with thymectomy; however, some symptoms can persist indefinitely. Distant metastases are rare in patients with thymoma; however, these are not infrequent in those with thymic carcinomas. There are no known risk factors for thymic malignancies.

There are different staging systems for thymic malignancies, but most thoracic oncology specialists use the Masaoka system, which incorporates both the presence of invasion and anatomic extent of disease (Table 49-4).33 Extent of invasion is the primary determinant of prognosis, with resected noninvasive (stage I) tumors recurring in less than 5% of cases.34 Histologic diagnosis of thymoma can be difficult, with heterogeneity within tumors confounded by small biopsy specimens, which limit classification and determination of degree of invasion. If there is a high suspicion of stage I or stage II thymoma on imaging, biopsies are often not pursued, with diagnosis reached after surgery.

Early stage and locally advanced thymoma and thymic carcinoma are generally approached surgically. The extent of surgery resection is crucial in determining prognosis, as reflected in another commonly used staging system (Gruppe d’Etude des Tumeurs Thymiques system [GETT]).35 For completely resected Masaoka stage I and stage II disease, no further treatment is indicated. Radiation is recommended for incompletely resected stage I–III stage IVB disease or in cases of microscopically positive surgical margins. Chemotherapy is often offered to such patients as well. The role of consolidation irradiation is unclear in completely resected stage III/IVA thymoma; however, it is generally considered if the surgeon feels that margins were close (despite report of pathologically negative margins, which does not always reflect events during surgery). For patients with locally advanced disease or bulky tumors on imaging, preoperative chemotherapy has been increasingly prescribed. Thymic malignancies are chemotherapy-sensitive tumors and use of chemotherapy upfront may increase chance of complete resection. Radiation following surgery in such cases is often prescribed. For patients with locally advanced disease that is not resectable, or in those who do not want or can’t tolerate surgery, definitive sequential or concurrent chemoradiation can be considered. In patients with metastatic or incurable local disease, palliation can be achieved with chemotherapy or radiation.

There is no clear consensus on surveillance strategies for definitively managed thymic malignancies, but most thoracic oncology specialists follow patients with CT imaging, annually or more frequently, up to 10 years after surgery. If an isolated recurrence is identified, particularly a “drop” pleural metastasis, resection can result in prolonged survival.

### References


KEY POINTS

- Gastric ulcers should be monitored closely and re-biopsied as many are gastric cancer.
- Postgastrectomy diet is a high-protein, high-fat, low-carbohydrate, and low-fluid diet in smaller portions six times a day.
- Dumping syndrome occurs with rapid flow of carbohydrate food from gastric pouch into the jejunum.
- Esophageal high-grade dysplasia should be considered and treated as early esophageal cancer and referred for esophagectomy.

GASTRIC CANCER

Gastric Cancer Incidence and Mortality

The incidence of gastric cancer in the United States declined from the 1930s to the 1980s but has remained steady since. The American Cancer Society estimates 21,520 new cases of gastric cancer in the United States in 2011, with 61% of the cases in men and 39% in women. An estimated 10,340 Americans will die from gastric cancer in 2011, with 60% of the deaths in men and 40% in women. For all patients with gastric cancer, the 5-year relative survival rate is 26%; 63% for cancer localized to the stomach, 27% for those with regional disease, and 3% for patients with distant disease. This overall survival rate has significantly improved from 16% in the 1970s (Table 50-4).

Gastric Cancer Pathology

An increased risk for gastric cancer is associated with atrophic gastritis, pernicious anemia, familial adenomatous polyposis (FAP), hereditary nonpolyposis colon cancer (HNPPCC), familial gastric cancer, Li-Fraumeni syndrome, and type A blood. Smoking increases the relative risk (RR) for gastric cancer (RR = 1.2 to 1.6), which can decrease with cessation of smoking. More recently, gastric infection with Helicobacter pylori has been strongly associated with the initiation and promotion of midgastric and distal gastric cancer as well as gastric lymphoma. The introduction of antibiotics in the 1940s and the treatment of H. pylori may account for the dramatic reduction of gastric cancer incidence since the 1930s.

Most (90% to 95%) gastric cancer is adenocarcinoma. The remainder consists of carcinoid, gastrointestinal stromal tumors (GIST), and lymphoma. Since the 1970s, the incidence of distal gastric cancer has been decreasing. In contrast, there is a rise in proximal (cardia) and gastroesophageal junction cancer.

Gastric Cancer Presentation and Diagnosis

The median age at presentation for gastric cancer is 70 years; half of the patients are aged 65 to 75 years. Early gastric cancer is asymptomatic, and symptoms-associated gastric cancer does not appear until the disease is advanced. However, these symptoms are not specific to gastric cancer. Most patients complain of weight loss (62%) and abdominal pain (52%); less common symptoms include nausea (34%), anorexia (32%), dysphagia (26%), melena (20%), and early satiety (17%).

These symptoms are also more commonly observed with gastritis and peptic ulcer disease. Empiric treatment for presumed benign gastric disease can lead to a delay in the diagnosis of gastric cancer. Findings on physical exam are uncommon until late in the disease process and include a palpable epigastric mass, umbilical mass (Sister Mary Joseph’s “node”), supraclavicular adenopathy (Virchow’s node), anterior pelvic mass on rectal exam (Blumer’s shelf), and ovarian mass on pelvic exam (Krukenberg tumor) (Table 50-1).

The definitive diagnostic test for gastric cancer is upper endoscopy, which allows for both localization of the tumor and a biopsy for pathologic diagnosis of cancer. Note that up to 17% of patients with gastric cancer initially had a benign biopsy. All nonhealing gastric ulcers and continued symptoms of dyspepsia should be reevaluated with repeat biopsy. Other helpful diagnostic tests include gastric contrast studies and computed tomography (CT) of the abdomen and pelvis. CT scan is also useful to evaluate for metastasis but can both understage and overstage gastric cancer. Tumor markers have not been found to be helpful. Because the essential therapy for gastric cancer is surgery, additional diagnostic modalities
Gastric Cancer Treatment

Surgical resection remains the mainstay treatment for local and regional gastric cancer. The extent of resection (partial vs. total) as well as the extent of lymphadenectomy (nodes adjacent to the tumor [D1] vs. nodes nearby [D2]) does not appear to significantly impact survival if the cancer is completely removed. However, up to 80% of curative resections develop recurrence, leading to investigation of adjuvant and neoadjuvant therapy for gastric cancer. Two large randomized studies have evaluated the role of chemoradiation therapy: one for gastric cancer and one for cancer of the gastroesophageal junction. The South West Oncology Group (SWOG) 9008 Intergroup trial by Macdonald et al., which randomized 556 patients with gastric cancer to surgery alone or with adjuvant chemoradiation, demonstrated an advantage in median survival (36 vs. 27 months, \( p = 0.005 \)) and 3-year overall survival (50% vs. 41%, \( p = 0.005 \)) with the addition of chemoradiation. However, the quality of the gastrectomy in the study has been criticized because many specimens contained no nodes. In addition, the survival for patients with adjuvant chemotherapy was no better than other gastrectomy-only series. For resectable cancer of the gastroesophageal junction, the MRC-ST02 trial by Cunningham et al., which randomized 503 patients to perioperative chemotherapy or surgery alone, demonstrated a 5-year overall survival benefit (36% vs. 23%, \( p < 0.001 \)) for perioperative chemotherapy. The biology of cancer of gastroesophageal junction appears different from gastric cancer in the body or antrum.

The primary treatment of patients with metastatic gastric cancer is palliative. A meta-analysis by Casaretto et al., of five randomized trials with 208 patients to palliative chemotherapy versus 182 to supportive care alone favored chemotherapy in 1-year survival (20% vs. 8%, \( p = 0.05 \)) and 6 month symptom-free survival (30% vs. 12%, \( p < 0.01 \)). Symptoms associated with the gastric mass including pain, obstruction, and bleeding may also be palliated with either partial gastrectomy or gastrointestinal bypass.

Postgastrectomy Care

Most patients who have undergone gastrectomy for gastric cancer will lose weight in the first 3 months following surgery. This weight loss is more substantial and prolonged with total gastrectomy than partial gastrectomy. Construction of a replacement “gastric” pouch may mitigate the malnutrition from total gastrectomy. Some patients develop delayed gastric emptying (<10%), which may be improved with promotility agents. More commonly, patients develop dumping symptoms (25% to 50%). Early dumping occurs 10 to 30 minutes after eating with symptoms of pain, bloating, nausea, vomiting, diarrhea, headache, flushing, fatigue, and hypotension and is attributed to rapid transit of ingested and hyperosmolar food from the stomach remnant into the jejunum. Late dumping syndrome occurs 1 to 3 hours after eating with symptoms of perspiration, weakness, confusion, shakiness, and hunger. Late dumping is believed to be caused by delayed insulin response and resultant hypoglycemia. For both dumping syndromes, the recommended treatment includes smaller, more frequent and well-chewed meals of high-protein, high-fat, high-fiber, low-carbohydrate foods. Limited intake of liquids during the meal is also recommended. Because of malabsorption, and frequently malnutrition, postgastrectomy patients are also at risk for anemia from vitamin B12 and/or iron deficiencies and may require nonoral replacement. Vitamin B12 deficiency may not appear for 3 to 4 years because most patients’ liver stores are adequate.

Patients who have undergone gastrectomy for cancer (with or without adjuvant chemoradiation therapy) are at high risk for recurrent cancer. Unfortunately, most recurrent gastric cancers are incurable; thus, routine surveillance regimen will not change the patient’s outcome and is not recommended. Symptomatic recurrence should be addressed with palliative therapy (Table 50-2).

TABLE 50-1 Symptoms and Signs

<table>
<thead>
<tr>
<th>Gastric Cancer Symptoms</th>
<th>Esophageal Cancer Symptoms</th>
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</thead>
<tbody>
<tr>
<td>• Weight loss</td>
<td>• Weight loss</td>
</tr>
<tr>
<td>• Enlarged liver</td>
<td>• Enlarged liver</td>
</tr>
<tr>
<td>• Discomfort or pain in the stomach area</td>
<td>• Difficulty swallowing and regurgitation</td>
</tr>
<tr>
<td>• Difficulty swallowing</td>
<td>• Pain when swallowing</td>
</tr>
<tr>
<td>• Feeling full or bloated after a small meal</td>
<td>• Pain in the chest or back</td>
</tr>
<tr>
<td>• Nausea and vomiting</td>
<td>• Heartburn</td>
</tr>
<tr>
<td>• Vomiting blood</td>
<td>• A hoarse voice or cough that doesn’t go away within 2 wk</td>
</tr>
<tr>
<td>• Blood in the stool</td>
<td>• Supraclavicular adenopathy (Virchow’s node)</td>
</tr>
<tr>
<td>• Palpable epigastric mass</td>
<td></td>
</tr>
<tr>
<td>• Umbilical mass (Sister Mary Joseph’s “node”)</td>
<td></td>
</tr>
<tr>
<td>• Supraclavicular adenopathy (Virchow’s node)</td>
<td></td>
</tr>
<tr>
<td>• Anterior pelvic mass on rectal exam (Blumer’s shelf)</td>
<td></td>
</tr>
<tr>
<td>• Ovarian mass on pelvic exam (Krukenberg tumor)</td>
<td></td>
</tr>
<tr>
<td>• Ascites</td>
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</table>

are usually unnecessary and may lead to delay in operation. Despite the common delay in the diagnosis of gastric cancer, screening programs in areas with a high incidence of gastric cancer (Asia) have not demonstrated a survival benefit.

ESOPHAGEAL CANCER

Esophageal Cancer Incidence and Mortality

The overall incidence of esophageal cancer in the United States has increased slightly for the past three decades. For 2011, the American Cancer Society estimates 16,980 new cases of esophageal cancer in the United States, with 79% of the cases in men and 21% of the cases in women. An estimated 14,710 Americans will die from esophageal cancer in this period, with 81% of the deaths in men and 19% in women. The 5-year relative survival rate of esophageal cancer is 17%: 37% for cancer localized to the esophagus, 19% for those with regional disease, and 3% for patients with distant...
A biopsy with severe or high-grade dysplasia is equivalent to carcinoma in situ, and the patient should be treated as having esophageal cancer. A chest, abdomen, and pelvic CT scan can help evaluate for metastasis and the tumor’s proximity to the membranous portion of the trachea for middle esophageal cancer. Suspected metastasis should be further characterized with positron emission tomography (PET) scan. Contrast esophagram can complement EGD and CT scans. Endoscopic ultrasonography (EUS) to assess the tumor depth of invasion (T stage) and detect local lymphadenopathy (N staging) has become standard for preoperative staging. EUS-directed fine needle aspiration of enlarged lymph nodes may provide histologic confirmation of nodal metastasis. Tumor markers are not helpful (Table 50-3).

### Esophageal Cancer Treatment

Patients with resectable esophageal cancer should undergo esophagectomy. The 5-year survival for localized cancer is 80% to 94% but only 10% to 14% for locally advanced esophageal cancer (see Table 50-4).\(^6\) Despite arguments for en bloc or extended resection, the approach for resection—whether transhiatal with cervical anastomosis, transabdominal, and transthoracic with intrathoracic anastomosis or transabdominal, transthoracic, and transcervical with a cervical anastomosis—does not appear to differ in overall disease-free or quality-adjusted survival.\(^6\) The pharyngeal gastric gap is usually reconstructed with direct gastric pull through. Alternatives include colon and even small bowel interposition. Regardless of the conduit chosen for reconstruction, there is a high rate of anastomotic leak. Thus, there has been much discussion and debate regarding where (neck or chest) the anastomotic leak would be less morbid. Current consensus favors a cervical instead of an intrathoracic anastomosis.

For patients with locally advanced esophageal cancer, multimodality treatment with neoadjuvant chemoradiation has become standard of care. A meta-analysis of 11 randomized controlled trials of 1,308 patients and a recent Dutch study...

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**TABLE 50-2**

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding and Notes</th>
<th>Specificity and Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Anemia</td>
<td>LOW</td>
</tr>
<tr>
<td>LFT</td>
<td>Elevated alkaline phosphatase</td>
<td>LOW</td>
</tr>
<tr>
<td>Tumor marker</td>
<td>Not necessary</td>
<td>LOW</td>
</tr>
<tr>
<td>Upper endoscopy</td>
<td>Visualize size and location of mass and biopsy</td>
<td>High</td>
</tr>
<tr>
<td>Barium upper GI series</td>
<td>Visualize mass and extent of initis platica</td>
<td>Intermediate</td>
</tr>
<tr>
<td>CT scan, with IV and GI contrast</td>
<td>Overestimates tumor depth; underestimates nodal spread; useful for evaluating metastasis</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Surveillance</td>
<td>Not indicated</td>
<td>LOW</td>
</tr>
</tbody>
</table>

CBC, complete blood count; LFT, liver function test; GI, gastrointestinal; CT, computed tomography.

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**TABLE 50-3**

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding and Notes</th>
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</tr>
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<tbody>
<tr>
<td>LFT</td>
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<td>Tumor marker</td>
<td>Not necessary</td>
<td>Low</td>
</tr>
<tr>
<td>Barium esophagogram upper GI series</td>
<td>Visualize mass and extent of proximal disease</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Upper endoscopy</td>
<td>Visualize location and size of mass and biopsy</td>
<td>High</td>
</tr>
<tr>
<td>Endoscopic ultrasound</td>
<td>Good estimates of tumor depth</td>
<td>High</td>
</tr>
<tr>
<td>CT scan, with IV and GI contrast</td>
<td>Overestimates tumor depth; underestimates nodal spread; useful for evaluating metastasis</td>
<td>Intermediate</td>
</tr>
<tr>
<td>PET scan</td>
<td>Useful for identifying metastasis</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Surveillance</td>
<td>Not indicated</td>
<td>Low</td>
</tr>
</tbody>
</table>

LFT, liver function testing; GI, gastrointestinal; CT, computed tomography; PET, positron emission tomography.
which can be given as a bolus, jejunostomy tube feeding is best with a continuous rate. To provide for patient mobility and independence, tube feeding can be cycled: on at night and off during the day. Tube feeding is usually gradually weaned by decreasing the rate as oral intake improves. The postesophagectomy diet requires small, frequent, well chewed meals. Dietary content should consist of high-protein, low-carbohydrate, high-fat foods with minimal fluid intake to minimize dumping syndrome. Patients with esophageal cancer are at high risk for recurrence. Recurrent esophageal cancer is usually incurable. Consideration should be given to surveillance for dysphagia secondary to locally recurrent cancer, which can be palliated with endoscopic stents.

ACKNOWLEDGMENT

Special thanks to Jenni Brumelle PhD for her review of this manuscript.

showed a survival advantage for neoadjuvant chemoradiotherapy before esophagectomy. In squamous cell carcinomas, the prospective RTOG-8501 study showed that chemoradiotherapy alone could provide up to 27% 5-year survival. Patients who are symptomatic from unresectable or locally recurrent cancer can be palliated with endoscopic intraluminal esophageal covered stents. A common complication of distally placed stents is symptomatic acid reflux. Unfortunately, stents designed to minimize reflux do not appear superior to standard covered stents. Covered stents are also useful as a treatment for malignant esophageal fistula to the trachea or the pleura.

### Postesophagectomy Care

Similar to the postgastrectomy state, most patients will lose weight after esophagectomy. To minimize the malnutrition risk, most patients with esophagectomy will also undergo concomitant tube jejunostomy for enteric feeding access in the postoperative period. Unlike gastrostomy tube feeding, which can be given as a bolus, jejunostomy tube feeding is best with a continuous rate. To provide for patient mobility and independence, tube feeding can be cycled: on at night and off during the day. Tube feeding is usually gradually weaned by decreasing the rate as oral intake improves. The postesophagectomy diet requires small, frequent, well chewed meals. Dietary content should consist of high-protein, low-carbohydrate, high-fat foods with minimal fluid intake to minimize dumping syndrome. Patients with esophageal cancer are at high risk for recurrence. Recurrent esophageal cancer is usually incurable. Consideration should be given to surveillance for dysphagia secondary to locally recurrent cancer, which can be palliated with endoscopic stents.

### ACKNOWLEDGMENT

Special thanks to Jenni Brumelle PhD for her review of this manuscript.

### References

KEY POINTS
- Symptoms including pain, nausea, and obstruction often accompany pancreatic and bile duct tumors.
- Resection is underused for patients with localized pancreatic cancer.
- Gemcitabine-based regimens or the combination therapy FOLFIRINOX are the preferred chemotherapy for the treatment of pancreatic cancer in advanced stages.
- Treatment of local cholangiocarcinoma depends on its location along the bile duct system.
- Temporary common bile duct stents for localized pancreatic cancer and cholangiocarcinoma can relieve biliary obstruction and gain time for referral to suitable center for resection.

INTRODUCTION
Adenocarcinomas that arise in organs derived from the embryonic foregut are difficult to manage. They are diagnosed late in their clinical course, are poorly responsive to systemic therapy, and lead to a relatively short survival time. Pancreatic cancer, cholangiocarcinomas, and gall bladder cancer are part of this group of diseases.

PANCREATIC CANCER
Etiology
Pancreatic adenocarcinoma arises from the cells of the exocrine portion of the pancreas. Like other cancers arising in ductal structures, a noninvasive precursor lesion characteristically precedes the cancer. For pancreatic cancer, this is called a pancreatic intraepithelial neoplasm (PANIN) and these progress through three stages of severity, each with progressive genetic mutation, prior to transforming into an invasive cancer. Several risk factors have been identified including tobacco use and obesity. Cigarettes contribute to the development of 20% to 30% of pancreatic cancers. Smoking cessation reduces this risk in one study approaching that of a never smoker after 5 years of cessation. Obesity and a low level of physical activity each increase the risk of pancreatic cancer. In a cohort study of 160,000 subjects, moderate activity resulted in decreased pancreatic cancer rates, and walking 1.5 hours or more per week was associated with a 50% reduction in pancreatic cancer.

An estimated 10% to 20% of pancreatic cancers are hereditary or have a familial link. Inherited mutations mediate increased risk of pancreatic cancer in patients with Peutz-Jeghers syndrome, familial atypical multiple mole melanoma syndrome, hereditary nonpolyposis colorectal cancer syndrome, hereditary pancreatitis, and BRCA2 mutations. But most familial aggregation of pancreatic cancers arise from no known genetic syndromes.

Clinical Course
Symptoms are initially nonspecific and dependent on the location of the tumor within the gland. Tumors near the bile duct often cause biliary obstruction, leading to episodes of biliary colic, anorexia, and ultimately jaundice. Tumors in other locations can present with anorexia, weight loss, pancreatitis, new-onset diabetes, or venous thrombosis. Pain, gastric outlet obstruction, ascites, and skin manifestations are signs of advanced disease.

Evaluation
Initial assessment should confirm the diagnosis of a pancreatic mass, relieve biliary obstruction, establish the extent of disease, and possibly obtain a histologic diagnosis (Table 51-1). A multiphase computed tomography (CT) scan is a diagnostic necessity. This shows the location and extent of the primary tumor, evaluates hepatic/distant metastases, and establishes...
operability. But it exposes the patient to high levels of radiation and will likely be repeated at the institution where resection is evaluated. Standard CT scans will usually suffice as an initial examination if the patient is to be referred to another center for resection. Endoscopic placement of stents for biliary obstruction stabilizes a patient for orderly transfer to a pancreatic center. But the stents should be placed in a manner that they do not interfere with a subsequent operative resection. The risk of surgical wound infection increases when the bile duct is decompressed with a prosthetic stent prior to pancreatic resection.5

Treatment of Localized Pancreatic Cancer

Cancers still confined to the pancreas can be resectable, borderline resectable, or locally advanced. Resectable cancers should be removed whenever feasible using a Whipple procedure, distal resection, or other type of pancreatectomy. But feasibility depends on the anatomy of any invasion, the patient’s comorbidities, and available resources. The National Cancer Data Base identified 9,559 patients with stage I pancreatic cancer; and in these subjects, survival was longer for those undergoing resection than those treated without resection (5-year survival 24.6% vs. 2.9%). But many patients who could potentially undergo resection are not treated with an operation. Of the stage I patients from this same study, 6,380 were likely eligible for resection based on age, comorbidities, acceptance of surgery, etc. Of these candidates, 2,736 were actually treated with pancreatectomy. This suggests that an operation that may increase the length of survival is often not used for patients with early pancreatic cancers.6

Additionally, contemporary adjuvant chemotherapy may incrementally extend survival for early-stage disease. Prospective randomized trials of adjuvant therapy over the past two decades have not consistently shown a survival benefit.11–14 But a recent multiinstitutional randomized trial using single-agent gemcitabine as an adjuvant has shown to be more effective than gemcitabine (median survival 11.1 months vs. 6.8 months) but also more toxic.20 This regimen should be considered in appropriate patients.

Supportive Care

In all patients with pancreatic cancer, symptoms can be severe and debilitating. This includes patients with early or late tumors and patients who are treated or managed with a palliative approach. Control of symptoms such as pain and nausea is paramount in the management of these patients. Most symptoms can be managed pharmacologically, but more innovative measures should be sought when needed from specialists in pain management or palliative care.

Many symptoms from anatomic compression can be managed without major invasive approaches. Gastric outlet obstruction may be controlled endoscopically with dilation, stenting, or a percutaneous gastrostomy tube for decompression. Biliary obstruction can usually be controlled with endoluminal or percutaneous transhepatic bile duct stents. Expandable metal bile duct stents are permanent and not interchangeable. But silastic biliary catheters, whether endoluminal or percutaneous, tend to fail and require serial replacement, with the frequency dependent on the type of stent used.

CHOLANGIOCARCINOMA AND GALL BLADDER CANCER

Bile ducts anatomically exist in an intrahepatic, extrahepatic, and distal intrapancreatic position. Cholangiocarcinoma arises in any of these positions with implications for presentation and treatment. Because of these differences, cholangiocarcinomas are considered separately as intrahepatic, perihilar, or distal cancers (Table 51-2). The most common type is a perihilar tumor otherwise known as a Klatskin tumor, but the incidence of intrahepatic tumors is rising.21,22

Intrahepatic tumors often present as a hepatic mass in a noncirrhotic liver, whereas perihilar and distal tumors with biliary obstruction. Cholangiography, either using magnetic resonance imaging (MRI) or endoscopic retrograde cholangiopancreatography (ERCP) and cross-sectional imaging with computed tomography (CT) or MRI characterizes the tumors. Perihilar tumors are classified based on the degree of left, right, and common bile duct involvement according to the Bismuth-Corlette classification.

### Treatment of Metastatic Pancreatic Cancer

In patients with metastatic disease, gemcitabine administration results in an improvement in symptoms and a small prolongation of survival from a median of 4.4 to 5.6 months.19 In a recent randomized trial, combination chemotherapy using oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) has shown to be more effective than gemcitabine (median survival 11.1 months vs. 6.8 months) but also more toxic.20 This regimen should be considered in appropriate patients.

### TABLE 51-1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to the pancreas</td>
<td>12%–14%</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond the pancreas without arterial involvement; regional lymph nodes may be involved</td>
<td>5%–7%</td>
</tr>
<tr>
<td>III</td>
<td>Tumor involves the celiac axis or superior mesenteric artery</td>
<td>3%</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Decompression of the biliary system is necessary in many patients with perihilar and distal tumors. This can be accomplished using a retrograde stent placed during ERCP or percutaneous transhepatic catheters. There is no agreement regarding which method is preferred, although temporary stents should be used.

Resection is indicated when feasible based on the tumor’s anatomical distribution as well as the patient’s hepatic dysfunction and overall suitability for an extensive procedure. Perihilar tumors usually require resection of the involved bile ducts along with partial hepatectomy. Concomitant hepatic resection during bile duct resection accomplishes both higher rates of negative margins and prolonged survival.

Overall, 5-year survival from intrahepatic cholangiocarcinomas is 30%, perihilar 12%, and distal tumors 25%.23

Gall bladder cancers are often found incidentally during cholecystectomy. Cholecystectomy alone is an inadequate treatment for gall bladder cancer. Patients with early-stage tumors should have further resection that includes a resection of the gall bladder bed and lymphadenectomy. More advanced resections should be used on a selected basis.24

An adjuvant chemotherapy regimen has not been established for cholangiocarcinoma or gall bladder cancer. But the combination of gemcitabine and cisplatinum has activity against metastatic disease.25

The pattern of recurrence is generally different for bile duct cancers arising in the gall bladder or bile ducts. Gall bladder cancers tends to recur with distant metastasis (72%), whereas hilar cholangiocarcinoma tends to recur locoregionally (65%).26

### TABLE 51-2 Staging of Bile Duct Cancers

<table>
<thead>
<tr>
<th>Cholangiocarcinoma: Intrahepatic</th>
<th>Stage</th>
<th>Description</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>Solitary tumor without vascular invasion</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Solitary tumor with vascular invasion or multiple intrahepatic tumors</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Invasion into local extrahepatic structures or perforation through visceral peritoneum</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>Periductal invasion or regional nodal involvement</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>NB</td>
<td>Distant metastasis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cholangiocarcinoma: Perihilar</td>
<td>I</td>
<td>Tumor confined to the bile duct</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Invades through bile duct into adjacent adipose or hepatic tissue</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Invasion into unilateral branch of the portal vein or hepatic artery or regional nodal involvement</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Invasion into main portal vein or common hepatic artery, distant nodal metastasis, or distant metastasis</td>
<td>NA</td>
</tr>
<tr>
<td>Cholangiocarcinoma: Distal</td>
<td>I</td>
<td>Tumor confined to the bile duct or invades beyond bile duct wall</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Invasion into adjacent organs without involvement of celiac axis/superior mesenteric artery or regional nodal involvement without involvement of celiac axis/superior mesenteric artery</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Tumor involves celiac axis or superior mesenteric artery</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Distant metastasis</td>
<td>NA</td>
</tr>
<tr>
<td>Gall Bladder Cancer</td>
<td>I</td>
<td>Tumor confined to the lamina propria or muscular layer</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Invades through perimuscular connective tissue, not beyond serosa or into hepatic tissue</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Invasion into liver/perforation through visceral serosa, invasion into neighboring structure or regional nodal involvement</td>
<td>7%–8%</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Invasion into main portal vein or hepatic artery, invasion into two extrahepatic organs, distant nodal metastasis, or distant metastasis</td>
<td>2%–4%</td>
</tr>
</tbody>
</table>

NA, not available.


References


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KEY POINTS

- The incidence of and mortality from colorectal cancer have decreased 33% over the last 20 years.
- Colonoscopy every 10 years, annual fecal occult blood testing, and sigmoidoscopy every 5 years with fecal occult blood testing every 3 years are all recommended screening strategies.
- Randomized trials have shown that low-dose aspirin reduces the incidence of and mortality from colorectal cancer.
- Intensive follow-up of patients after initial treatment of colorectal cancer is associated with a survival benefit.

It is important for a primary care clinician to understand colorectal cancer (CRC) because it is a common problem, and primary care clinicians play important roles in prevention, early detection, and management. In 2012, it is estimated that 143,460 people will develop CRC in the United States, and 51,690 will die from CRC. It is the third most common cancer in males and females and third most common cause of cancer mortality. One out of every 20 Americans develops CRC.

Sobering as these statistics are, it is remarkable that both the incidence of CRC and CRC mortality have markedly declined in the last 20 years. The incidence of CRC in American men and women has decreased roughly 33% from 75 and 56 per 100,000 in 1985 to 50 and 37 per 100,000 in 2008. The death rate from CRC has similarly decreased from 33 men and 23 women per 100,000 in 1985 to 19 and 15 per 100,000 in 2008. Microsimulation modeling studies by the National Cancer Institute (NCI) and U.S. Centers for Disease Control and Prevention (CDC) have estimated that changes in risk factors, screening, and more effective treatment accounted for 35%, 53%, and 12% of the decline in mortality, respectively. These studies highlight the importance of the primary care clinician, who can potentially affect both risk factor modification and screening rates, in the eradication of CRC.

SCREENING RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) recommends CRC screening for patients between the ages of 50 and 75 years at average risk (no personal history of adenomas or CRC, negative family history, no inflammatory bowel disease) with one of the following three strategies. Strategy 1: annual screening with high-sensitivity fecal occult blood testing (FOBT). Strategy 2: sigmoidoscopy every 5 years, with high-sensitivity FOBT every 3 years. Strategy 3: screening colonoscopy every 10 years. Similar recommendations have been made by the National Comprehensive Cancer Network (NCCN). In 2008, the CDC reported that 64% of Americans underwent some form of CRC screening, up from 53% in 2002. A randomized controlled trial (RCT) from Italy demonstrated that primary care clinicians can play a crucial role in patient’s compliance with CRC screening. Currently, more than half of patients who have insurance and are screened undergo colonoscopy as the screening modality.

Fecal Occult Blood Testing

It is clear that testing stool samples for occult blood can reduce mortality from CRC. In 1993, the Minnesota Colon Cancer Study, a randomized prospective trial, demonstrated that annual FOBT resulted in a 33% decrease in CRC mortality. A recent meta-analysis of four RCTs of more than 320,000 patients showed that screening for fecal occult blood led to a 16% reduction in the relative risk of death from CRC (95% confidence interval [CI], 0.78 to 0.9). These studies relied on serial sampling of stools (two samples from a stool on each of 3 days) tested with guaiac impregnated filter paper slides, which detect the peroxidase activity of heme in human blood. Testing for occult blood in a single stool sample in the office at the time of digital rectal examination has extremely low sensitivity and is not recommended for effective screening. In a study of 2,665 patients, the sensitivity for detection of advanced neoplasia was 24% for a six-sample FOBT compared to only 5% for the single digital FOBT. Unfortunately, many primary care clinicians continue to rely on the single digital FOBT for CRC screening. In a recent survey of more than 1,100 primary care clinicians who indicated that they used FOBT for CRC screening, 25% used only the single sample digital FOBT. Fifty-three percent reported using both digital and three sample tests in their patients.

Primary care clinicians have a choice of various methods of testing for fecal occult blood, including Hemoccult II (Beckman Coulter, Fullerton, California); a newer test, Hemoccult SENSA; and fecal immunochemical tests (which use antibodies to detect human hemoglobin in stool). The Hemoccult tests require one to omit red meat, horseradish, cantaloupe, and uncooked fresh vegetables for 2 days before treatment.
the first sample is obtained to minimize false-positive tests. In a comparison study, Hemoccult SENSA was more sensitive than Hemoccult II for the detection of CRC (79% vs. 37%) but somewhat less specific (87% vs. 98%). Immunochemical tests also have been shown to have higher sensitivity and lower specificity than Hemoccult II. Because the next step for patients with a positive FOBT is colonoscopy, the lower specificity of Hemoccult SENSA and immunochemical tests would lead to increased colonoscopic evaluations. In their most recent analysis, the USPSTF specifically recommends a high-sensitivity FOBT (Fig. 52-1) rather than the Hemoccult II. In a 2007 survey of primary care clinicians, high-sensitivity guaiac tests and immunochemical tests were used by only 27% and 9% of physicians, respectively.

### COLONOSCOPY AND FLEXIBLE SIGMOIDOSCOPY

A recent randomized prospective study comparing flexible sigmoidoscopy once between the ages of 55 and 64 years to no screening resulted in a 33% reduction in CRC incidence and 43% reduction in CRC mortality. However, sigmoidoscopy only evaluates the left colon and therefore misses 30% to 50% of cancers. Colonoscopy is the gold standard CRC screening procedure, enabling evaluation of the entire large intestine. Although three RCTs have recently been initiated to evaluate the effectiveness of colonoscopic screening on CRC mortality, definitive results are not expected to be available for the next decade. Several case control studies show that colonoscopy and polypectomy decrease the incidence of CRC by more than 50%. A recent analysis of patients in the National Polyp Study demonstrated that the risk of death from CRC was 53% less in patients who had polyps removed than it was in the general population. A population-based Canadian study of 2.4 million persons showed that for every 1% increase in colonoscopy rate, the risk of death from CRC decreased by 3%. Colonoscopy and sigmoidoscopy both require a bowel prep to adequately visualize the colonic mucosa. Both have a very small risk of perforation. In a recent study of screening colonoscopy from Spain, there was only 1 perforation in 26,703 exams. Advantages of colonoscopy over sigmoidoscopy include evaluation of the entire colon, the ability to safely remove polyps during the same procedure, and the 10-year interval between negative exams. Colonoscopy requires sedation and has increased associated costs.

### PATIENTS AT HIGH RISK FOR COLORECTAL CANCER

Because the risk of developing CRC is doubled for patients with a first-degree relative with CRC, these patients are recommended to undergo screening colonoscopy starting at the age of 40 years, or 10 years younger than the earliest age a family member was diagnosed with CRC, and repeated every 5 years. Three percent of all CRCs occur in patients with hereditary nonpolyposis colon cancer (Lynch syndrome). Such patients are identified using the Amsterdam II criteria (at least three relatives with colorectal, endometrial, small bowel, or ureteral cancer; one must be a first-degree relative of the other two; at least two successive generations must be affected; and at least one of the cancers should be diagnosed before the age of 50 years). Tumors from patients who meet these criteria should be tested for microsatellite instability or immunohistochemistry for protein expression of the four mismatch repair genes mutated in Lynch syndrome. If subsequent analysis identifies germline mutations in the MLH1 and MSH2 genes, family members can be genetically screened. Affected individuals should undergo colonoscopy every 1 to 2 years starting at the age of 25 years or 10 years younger than the earliest case.

### DIETARY RISK FACTORS FOR COLORECTAL CANCER

Epidemiologic data showing associations between dietary factors and an increased risk of CRC suggest an additional potential avenue for the primary care clinician to influence the incidence of CRC. Classic studies have shown that migrants from countries with a low incidence of CRC to areas of high incidence develop CRC at the higher incidence within one generation. Total caloric intake; higher body mass index (BMI); and diets rich in red, fried, or barbecued meat are associated with increased CRC risk. Evidence from several studies has failed to show a protective effect of a high-fiber diet on CRC incidence. However, evidence suggests a protective effect of vegetables and fruits.
USE OF ASPIRIN TO REDUCE THE RISK OF COLORECTAL CANCER

Most CRCs develop from adenomas. A meta-analysis of four RCTs designed to evaluate the preventive effect of low-dose (81 to 325 mg) daily aspirin on the development of new adenomas in patients with a history of adenomas or CRC demonstrated that aspirin use led to a 20% reduction in the rate of adenoma formation. Analysis of CRC incidence and mortality in five randomized trials evaluating low-dose aspirin for prevention of vascular events revealed that aspirin reduced both the incidence of and mortality from CRC. Five years of aspirin therapy led to an absolute reduction of 1.7% in the 20-year mortality from CRC. The greatest incidence reduction occurred in the risk of proximal colon cancers, suggesting a synergistic role for aspirin with sigmoidoscopic or colonoscopic screening.

PRESENTATION AND DIAGNOSTIC EVALUATION OF PATIENTS WITH COLORECTAL CANCER

The presentation and diagnostic evaluation of patients with CRC is summarized in Tables 52-1 and 52-2. A positron emission tomography–computed tomography (PET–CT) is not recommended as a baseline test because CT alone is as sensitive and has fewer false positives.

TREATMENT OF PRIMARY COLON CANCER

Treatment of colon cancer involves en bloc resection of the cancer and the regional lymph nodes. RCTs have indicated that long-term overall survival is similar after laparoscopic or open colon resection. Laparoscopic surgery takes longer, and approximately 25% of cases require conversion to open surgery. Although some RCTs indicate that duration of analgesic use and length of stay were less after laparoscopic resection, a randomized prospective trial that employed fast-track recovery techniques to both groups and used blinding of both patients and caregivers to minimize bias found no difference in pain, gastrointestinal (GI) function, length of stay, or return to normal daily activities.

Colon cancer is staged via the TNM system (Table 52-3). T1 tumors are limited to the submucosa, T2 invade the muscularis propria, T3 invade through the muscularis propria, and T4 tumors invade other organs. T1 and T2 patients are stage I; T3 and T4 are stage II. Patients with nodal metastases are stage III; patients with distant metastases are stage IV. With surgery alone, 5-year survival for stage I patients is 95% and for stage II patients is 80%. No adjuvant therapy has been proven to improve survival for these patients. Clinical trials in the 1990s demonstrated improved survival for stage III patients when 5-fluorouracil (5-FU) and leucovorin were administered after surgery. More recent trials showed that the combination of oxaliplatin, 5-FU, and leucovorin (FOLFOX) is more efficacious than 5-FU and leucovorin alone, with a 5-year survival of 73%. Complications of FOLFOX therapy include peripheral neuropathy (44%), neutropenia (40%), and diarrhea (11%). Neuropathy may be long lasting: 27% of patients had neuropathy 1 year after treatment and 11% still had neuropathy 4 years after therapy. No intervention has been proven effective to ameliorate oxaliplatin-induced neuropathic symptoms.

TREATMENT OF PRIMARY RECTAL CANCER

Surgical treatment of rectal cancer is determined by the location of the tumor in the rectum and the T stage as determined by endorectal ultrasound (US) or magnetic resonance imaging (MRI). T1 tumors close to the anal verge that are small (<3 cm) and involve <30% of the rectal circumference can be treated with transanal excision. If negative margins are obtained, this is adequate therapy, and the risk of local recurrence is low (8% at 10 years). Patients with T2 to T4 tumors should be treated with a transabdominal resection: either a low anastomosis and sphincter or the levator muscles. Patients with clinical T3, T4, or node-positive tumors treated with preoperative (neoadjuvant) continuous infusion 5-FU plus radiation therapy have a lower local recurrence rate and less treatment-associated toxicity than...
patients treated with the same regimen after surgery. Adjuvant chemotherapy is recommended for all patients with stage II or III rectal cancer after neoadjuvant chemoradiation and surgery. Most medical oncologists extrapolate from the colon cancer trials and use FOLFOX as the adjuvant regimen.

**FOLLOW-UP OF PATIENTS WITH COLORECTAL CANCER AFTER INITIAL TREATMENT**

The main goal of surveillance after initial therapy of CRC is to identify distant metastases or local recurrences, which are potentially curable with surgery. Because patients have a history of CRC are at increased risk for a second primary, an additional goal is to identify new colorectal neoplasms at an early stage. Four RCTs, involving 745 patients, have compared intensive follow-up (with frequent carcinoembryonic antigen [CEA] measurements, CT scans, or both) with minimally intensive follow-up. A meta-analysis of these trials concluded that intensive follow-up was associated with a marked reduction in mortality (relative risk [RR] of 0.73; CI, 0.6 to 0.89). They determined that surveillance of 8 to 11 patients was needed to prevent one death from CRC.

NCCN guidelines for the follow-up of patients with CRC are summarized in Table 52-4.

If a rising CEA is detected on two consecutive measurements in the absence of detectable metastases on CT scan, a PET–CT scan should be obtained because it predicts those patients who would benefit from laparotomy and surgical resection of recurrent disease.

**TREATMENT OF PATIENTS WHO DEVELOP METASTASES AFTER INITIAL THERAPY**

Approximately 50% of patients diagnosed with CRC will develop metastases. The liver and lung are the most common sites of metastases. Five-year survival rates for patients who do not undergo surgical resection of metastases are very low. In contrast, large series have demonstrated that 25% of patients are alive 5 years after surgical resection of hepatic metastases. Surgical resection of hepatic metastases can be accomplished with low mortality (<1%) and morbidity. Therefore, surgery is the standard of care for patients with resectable metastatic CRC. Chemotherapy is commonly combined with surgery: one study has demonstrated that perioperative FOLFOX chemotherapy (before and after hepatic metastasis resection) improved recurrence-free survival at 3 years.

Use of systemic therapy in patients with unresectable metastases depends on patients' performance status and patients' preference after discussing the survival benefits versus toxicity of chemotherapy. Intensive initial therapy options include FOLFOX, FOLFIRI (5-FU/leucovorin/irinotecan), or capecitabine and oxaliplatin. Median overall survival for patients with unresectable metastases treated with aggressive chemotherapy regimens is approximately 16 to 20 months. Addition of bevacizumab (an antibody that blocks vascular endothelial growth factor) or the antipidermal growth factor antibody cetuximab (in patients with nonmutated KRAS genes) in combination with chemotherapy has been shown to provide a modest survival benefit in some trials.

**TREATMENT OF PATIENTS WHO INITIALLY PRESENT WITH METASTATIC COLORECTAL CANCER**

Management of patients who present with a primary colon or rectal cancer and synchronous metastases is best accomplished in a multidisciplinary fashion with input from surgical, medical, and radiation oncologists. Patients with a primary colon cancer and resectable metastatic disease, such as limited liver or lung metastases, are usually able to undergo simultaneous resection of the primary tumor and the metastases, followed by chemotherapy. Initial treatment of patients presenting with primary colon cancer and unresectable metastases depends on the extent of metastatic disease and how symptomatic the primary is. Patients with an obstructing colon cancer or one that is bleeding enough to require frequent transfusions are best initially treated with resection for symptom control. Patients with asymptomatic colon cancer primaries and unresectable metastases may undergo chemotherapy as their initial treatment. In one study, 93% of such patients never required surgical palliation of their primary tumor.

Patients who present with a primary rectal cancer and metastatic disease are commonly managed initially with chemotherapy. Responding patients may proceed to neoadjuvant chemoradiotherapy to the primary tumor, followed by staged resection of the primary cancer and the metastases. Radiation therapy is very effective at controlling bleeding rectal cancers in patients with unresectable metastases. Patients who present with obstructing rectal cancer and unresectable metastases may be palliated with a stent or a colostomy.

**References**


KEY POINTS

- Anal carcinomas are relatively rare and present most commonly with symptoms that may mimic more benign disorders of the anus; symptoms often include rectal bleeding, perineal pain, pruritus, mass sensation at the level of the anus, and a change in bowel habits.
- Diagnosis and workup should include a physical and rectal exam, biopsy, and CT imaging of the pelvis with contrast. Prognosis is related to the tumor size, nodal involvement, and presence of distant metastasis.
- Combined modality radiation therapy and chemotherapy is the standard treatment for anal carcinoma. Most patients retain sphincter function.
- Long-term complications of radiochemotherapy are predictable and can be managed by the primary care clinician, although routine close follow-up for disease recurrence should continue for at least 5 years after treatment given the continued risk of disease recurrence at 5 years.

Epidemiology

Carcinoma of the anal canal accounts for approximately 2.2% of all malignant tumors of the digestive tract, with an estimated 6,200 cases diagnosed annually. The median age at diagnosis is 62 years, although this median age has steadily declined over the past two decades reflecting the populations at greatest risk. Risk factors for anal carcinoma include female gender; infection with human papillomavirus (HPV); >10 lifetime sexual partners; history of anal or genital warts, cigarette smoking; receptive anal intercourse, especially before the age of 30 years old; and infection with human immunodeficiency virus (HIV). These risk factors more closely resemble those for genital malignancies than gastrointestinal tract tumors.

Despite the recent rise in the incidence of anal carcinomas, recent data from HPV vaccination trials suggest that the vaccine may be effective in preventing precancerous and cancerous lesions. HPV types 16 and 18 are found in 72% of anal cancers and 69% of precancerous anal intraepithelial neoplasia (AIN) grades 2 and 3. A recent placebo-controlled international trial of HPV immunization in >4,000 males between 16 and 26 years old showed AIN was effectively prevented in 78% and 50% of the patients treated per protocol and with intention to treat, respectively. Thus, HPV vaccination may be effective in preventing AIN and anal carcinoma in males as well as females.

Anatomy and Pathology

The anal canal is 3 to 4 cm long and extends from anal verge to the anorectal ring. Two categories of tumors arise in the anal region: squamous cell carcinomas (SCCs), which comprise 85% of all anal cancers and are often found below the most proximal portions of the anus, and adenocarcinomas (ACs), which represent 10% to 15% of all anal cancers and are found more distally near the dentate line (anorectal junction). Tumors arising within the hair-bearing skin at or distal to the squamous mucocutaneous junction are termed perianal skin cancers and, with the exception of melanomas, are staged and treated as skin cancers. Lesions above the dentate line tend to spread along the hemorrhoidal vessels to perirectal and internal iliac nodes. Lesions below the dentate line and at the anal verge drain to the inguinal nodes.

Diagnosis and Staging

Rectal bleeding, the most common presenting symptom of anal malignancy, occurs in approximately 40% of patients. Associated symptoms may also include perineal pain, pruritus, mass sensation at the level of the anus, and a change in bowel habits such as decreased caliber of stools or urgency. These signs and symptoms may mimic those of hemorrhoids, anal fissures, or anal fistulas. The physical exam includes inspection of the anal area and a digital rectal exam, which should focus on tumor location (both distance from the anal verge and circumferential involvement), size, and superior extent as well as anal sphincter function and tone. The exam should also determine if there are suspicious inguinal lymph nodes. For women, a gynecologic exam should be performed.

Routine laboratory evaluation should include complete blood count (CBC), liver function testing (LFT), HIV testing, and cluster of differentiation (CD4) counts and viral load if HIV positive. An anoscopy or proctoscopy with biopsy should be performed to confirm diagnosis. If clinically apparent inguinal lymph nodes exist, these may be biopsied but should be done with fine needle aspiration (FNA). Open biopsy should be avoided because it may increase the risk of leg edema after chemoradiation to these regions (see the following text). Imaging to complete staging should include a chest X-ray (CXR) or chest computed tomography (CT), CT or magnetic resonance imaging (MRI) of the abdomen and pelvis with contrast, and...
possibly a positron emission tomography (PET)/CT to evaluate extent of disease including lymph nodes and/or distant metastases. Transanal ultrasound should be performed to visualize perirectal nodes and evaluate depth of tumor invasion.

At initial presentation, most patients have a T1 or T2 lesion, and fewer than 20% are node positive. The probability of nodal spread is directly related to tumor size and location. Tumor size (T stage) and nodal status (N stage) are the most significant prognostic factors for patients with anal SCC with associated 5-year overall survival found in Figure 53-1.10

**TREATMENT**

In the past, anal canal tumors were treated by abdominoperineal resection (APR). However, radiotherapy with concurrent chemotherapy is now the treatment of choice for most patients. The 5-year survival rates after chemoradiation are superior to surgery (from 65% to 80% depending on the stage; about 15% superior to surgery, stage for stage). In addition, local control with anal preservation is achieved in more than 95% of patients with tumors less than 2 cm in size and 60% possible.

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>T0</th>
<th>Tis</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor cannot be assessed</td>
<td>No evidence of primary tumor</td>
<td>Carcinoma in situ (Bowen disease, high-grade squamous intraepithelial lesion (HSIL), anal intraepithelial neoplasia (AIN) II–III)</td>
<td>Tumor 2 cm or less in greatest dimension</td>
<td>Tumor more than 2 cm but not more than 5 cm in greatest dimension</td>
<td>Tumor more than 5 cm in greatest dimension</td>
<td>Tumor of any size invades adjacent organ(s), (e.g., vagina, urethra, bladder, etc.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No regional lymph node metastasis</td>
<td>Metastasis in perirectal lymph node(s)</td>
<td>Metastasis in unilateral internal iliac and/or inguinal lymph node(s)</td>
<td>Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th>M0</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No distant metastasis</td>
<td>Distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomic stage/prognostic groups</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>IIIA</th>
<th>IIIB</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis N0 M0</td>
<td>T1 N0 M0</td>
<td>T2 N0 M0</td>
<td>T3 N0 M0</td>
<td>T1 N1 M0</td>
<td>T4 N0 M0</td>
<td>Any T N2 M0</td>
</tr>
<tr>
<td>T4 N1 M0</td>
<td>Any T N3 M0</td>
<td>Any T Any N M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall survival by stage and nodal status</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis N0 M0</td>
<td>86%</td>
<td>86%</td>
<td>60%</td>
</tr>
<tr>
<td>Any T N2 M0</td>
<td>45%</td>
<td>76%</td>
<td>54%</td>
</tr>
</tbody>
</table>

**FIGURE 53-1.** The cTNM is the clinical classification; pTNM is the pathologic classification. *Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.* (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.)

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to 75% for patients with larger tumors. Likewise, concurrent radiotherapy and chemotherapy is superior to radiation alone (for all but the smallest tumors) in achieving complete response, local control, progression-free survival, and colostomy-free survival. Patients are typically treated using 3-D conformal techniques or, more recently, intensity-modulated radiation therapy (IMRT) with approximately 30 treatments (6 weeks). Chemotherapy consisting of mitomycin C and 5-fluorouracil (5-FU) is administered concurrently with the first and fifth weeks of radiation therapy.

**Treatment Side Effects**

Acute complications of chemoradiation include substantial skin reactions (including moist desquamation), leukopenia, thrombocytopenia, proctitis, diarrhea, and cystitis. Moist skin desquamation is managed with topical antibiotic creams such as 1% Silvadene cream. Diarrhea is also common and is managed with anti-diarrheal medications as first-line treatment. For chronic diarrhea after radiation therapy, dietary adjustments, especially elimination of raw vegetables, may be of benefit. Low-fat diets, probiotic supplementation, and elemental diets also may be beneficial among patients treated with pelvic radiation. For refractory cases, one can consider 2-week trial courses of pancrelipase (Creon), cholestyramine resin (Questran), and finally prednisone. Available options for treatment of fecal incontinence include medical therapy to reduce stool frequency and improve stool consistency, biofeedback therapy to improve control of the pelvic floor and abdominal wall musculature, and surgery. Unfortunately, tumor-induced damage to the sphincter does not typically improve even after cure.

Subacute and late complications of treatment are rare but can include rectal urgency, sterility, and impotence. In women treated with radiation therapy, vaginal stenosis may occur after radiation, which can be prevented with vaginal dilator use in women who do not engage in frequent (more than twice a week) intercourse. Men may notice a decrease in ejaculate as well as testosterone levels after chemoradiotherapy. The incidence of anal ulcers, stenosis, and necrosis is dose dependent; such toxicities may necessitate a colostomy in ~10% of patients who are otherwise free of disease.

Patients treated with pelvic radiation therapy for anal cancer may rarely develop chronic radiation proctitis 1 to several years after the completion of radiotherapy. Symptoms may include diarrhea, rectal urgency and/or pain, obstruction, and bleeding. Initial therapy should include steroid suppositories including a 2-week trial of hydrocortisone retention enema (Colocort). If improvement is noted, this can be continued for four additional weeks. Alternatively, if symptoms persist, oral sulfasalazine (Azulfidine) or balsalazide (Colazal) may be of benefit.

**FOLLOW-UP AND CONTINUED SURVEILLANCE**

A history, physical, and anal exam should be performed every 6 weeks until a complete response is obtained, then every 3 months for first year, every 4 months for second year, every 6 months for third year, then annually for the first 5 years. Distant metastases are rare, occurring in only 10% of patient with advanced-stage disease at 5 years, with the liver being the most common site. Routine rebiopsy at 6 weeks posttreatment should not be performed to avoid a nonhealing ulcer. Tumor regression will continue for up to 12 months, with a mean time to regression of 3 months. The use of surveillance PET/CT at 2 months after treatment should be considered because persistently abnormal fluorodeoxyglucose (FDG) uptake was correlated with poor 2-year cause-specific survival of 39% and may necessitate salvage therapy with APR. In patients who initially presented with T3 to T4 tumors or lymph node–positive disease, annual CXR and pelvic CT for 3 years should be performed. If disease recurs, an APR may be performed and will cure about one-third of patients. It is important to note that most recurrences occur within 2 years and are found mostly at the primary site.

**References**


KEY POINTS

- There are multiple curative and palliative treatment options for HCC.
- Treatment decisions are driven by hepatic function and performance status in addition to tumor burden.
- Patients require complex, multidisciplinary evaluation and care.
- Effective screening and access to specialty care are required for early detection and prolonged survival.

EPIDEMIOLOGY AND RISK FACTORS

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer worldwide and the leading cause of death in cirrhosis.¹,² The incidence is rising in the United States, with 20,000 new cases per year.³ Cirrhosis, regardless of underlying etiology, is considered to be the leading risk factor for the development of HCC and is present in 80% to 90% of patients diagnosed with HCC. The rising incidence of HCC in the United States is attributed to hepatitis C (HCV).³ Most patients with HCV in the United States acquired the virus in the 1960s–1980s. An estimated 10% to 25% of patients with chronic HCV develop cirrhosis after 20- to 30-year latency. The risk of developing HCC is 1% to 5% per year in patients with cirrhosis, and the risk of HCC increases as cirrhosis advances. Therefore, as the population with HCV-related cirrhosis ages, the rise in HCC is expected. HCV-related HCC is now the fastest rising cause of cancer in the United States, and the 5-year survival remains a dismal 12%.⁵ Although the threefold increased incidence of HCC in the United States over the past 20 years is alarming, it is important to underscore that the incidence of HCC is far greater in developing countries where hepatitis B (HBV), a vaccine-preventable infection, is endemic. Globally, there are 750,000 new cases of HCC per year.⁶ HCC can arise in the absence of cirrhosis in people with chronic HBV.

Other common causes of cirrhosis in the United States include alcoholic liver disease and nonalcoholic fatty liver disease (NAFLD). Heavy alcohol use is a known risk factor for HCC, but the combination of alcohol use and chronic HCV infection markedly increases the risk of HCC.⁷ HCC is also diagnosed in a minority of patients without cirrhosis. Several studies suggest that this may be attributed to NAFLD-related cirrhosis, and the prevalence of NAFLD is rising in parallel with the epidemic of obesity and metabolic syndrome. Studies have shown that people with type 2 diabetes have a twofold higher risk of developing HCC.⁸,⁹

Antiviral therapy to control the viral load in patients with HBV or eradicate the virus in patients with HCV has been shown to mitigate the risk of developing HCC.¹⁰,¹¹ It is not known if alcohol cessation or glycemic control and weight reduction reduce the risk of HCC in patients with cirrhosis related to alcoholic liver disease and NAFLD; however, these lifestyle modifications are recommended to slow the progression of cirrhosis.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients are often asymptomatic, so early diagnosis depends on a high index of suspicion for cirrhosis (Table 54-1) and awareness of the recommended screening guidelines discussed in Chapter 14. HCC is one of the only solid organ tumors that can be diagnosed without a tissue biopsy. These tumors are usually highly vascular and derive their blood supply from the hepatic artery. The diagnosis may be established by dynamic imaging showing the typical enhancement pattern of early arterial enhancement and delayed venous washout on a multiphase (precontrast, arterial, venous, delayed) contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) (Table 54-2).¹² Recent guidelines from the American Association for the Study of Liver Diseases (AASLD) suggest that one image may be enough for lesions 1 to 2 cm in diameter.¹³ However, studies have shown significant lack of sensitivity of one image in these small tumors, so corroborating CT and MRI many physicians still rely on.¹⁴ Biopsy should be performed when imaging is equivocal or if the patient does not have underlying cirrhosis.¹² When the underlying etiology of cirrhosis is in question, or if the diagnosis of cirrhosis is not established, a background parenchymal biopsy may be helpful to determine the extent of fibrosis and etiology of underlying liver disease. This can be performed concomitantly with the tumor biopsy at a distance from the tumor to avoid architectural distortion caused
by compressive mass effect. If the tumor biopsy results are negative, surveillance of the lesion at a 3- to 6-month interval should be continued. Lesions less than 1 cm should be surveyed at 3- to 6-month intervals.3 Once a patient has a suspicious lesion, CT or MRI is used for surveillance. At an interval of 3 to 6 months, MRI is preferable to CT to spare the effects of radiation and the risk of contrast-induced nephropathy. An unintended consequence of the reliance on radiographic diagnosis is the paucity of tissue to study the molecular pathogenesis of HCC. The risk of tumor seeding is very low, with conservative estimates at roughly 3%.15

**TABLE 54-1** Symptoms and Signs of Cirrhosis and HCC

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Symptoms</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Muscle wasting/weight loss</td>
<td>Muscle wasting/weight loss</td>
</tr>
<tr>
<td>Development of hepatic decompensation</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Ascites</td>
<td>Development of otherwise unexplained hepatic decompensation</td>
</tr>
<tr>
<td>Variceal bleeding</td>
<td></td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td></td>
</tr>
</tbody>
</table>

**Signs**

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spider angiomata</td>
<td>All signs associated with cirrhosis</td>
</tr>
<tr>
<td>Palmar erythema</td>
<td>Biochemical</td>
</tr>
<tr>
<td>Caput medusae</td>
<td>All biochemical signs associated with cirrhosis</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Elevated alkaline phosphatase</td>
</tr>
<tr>
<td>Bulging flanks/shifting dullness</td>
<td>Elevated AFP</td>
</tr>
<tr>
<td>Irritability to frank confusion</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
</tr>
</tbody>
</table>

**Biochemical**

| Hypoalbuminemia | |
| Thrombocytopenia | |
| Elevated INR | |
| Abnormal liver enzymes | |

HCC, hepatocellular cancer;AFP,a-fetoprotein;INR,international normalized ratio.

**TREATMENT**

Treatment for HCC can be divided into curative or palliative. The choice of treatment depends on many factors, including tumor burden and the patient’s hepatic synthetic reserve and performance status. It is important to remember that HCC most often arises in an already diseased organ, and treatment choices should be tempered by this. Very few randomized, controlled trials have compared treatment, and much of these decisions are guided by observational studies and the opinions of experts. Although more than seven different staging systems are in existence for HCC, the Barcelona Clinic Liver Cancer (BCLC) staging classification has been validated and accepted as the standard means of assessing prognosis and providing a treatment algorithm for patients with HCC.16 The BCLC staging system uses tumor burden as well as validated oncology (Eastern Cooperative Oncology Group [ECOG] performance status) and hepatology (Child-Turcotte-Pugh [CTP] scoring system) standards for assessing candidacy for treatment (Table 54-3).

The multitude of treatment options, all of which must be considered in the context of the patient’s hepatic function and performance status, require many different specialists to be involved in treatment decisions (see Table 54-3). These cases are best handled by a multidisciplinary tumor board represented by hepatology, oncology, surgery, interventional radiology, general radiology, and pathology. Survival varies greatly according to extent of disease at diagnosis.

A rare subtype of HCC, called fibrolamellar HCC, develops in younger women who do not have cirrhosis. It follows a more indolent course and is often more successfully treated. Angiosarcoma and epithelioid hemangioendothelioma of the liver are rare cancers. Hepatoblastoma is also a rare type of primary liver cancer that primarily affects young children.

There are no established guidelines for surveillance of patients after treatment or in remission, but an accepted approach is delineated in Table 54-4.3

Although there are many treatment modalities that may cure HCC or prolong survival, the rates of screening are far from optimal as noted by several US population-based studies.17,18 Survival rates would improve dramatically if HCCs were detected at very early and early stages. Studies have also shown that the number of patients receiving treatments, both curative and palliative, is low.19 Efforts should be directed to establishing screening and recall programs and to improving access to multidisciplinary specialty care.
### TABLE 54-3  Stage-Specific Treatment of Hepatocellular Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Burden</th>
<th>CTP Score</th>
<th>ECOG PS</th>
<th>Treatment</th>
<th>Survival Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early</td>
<td>• A single lesion ≤2 cm</td>
<td>A</td>
<td>0–1</td>
<td>Surgical resection if no portal hypertension</td>
<td>Curative: 70% 2-y survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence: 70% at 5 y&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td>Early</td>
<td>• 1 nodule ≤5 cm</td>
<td>A/B</td>
<td>0–1</td>
<td>Resection of solitary tumors if no portal</td>
<td>Curative (as above)</td>
</tr>
<tr>
<td></td>
<td>• No more 3 nodules, each ≤3 cm</td>
<td></td>
<td></td>
<td>hypertension</td>
<td>Curative: 75% 5-y survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liver transplantation reserved for patients</td>
<td>Recurrence 15% at 5 y&lt;sup&gt;21,22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>within Milan criteria (a single nodule ≤5 cm or three nodules none &gt;3 cm)</td>
<td></td>
<td></td>
<td>Ablative therapy</td>
<td>Curative: 70% 2-y survival&lt;sup&gt;23,24&lt;/sup&gt; (lesions ≤3 cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ablation ± TACE (often used as a bridge to</td>
<td>Recurrence 70% at 5 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>transplantation)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>• Large or multifocal lesions</td>
<td>A/B</td>
<td>0–1</td>
<td>TACE</td>
<td>Palliative may prolong 2-y survival by as much as 25%&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yttrium-90 radioembolization</td>
<td>Palliative: insufficient data</td>
</tr>
<tr>
<td>Advanced</td>
<td>• Any lesion with vascular invasion or</td>
<td>A/B</td>
<td>0–2</td>
<td>Sorafenib</td>
<td>Palliative: improves overall survival by 2–3 mo&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Extrahepatic spread</td>
<td></td>
<td></td>
<td>TACE</td>
<td>Palliative: as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yttrium-90 radioembolization</td>
<td>Palliative: as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sorafenib</td>
<td>Palliative: as above</td>
</tr>
<tr>
<td>Terminal</td>
<td>Symptoms related to</td>
<td>B/C</td>
<td>≥2</td>
<td>Best supportive care</td>
<td>Palliative</td>
</tr>
<tr>
<td></td>
<td>• liver failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• vascular involvement or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• extrahepatic spread</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ablation, percutaneous or laparoscopic direct thermal, toxic, or microwave destruction of tumor tissue; TACE, transarterial chemoembolization—intra-arterial delivery of doxorubicin-loaded beads followed by occlusion of the feeding artery; yttrium-90 radioembolization, intra-arterial delivery of yttrium-90–loaded beads; sorafenib, oral multityrosine kinase inhibitor, a systemic therapy; CTP, Child-Turcotte-Pugh scoring system; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

### TABLE 54-4  Hepatocellular Cancer—Surveillance of Patients After Treatment and in Remission

- After resection: contrast-enhanced CT/MRI at 4–6 wk, then every 3 mo for 2 y
- After locoregional therapy: contrast-enhanced CT/MRI at 4–6 wk, then every 3 mo for 2 y
- After 2-y recurrence free survival: contrast-enhanced CT/MRI every 6 mo for life
- After transplant: contrast-enhanced CT/MRI at 3, 6, and 12 mo, then yearly for 5 y

CT, computed tomography; MRI, magnetic resonance imaging.
References

intraepithelial neoplasia (PIN) may be a precancerous lesion of the prostate, but not all cases progress to invasive adenocarcinoma. Genetic abnormalities of the androgen receptor and alterations of molecules regulating cell survival and apoptosis are involved in a multistep process leading to cellular transformation of normal prostatic epithelium to PIN, invasive castrate-sensitive cancer, and the development of castrate-resistant disease.5,6

**CLINICAL MANIFESTATIONS**

As a result of widespread use of PSA testing, most men diagnosed with prostate cancer today are asymptomatic. Patients who are not diagnosed as a result of PSA screening may initially present with asymmetric firmness or nodularity in the prostate on digital rectal examination (DRE), with genitourinary symptoms, and/or with manifestations of metastatic disease including bone pain, weight loss, and symptoms of renal failure (Table 55-1).

<table>
<thead>
<tr>
<th>TABLE 55-1 Presenting Signs and Symptoms of Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Urinary urgency</td>
</tr>
<tr>
<td>• Urinary hesitancy</td>
</tr>
<tr>
<td>• Increased urinary frequency</td>
</tr>
<tr>
<td>• Nocturia</td>
</tr>
<tr>
<td>• Dysuria</td>
</tr>
<tr>
<td>• Blood in the urine</td>
</tr>
<tr>
<td>• Painful ejaculation</td>
</tr>
<tr>
<td>• Symptoms of metastatic disease</td>
</tr>
<tr>
<td>• Bone pain</td>
</tr>
<tr>
<td>• Renal failure symptoms (from hydronephrosis)</td>
</tr>
<tr>
<td>• Weight loss, fatigue</td>
</tr>
</tbody>
</table>

**DIAGNOSIS**

The workup for prostate cancer includes history and physical examination with a rectal exam, laboratory testing including PSA, blood counts, and chemistries including creatinine and blood urea nitrogen (BUN). The diagnosis is established in most cases by a transrectal ultrasound–guided biopsy of the prostate gland. This procedure can usually be performed in the outpatient setting with local anesthesia only and without...
STOPPING ASPIRIN. CLOPIDOGREL AND WARFARIN ARE USUALLY HELD.

Prophylactic periprocedure antibiotics are recommended. Yield is increased by extended core biopsy, which involves obtaining 5 to 7 cores from each side of the prostate.  

### STAGING AND PROGNOSIS

The current staging system for prostate cancer is presented in Table 55-2. Patients are commonly divided into three risk groups based on T stage, pretreatment PSA level, and Gleason score (Table 55-3). The Gleason score is assigned by the pathologist by grading the degree of differentiation of the two most prevalent areas of prostate cancer on a scale of 1 to 5 and adding the two scores to a number that ranges from 2 (very well differentiated) to 10 (very poorly differentiated). Other factors that influence the patient’s prognosis include the presence of perineural invasion, which is a marker for extracapsular extension of disease and the percentage of positive biopsies, which is a surrogate for tumor volume.

Prostate cancer spreads via direct extension to local structures and metastasizes primarily to the bones and pelvic and abdominal lymph nodes. Visceral metastases to the liver and lung are rare and usually seen in poorly differentiated cancer. Staging tests should be guided by risk stratification (see Table 55-3) with bone scans recommended in patients with intermediate or high-risk disease and computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis reserved for patients with high-risk disease. Scans in patients with low-risk disease are not recommended because their yield is extremely low and false-positive findings can lead to unnecessary tests and expense, anxiety, and delays in treatment.

The most important decision to be determined in the staging of the disease is whether the cancer is confined to the prostate (clinically localized prostate cancer) or not. Clinical staging based on whether the disease is palpable, the patient’s PSA level, and the predominant histologic grade of the cancer are used to estimate the probability that the disease is localized. Multiple predictive tables and nomograms are also available to enable clinicians to use clinical and demographic data to predict outcomes for patients with prostate cancer under different clinical scenarios. Clearly, no predictor is completely accurate; what occurs on average for a thousand similar patients may be very different from what happens to the individual subject. This unknowingness must be factored into any discussion of the treatment of the disease.

### MANAGEMENT OF PROSTATE CANCER

The management options for prostate cancer include watchful waiting, active surveillance, surgery, radiation therapy, and/or androgen deprivation therapy (ADT) (Table 55-4). Unfortunately, most strategies have not been compared in prospective trials.

**TABLE 55-2**  
American Joint Committee on Cancer, Seventh Edition, Prostate Cancer Staging

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Pathologic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1a</td>
<td>Incidental finding in ≤5% of tissue removed</td>
</tr>
<tr>
<td>cT1b</td>
<td>Incidental finding in &gt;5% of tissue removed</td>
</tr>
<tr>
<td>cT1c</td>
<td>Tumor identified on needle biopsy</td>
</tr>
<tr>
<td>cT2a</td>
<td>Tumor confined to ≤50% of one lobe</td>
</tr>
<tr>
<td>cT2b</td>
<td>Tumor involves &gt;50% of one lobe</td>
</tr>
<tr>
<td>cT2c</td>
<td>Tumor involves both lobes</td>
</tr>
<tr>
<td>cT3a</td>
<td>Extracapsular extension of tumor</td>
</tr>
<tr>
<td>cT3b</td>
<td>Seminal vesicle invasion</td>
</tr>
<tr>
<td>cT4</td>
<td>Tumor invades adjacent organs</td>
</tr>
<tr>
<td>N1</td>
<td>Regional nodal involvement</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis to nonregional nodes</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastasis to bones</td>
</tr>
<tr>
<td>M1c</td>
<td>Metastasis to other sites</td>
</tr>
</tbody>
</table>

**TABLE 55-3**  
Risk Stratification of Localized Prostate Cancer (American Urological Association)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Characteristics</th>
<th>10-Year PSA Failure-Free Survival after Radical Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>T1c–T2a, PSA &lt;10, Gleason score ≤6</td>
<td>83%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>PSA &gt;10 but ≤20 or Gleason score 7 or T2b and not qualifying for high risk</td>
<td>46%</td>
</tr>
<tr>
<td>High</td>
<td>T2c or PSA &gt;20 or Gleason score ≥8</td>
<td>29%</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen.
controlled studies. When selecting a management strategy for a man with newly diagnosed prostate cancer, one must take into account the patient’s preferences, his cancer risk stratification, and his life expectancy and comorbid conditions.

The patient making a decision about the treatment of this disease, particularly clinically localized cancer, is faced with a dizzying variety of decisions that will potentially have a huge impact on the rest of his life. Factors such as the patient’s own concerns about quality and quantity of life, the likelihood of side effects and their importance to the particular individual, the likelihood or lack thereof of disease progression and death from prostate cancer, and the potential bias of those counseling the patient—all of these have to be integrated into a therapeutic decision by the patient. The primary care clinician is of critical importance here as he or she is a trusted advisor. The patient should be encouraged to seek as many opinions as necessary to reach a decision; in particular, the risks and expectations of the outcomes of treatment should be described to the patient by a physician who performs and has experience with the treatment under discussion.

Watchful Waiting and Active Surveillance

Watchful waiting (WW) or observation indicates a management approach in which the patient undergoes testing and treatment only if he develops symptoms of prostate cancer. In active surveillance (AS), the goal is to use information gathered during the observation period to identify patients that may benefit from prostate cancer treatment while avoiding treatment in men who are unlikely to become symptomatic from their cancer. AS regimens typically include periodic physical examination and PSA testing and sometimes repeat prostate biopsies to assess for sampling error and progression in tumor grade and/or volume. Of the two prospective randomized studies comparing WW to prostatectomy, one study conducted before the availability of widespread PSA testing found a reduction in all cause and prostate cancer mortality among men who underwent surgery.11 The second study, known as the Prostate Cancer Intervention Versus Observation Trial (PIVOT), was conducted in the PSA testing era in the U.S. Veteran population. In the PIVOT, there was no statistically significant improvement in survival in men who underwent prostatectomy compared to observation. In men with low-risk disease, the lack of difference was even stronger.12 Most urologists recommend AS for low-risk patients (see Table 55-3) and WW for asymptomatic patients with a short life expectancy.

Surgery

Radical prostatectomy (RP) using a retropubic approach is the standard surgical oncologic procedure for the treatment of clinically localized prostate cancer. Patients with high-risk disease should undergo a staging pelvic lymph node dissection as part of the procedure. Post-surgery radiation therapy may benefit patients with seminal vesicle invasion, extracapsular extension, positive surgical margins, or persistently elevated PSA after surgery.13 Urinary incontinence and erectile dysfunction are the most common long-term complications of retropubic prostatectomy. Their incidence is high in the immediate postoperative period and decreases over time. There is great variation in the reported rates of erectile dysfunction and urinary incontinence after radical prostatectomy; in one study of 3,477 patients, erectile dysfunction occurred in 25% to 50% and significant urinary incontinence in 10%.14

In recent years, the use of the daVinci robot–assisted laparoscopic radical prostatectomy has increased dramatically; this procedure is now the most commonly used surgical treatment for prostate cancer. The robot assists the laparoscopic surgeon in performing the procedure in the relatively small space of the deep pelvis where the gland is located. It was hoped that the device would improve the rates of the major functional side effects of surgery, erectile dysfunction, and incontinence. Unfortunately, this has not happened. Although no level I evidence comparing open versus robot-assisted prostatectomy is available, reviews of lower evidence level studies show no readily discernible difference in potency, incontinence, or urethral stricture formation comparing the two procedures. The robotic approach does result in lower blood loss but transfusion of heterologous blood is the same when autologous blood donation is used, comparing open and robot-assisted prostatectomy. Length of hospital stay and return to functionality are better in the robotic procedure but the robotic procedure adds dramatically to the cost of treatment.

Radiotherapy

Radiotherapy consists of either external beam radiation or brachytherapy (seed implantation). Either modality can be used alone for low-risk patients, whereas external beam radiation is usually combined with between 6 months and 3 years of androgen deprivation to treat intermediate and high-risk patients.6,17 Brachytherapy is typically carried out in a single session in the operating room, whereas curative external beam regimens typically require 8 to 9 weeks of outpatient visits (42 to 45 treatments).18 Short-term side effects of radiation therapy include fatigue, urinary obstructive symptoms, rectal irritation, bleeding, and diarrhea. The risk of erectile dysfunction increases with time and is approximately 30% to 45% at 2 years.19 Long-term risks also include radiation cystitis, proctitis and urethral strictures, and secondary malignancies.

Biochemical Failure After Definitive Treatment of Prostate Cancer

Biochemical or PSA-only failure after definitive local treatment of prostate cancer (either radical prostatectomy or radiation) is common and usually occurs many years before the patient develops metastatic disease. For example, in one single institution series of 450 men with a biochemical recurrence after RP, the median metastasis-free survival was 10 years.20 Biochemical recurrence is defined differently after radical prostatectomy (when the PSA is expected to drop to undetectable) and radiation (when the PSA nadirs 12 to 18 months after treatment in the absence of adjuvant ADT). The most common definitions of PSA recurrence include, after RP, an increase of ≥0.2 ng per mL on repeated tests; and after radiation, a rise by 2 ng per mL or more above the nadir PSA.21-22

Management of a rising PSA after primary treatment of prostate cancer depends on the patients’ disease risk, previous treatments administered, the interval between the primary treatment and the rise in PSA, the absolute PSA level, the PSA doubling time, and the patients’ age and comorbid conditions. Salvage radiation after RP can result in long-term PSA-free survival, especially in patients in which the interval between surgery and PSA was long and the Gleason score is less than 8.23 ADT is also widely used for patients with biochemical recurrence, although there are no randomized studies addressing the timing of this therapy. One trial has shown that patients...
found to have lymph node disease after radical prostatectomy had a survival benefit if they received early ADT; although this is a different clinical scenario than biochemical recurrence, it is evidence that hormonal therapy can extend survival in some men with prostate cancer. Given the multiple side effects of ADT, however, this decision must be individualized and discussed with the patient. Early therapy is likely beneficial for patients with high-risk disease and a short PSA doubling time. Delayed and intermittent ADT is recommended for patients with low-risk disease and/or multiple comorbid conditions.

Bone Health
Patients with prostate cancer are at risk for skeletal-related events both from metastatic disease in the bones and from ADT-induced bone loss. All patients should receive supplemental calcium and vitamin D (we recommend 1,000 mg calcium and 400 to 500 IU vitamin D daily). Bone density scans should be performed periodically in patients on extended ADT. Denosumab, a receptor activator of nuclear factor-κB ligand (RANKL) inhibitor, has been shown to prevent skeletal events in patients with osteopenia or osteoporosis who are being treated with ADT. Both denosumab and zoledronic acid reduce skeletal-related events in patients with prostate cancer metastatic to the bone. Both drugs can cause hypocalcemia, hypomagnesemia, hypophosphatemia, and osteonecrosis of the jaw.

Treatment of Advanced Prostate Cancer
Castrate-Sensitive Prostate Cancer
Androgens stimulate the growth of normal and cancerous prostate cells. The critical role of androgens for prostate cancer growth was established in 1941 by Charles Huggins and provided the foundation for ADT as the primary treatment for men with advanced prostate cancer in whom systemic therapy is indicated. Although ADT is palliative and not curative, it is a very effective intervention with benefit in more than 90% of patients with metastatic, androgen-dependent, or also called castrate-sensitive disease. Either surgical castration with bilateral orchectomy or medical castration with a gonadotropin-releasing hormone (GnRH) agonist or antagonist is indicated for patients with symptomatic metastatic disease. The use of GnRH agonists causes an initial surge of androgen release and may result in a flare at a metastatic disease site. A lead-in period of 2 to 4 weeks with a direct antiandrogen receptor blocker, such as bicalutamide (Table 55-5), should be used to prevent this flare. Degarelix, a pure GnRH agonist, does not cause this flare but is significantly more expensive than GnRH agonists and surgical castration. After the lead-in period, monotherapy with GnRH agonist is preferred over combined androgen blockade (CAB; combination of GnRH agonist and a direct antiandrogen receptor) because of the higher side effect profile and greater cost of CAB. Monotherapy with an antiandrogen receptor blocker is inferior to castration and is not recommended. Side effects of ADT include fatigue, decreased sexual function, gynecomastia, osteoporosis, and the metabolic syndrome.

Castrate-Resistant Prostate Cancer
The median castrate-sensitive period is approximately 20 months, and androgen independence or “castration resistance” eventually develops in all men with metastatic prostate cancer. Potential secondary hormonal manipulations include CAB with the addition of a direct antiandrogen blocker, withdrawal of an antiandrogen receptor blocker, and high-dose ketoconazole.

Several treatment options exist for men with castrate-resistant prostate cancer. A cancer vaccine called sipuleucel-T, which works by inducing an immune response to the prostate cancer cells, provides a modest survival benefit in men with low-burden disease; however, it is very expensive and logistically difficult to administer. In men with a good performance status, chemotherapeutic interventions can provide palliation.

### TABLE 55-5
Management of Castrate-Resistant Prostate Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Route of Administration</th>
<th>Main Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiandrogens (bicalutamide, nilutamide, flutamide)</td>
<td>Oral</td>
<td>Liver toxicity, gynecomastia, hot flashes, impotence</td>
</tr>
<tr>
<td>Ketoconazole (high dose)</td>
<td>Oral with prednisone or hydrocortisone</td>
<td>Fatigue, nausea, liver toxicity, adrenocortical insufficiency, drug interactions (statins, calcium channel blockers, warfarin)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>IV q21d</td>
<td>Pancytopenia, infection, bleeding, alopecia (&gt;90%), allergic reactions, peripheral edema, peripheral neuropathy, diarrhea</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>Oral with prednisone 5 mg bid</td>
<td>Liver toxicity, adrenocortical insufficiency, diarrhea, muscle aches, hypophosphatemia</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>IV q21d</td>
<td>Pancytopenia, infection, bleeding, diarrhea, alopecia (10%), peripheral neuropathy</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>Oral</td>
<td>Fatigue, hot flashes, diarrhea, seizures</td>
</tr>
<tr>
<td>Zoledronic acid (to prevent skeletal complications)</td>
<td>IV q21–28d with supplemental calcium/vitamin D</td>
<td>Infusion reactions, muscle aches, renal failure, hypocalcemia, hypomagnesemia, osteonecrosis of jaw</td>
</tr>
<tr>
<td>Denosumab (to prevent skeletal complications)</td>
<td>Subcutaneous q28d with supplemental calcium/vitamin D</td>
<td>Muscle aches, hypocalcemia, hypomagnesemia, osteonecrosis of jaw</td>
</tr>
<tr>
<td>Samarium 153 or strontium-89 (for palliation of bone pain)</td>
<td>IV by nuclear medicine, one time</td>
<td>Bone marrow suppression</td>
</tr>
</tbody>
</table>

All patients who have not undergone surgical castration should remain on gonadotropin-releasing hormone (GnRH) agonists or antagonists long term.

q, every; bid, twice a day.
and a modest survival benefit. Docetaxel and cabazitaxel are microtubule inhibitors that have benefit as first- and second-line therapy, respectively. Common side effects of these chemotherapy agents include fatigue, myelosuppression, neuropathy, diarrhea (especially cabazitaxel), nausea, vomiting, and alopecia (especially docetaxel). Abiraterone is a new androgen synthesis inhibitor that blocks the androgen formation in the tumor cells, testes, and adrenal glands by irreversibly inhibiting the CYP17 gene. It is an oral agent, which is usually well tolerated and effective both in the first- and second-line setting for patients with castrate-resistant prostate cancer. However, it must be administered with concurrent corticosteroids (usually prednisone 5 mg twice a day) to prevent mineralocorticoid deficiency, and patients are at risk for adrenocorticol insufficiency during periods of infections and other stress. Common side effects include hepatotoxicity, edema, diarrhea, hypokalemia, and hypophosphatemia, and patients need liver function tests checked every 2 weeks for the first 3 months on therapy and then monthly. Drug interactions with certain CYP inducers and inhibitors are also a common cause of toxicity in patients on abiraterone.

Another treatment option for patients whose prostate cancer has progressed after first-line chemotherapy is enzalutamide (formerly called MDV3100). Enzalutamide is an androgen receptor antagonist that targets multiple steps in the androgen receptor signaling pathway. A phase III, double-blind, placebo-controlled trial in 1,199 men with castration-resistant prostate cancer after first-line chemotherapy showed a median overall survival of 18.4 months in the enzalutamide group versus 13.6 months in the placebo group, with an improvement in quality of life in the treated group. Side effects of enzalutamide include fatigue, diarrhea, hot flashes, and seizures (reported in five patients [0.9%]). Enzalutamide is currently under investigation as a first-line agent for castrate-resistant prostate cancer.

**SURVEILLANCE**

There are no randomized studies evaluating the optimal surveillance strategy in patients who have undergone definitive treatment for prostate cancer. National Comprehensive Cancer Network (NCCN) guidelines suggest a DRE annually (may be omitted if PSA is undetectable) and PSA every 6 months for the first 5 years, and then annually. In patients with biochemical recurrence after definitive treatment, patients should undergo physical exam including DRE and PSA testing every 3 to 6 months. A bone density scan should be obtained after 2 years of ADT (earlier in patients at high risk for osteoporosis) and periodically after that, with frequency determined by the initial findings.

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**References**


There are several known risk factors for developing bladder cancer. Chemical carcinogenesis from cigarette smoking is the most important risk factor in western countries. Although smoking cessation can decrease the risk of bladder cancer, a meta-analysis demonstrated that even after 25 years of smoking cessation, the risk of former smokers did not reach the level of never smokers. Some data suggest that secondhand smoke exposure may also increase the risk for bladder cancer. Other sources of bladder carcinogenesis are occupational exposures to chemicals, including paint components, plastic, textile and petroleum manufacturing, diesel exhausts, dry cleaning agents, and certain hair dyes. Chronic inflammation of the urothelium because of chronic bacterial urinary tract infections, indwelling catheters, schistosomal infections, and infection with high-risk serotypes of human papilloma virus can lead to the development of bladder cancer. Prior exposure to chemotherapeutic agents, such as cyclophosphamide, or radiation with bladder exposure may also increase the risk of bladder cancer.

### CLINICAL MANIFESTATIONS

Symptoms associated with bladder cancer can be nonspecific and can be mistaken for signs of urinary tract infection or kidney stone. In most cases, there is painless microscopic or gross hematuria. Gross hematuria, especially gross, painless hematuria that lasts throughout the voided urinary stream is highly suggestive of bladder cancer. It is critical for the primary care provider to understand that blood in the urine is never normal. Although most patients, particularly those with microscopic hematuria are found to have no discernible cause, it is important that the small population of those with newly presenting bladder cancer are not missed. Urine infection is the most common cause of hematuria; and once infection is ruled out or adequately treated, persistent hematuria should be evaluated. A patient with microscopic hematuria who has been evaluated with no cause found and whose hematuria persists at 1 year should undergo a repeat evaluation by a urologist.

Irritative symptoms like urinary frequency, urgency, or dysuria are more commonly seen with invasive or higher grade tumors. An elderly patient with new-onset urinary urgency should always be referred because diffuse carcinoma in situ of the bladder can present with only this new symptom. Flank or back pain can occur with ureteral obstruction and/or peritoneal metastasis. Pelvic pain can occur because of locally
advanced disease. Bone pain is usually indicative of distant metastatic spread to the bone.

**DIAGNOSIS**

The American Urological Association\(^{16,17}\) recommends that all patients older than the age of 35 years with idiopathic hematuria undergo cystoscopy and upper tract imaging (Table 56-1). Patients who cannot tolerate intravenous contrast need some form of imaging of the renal parenchyma such as noncontrast computed tomography (CT) or ultrasound and retrograde pyelography to fully evaluate the upper urinary tract for filling defects. It is very important to realize that renal ultrasonography cannot see small lesions of the upper tract urothelium. Without retrograde pyelography, these will be missed. Because retrograde pyelography is performed at the time of cystoscopy, it is best that the upper tract imaging take place prior to cystoscopy; because if a lesion is seen on the CT urogram, then retrograde pyelography can be performed at the time of cystoscopy. If the screening cystoscopy is done first, then the identification of a lesion on later upper tract imaging will require a second cystoscopy procedure for retrograde pyelography.

Bladder cancers occur in two forms, and distinguishing which the patient has is critical. The most common form of bladder cancer is the superficial tumor. These tumors have a papillary appearance on cystoscopy and look like a berry attached to the urothelium by a stalk. It is common to have more than one of these in the bladder. These tumors may invade into the lamina propria of the epithelium but are confined to the epithelium and do not extend into the underlying detrusor muscle. These tumors can manifest different degrees of differentiation, now basically separated into high- or low-grade tumors. Superficial bladder tumors are similar to skin cancer where superficial lesions are resected and then the patient is followed. Because the field changes in the bladder that led to the tumor in the first place are diffuse, like sun exposure to the skin, these patients can develop recurrent lesions that likely will also be superficial and will need to be excised once again. For this reason, patients with superficial bladder cancer require interval surveillance cystoscopy. Overall, the chance of recurrent superficial bladder tumors after resection is very high, approximately 80%. However, most of these patients do not progress to muscle-invasive disease and can be managed for years without a major risk to their survival.

Although diagnostic cystoscopy is done as an outpatient setting in the office, resection of bladder tumors requires a surgical procedure.

Patients with bladder cancer invading the detrusor muscle, on the other hand, have a potentially lethal disease. These patients tend to present with such a tumor rather than progressing from superficial to invasive disease. At the time of cystoscopy, these tumors may appear as a large sessile lesion or low-grade tumors. Superficial bladder tumors are similar to skin cancer where superficial lesions are resected and then the patient is followed. Because the field changes in the bladder that led to the tumor in the first place are diffuse, like sun exposure to the skin, these patients can develop recurrent lesions that likely will also be superficial and will need to be excised once again. For this reason, patients with superficial bladder cancer require interval surveillance cystoscopy. Overall, the chance of recurrent superficial bladder tumors after resection is very high, approximately 80%. However, most of these patients do not progress to muscle-invasive disease and can be managed for years without a major risk to their survival.

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**STAGING AND PROGNOSIS**

The standard staging follows the TNM (tumor, node, metastasis) staging system, which is based on pathologic studies of cystectomy specimen\(^{18}\) and is applied to all histologic subtypes of bladder cancer. Staging for distant metastatic disease is usually based on imaging (Table 56-2). Stage is the most important prognostic indicator for bladder cancer, with the major determinant being organ-confined disease ($\leq T2$) versus non–organ-confined disease ($\geq T3$). The accuracy of available methods including imaging and biopsy to determine the degree of muscle invasiveness and organ confinement prior to a cystectomy is unfortunately only
TABLE 56-2  TNM Staging and Survival of Bladder Cancer

<table>
<thead>
<tr>
<th>Tumor (T) stage</th>
<th>TNM</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td><strong>T</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>0</td>
<td>TaN0M0 or TisN0M0</td>
<td>98</td>
</tr>
<tr>
<td>I</td>
<td>T1N0M0</td>
<td>88</td>
</tr>
<tr>
<td>II</td>
<td>T2N0M0</td>
<td>63</td>
</tr>
<tr>
<td>III</td>
<td>T3a–nT4aN0M0</td>
<td>46</td>
</tr>
<tr>
<td>IV</td>
<td>T4bN1—nM0 or Tany, Nany, M1</td>
<td>15</td>
</tr>
</tbody>
</table>

**Nodal (N) disease**
- N1: single lymph node metastasis in the true pelvis
- N2: multiple lymph nodes in the true pelvis
- N3: involvement of the common iliac nodes; lymph node sampling should include excision of >12 lymph nodes

**Metastatic (M) disease**
- Spread to distant sites such as bone, lungs, liver, and retroperitoneal lymph.


---

**TABLE 56-3 Treatment Options for Bladder Cancer**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TURBT</td>
<td>All patients with bladder cancer; can be the only treatment in non–muscle-invasive cancer</td>
<td>Requires general anesthesia</td>
</tr>
</tbody>
</table>
| Intravesical therapy | • Partially resected carcinoma in situ  
• Multifocal and/or large volume low-grade disease  
• High-grade disease  
• Recurrent local disease | • BCG and mitomycin C most commonly used in the United States  
• Typical course of BCG—six weekly doses followed by maintenance  
• Side effects of BCG include fevers, aches; rarely can cause disseminated infection  
• BCG contraindicated in patients who are immunosuppressed |
| BCG      | Muscle-invasive tumors in patients with good performance status | Requires normal renal and cardiac function  
3 mo of chemotherapy given prior to surgery |
| Mitomycin C | Muscle-invasive tumors in patients who can tolerate surgery but not candidates for chemotherapy |  |
| Thiotepa  | Muscle-invasive tumors in patients who can tolerate surgery but not candidates for chemotherapy |  |
| Interferons | Muscle-invasive tumors in patients not able or not willing to undergo cystoscopy | 6–7 wk of radiation with concurrent chemotherapy |
| Doxorubicin | For metastatic disease | Common agents include cisplatin, carboplatin, gemcitabine, paclitaxel |
| Laser ablation | For low-grade tumors |  |
| Neoadjuvant chemotherapy (MVAC) followed by cystectomy | Muscle-invasive tumors in patients with good performance status |  |
| Cystectomy | Muscle-invasive tumors in patients who can tolerate surgery but not candidates for chemotherapy | Cystectomy should also be considered for patients with disease that is high grade, large tumor size, diffuse, difficult to resect, and recurrent after intravesical therapy even if muscle invasion has not been demonstrated. |
| Bladder conservation therapy with chemoradiation | Muscle-invasive tumors in patients not able or not willing to undergo cystoscopy |  |
| Palliative chemotherapy | For metastatic disease |  |
| Palliative radiation | To sites of painful or symptomatic metastatic disease or to palliate hematuria |  |
| Palliative TURBT | For hematuria, obstructive symptoms in patients with metastatic disease |  |

TURBT, transurethral resection of bladder tumor; BCG, bacillus Calmette-Guérin; MVAC, methotrexate, vinblastine, Adriamycin (doxorubicin), cisplatin.

modest. Another important prognosticator that tends to correlate with stage is the degree of differentiation of the tumor. Most superficial tumors are well differentiated, whereas deeply invasive tumors tend to be less differentiated. Patients with superficial tumors that are poorly differentiated, large, or affecting multiple areas of the bladder are at increased risk for recurrence and development of invasive cancer.19–21 These patients are offered radical cystectomy if their disease cannot be controlled with local resection and intravesical chemotherapy.

**TREATMENT**

The mainstay of management of superficial bladder cancer (T0–T1) is transurethral resection of bladder tumor (TURBT), with adjuvant intravesical therapy added in patients at high risk for recurrence or with partially resected in situ cancer (Table 56-3). Cystectomy is considered standard of care for patients with muscle-invasive disease (T2 and above).22 However, about 50% of patients with muscle-invasive disease will recur despite cystectomy. Several studies suggest a modest improvement in survival with neoadjuvant, aggressive combination chemotherapy prior to cystectomy for patients with muscle-invasive bladder cancer.23–25 There is no clear evidence, however, that chemotherapy administered after cystectomy is beneficial, but no high-level evidence is available to suggest that adjuvant chemotherapy is clearly different from neoadjuvant chemotherapy. Patients with muscle invasive bladder cancer that are not surgical candidates for cystectomy can be considered for definitive radiation therapy with concurrent systemic chemotherapy.26 Patients with stage IV bladder cancer have a poor prognosis with a median survival measured in months. Palliative...
systemic chemotherapy and radiation therapy targeted at symptomatic disease sites can be considered in addition to best supportive care. Very few patients with stage IV bladder cancer with pelvic lymph node involvement and no distant metastases have long-term survival with an aggressive combined modality approach.

**SURVEILLANCE**

Patients who have survived bladder cancer are at lifelong risk for recurrence and new primary cancers. Table 56-4 outlines the most commonly used surveillance plan; however, the plan should be individualized based on the patients’ risk of recurrence.

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### References

Kidney cancer is defined as any malignant tumor arising from the anatomical kidney. This includes renal cell carcinoma, urothelial carcinoma of the collecting system, sarcomas, pediatric tumors, lymphomas, and metastases. The following discussion is relevant to renal cell carcinoma or kidney cancer. For 2012, an estimated 64,700 new cases will be diagnosed, and 13,570 will die of this disease in the United States. The median age at diagnosis is 65 years and it affects men twice as often as women. The incidence of kidney cancer is increasing by 2% each year, and, with the increase in abdominal imaging, more than 50% of cases are diagnosed incidentally. The primary care clinician (PCC) is instrumental in ensuring these patients and patients with symptomatic kidney cancer are referred to urologic care in a timely fashion. Furthermore, the treatment of metastatic disease has improved significantly over the past 6 years, and the median survival of these patients is approaching 2 years. Many of the new treatments for kidney cancer cause hypertension, cardiovascular events, and metabolic and endocrine abnormalities, and PCCs are instrumental in managing these side effects. PCCs will also find themselves following patients who have undergone nephrectomy and are under surveillance for recurrence. This is of particular importance now because treatments for relapses or metastases are available; patients who have evidence of relapse will need prompt referral for additional therapy.

**PATHOGENESIS, RISK FACTORS, AND PATHOLOGY**

Tobacco exposure, hypertension, and obesity are the main risk factors for kidney cancer. Other less common risk factors include end-stage renal disease and polycystic kidneys. Familial syndromes are associated with 2% to 4% of kidney cancers, and these syndromes should be considered when a patient presents with the diagnosis of kidney cancer with an early age of onset and/or bilateral or multifocal disease (Table 57-1).

Renal cell carcinoma (RCC) comprises approximately 90% of all cancers arising from the kidney, and the main subtype of RCC is clear cell renal carcinoma (80%). Other cell types include papillary, chromophobe, and collecting duct tumors. Less than 10% of kidney tumors are urothelial carcinomas.

**SIGNS AND SYMPTOMS**

Early-stage kidney cancer rarely causes symptoms and is usually diagnosed when patients undergo imaging for other reasons. Patients in advanced stages may experience flank pain, a palpable flank mass, and/or hematuria. RCC metastasizes primarily to the lung, bone, brain, liver, and adrenal gland; and patients with metastatic disease may present with fatigue, cough, weight loss, bone pain, fever, lymphadenopathy, neurologic symptoms, or blood work abnormalities. Kidney cancers are also associated with several paraneoplastic syndromes (Table 57-2).

**DIAGNOSIS**

Most kidney cancers are diagnosed by computed tomography (CT) with intravenous contrast. Magnetic resonance imaging (MRI) can be used in patients with impairment of renal function.
function and for locally advanced disease to evaluate tumor invasion into structures such as the renal vein and vena cava. CT of the chest, bone scan, and MRI of the brain are used for staging when the patient is felt to be at high risk for metastatic disease. Positron emission tomography (PET) is not routinely used for the diagnosis or staging of kidney cancers.

Solid renal masses are usually not biopsied once surgical therapy is planned. This is because a solid renal mass has a greater than 90% chance of being a renal cancer, a negative biopsy does not reliably exclude cancer because of the heterogeneity of the tumors, and a biopsy positive for renal cell carcinoma will result in surgery anyway. The surgical procedure will generate the tissue diagnosis; patients are counseled in advance that their lesion may be benign. The risks of a needle biopsy are low; but if bleeding or a pseudoaneurysm does occur, then the surgery will be taking place under the worst of conditions instead of the best. Certainly, if there is suspicion regarding the diagnosis based on the appearance of the lesion or other factors, a biopsy should be performed to establish a tissue diagnosis.6

Biopsies should be performed in patients who are undergoing thermal ablation procedures to establish a tissue diagnosis or if there is a clinical suspicion of lymphoma, metastatic disease, or abscess7 because the identification of these would change the patient’s management.

### STAGING AND PROGNOSIS

Stage is the most important determinant of survival in kidney cancer8 (Table 57-3). Patients with larger tumors, invasion through the renal capsule, or invasion through Gerota’s fascia portend a worse prognosis following surgical therapy. Patients with metastatic disease have a median survival of 16 to 20 months with treatment. Poor prognostic features in advanced disease include high lactic dehydrogenase, anemia, hypercalcemia, a poor performance status, more than two organs involved with metastatic disease, and a short interval between the original diagnosis and the need for systemic therapy.9

### MANAGEMENT OF KIDNEY CANCER

#### Localized Disease

Selection of treatment in patients with localized disease takes into account the stage of the tumor and the patient’s kidney function reserve, comorbidities, and life expectancy (Table 57-4).10–14

Surgery is the principal established treatment for kidney cancer. Active surveillance with delayed intervention is an appropriate choice for patients with incidentally found kidney cancers who are elderly and/or have significant comorbidities. In patients under surveillance, the risk/benefit ratio of a curative intervention should be assessed periodically, especially in patients with rapidly growing masses. For years, given the presence of normal contralateral kidney, the treatment of choice for a newly diagnosed renal tumor was radical nephrectomy. Partial nephrectomy or nephron-sparing surgery11–13 involves removing the tumor and a small margin of healthy tissue rather than removing the entire kidney. It can be done either openly or laparoscopically.

---

**TABLE 57-2** Paraneoplastic Syndromes Associated with Kidney Cancer

- Erythrocytosis: occurs in 3% of patients, secondary to inappropriate secretion of erythropoietin from cancer cells
- Hypercalcemia: occurs in 5% of patients, poor prognosis, often associated with metastatic disease to the bones
- Fever
- Abnormal LFTs (Staufer syndrome), not associated with hepatic metastasis

*LFTs, liver function tests.*

**TABLE 57-3** TNM Staging of Kidney Carcinoma and 5-Year Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1NM0</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>II</td>
<td>T2 N0 M0</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>III</td>
<td>T1 N1 M0</td>
<td>59%–70%</td>
</tr>
<tr>
<td></td>
<td>T2 N1 M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 N0–N1 M0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>T4 Nany M0</td>
<td>&gt;10%</td>
</tr>
<tr>
<td></td>
<td>Tany Nany M1</td>
<td></td>
</tr>
</tbody>
</table>

*Table used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.*
and is the preferred approach for tumors smaller than 4 cm or in patients who have limited renal reserve. Percutaneous or laparoscopic thermal ablation is associated with an increase in local recurrence. However, it is a good option for patients who are not surgical candidates and have relatively small tumors.14

Renal tumors can invade the venous system of the kidney and extend into the renal vein; the infrahepatic, infrahepatic, suprahepatic vena cava; or heart. The level to which the tumor extends greatly influences the difficulty and risk of the operation but patients who successfully undergo such surgery can have long-term survival. The presence of extensive venous involvement should not be a hindrance to the referral of these patients for surgical therapy.15

### TABLE 57-4

<table>
<thead>
<tr>
<th>Modality</th>
<th>Indications and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active surveillance with delayed intervention</td>
<td>For elderly patients, patients with comorbidities</td>
</tr>
<tr>
<td>Radical nephrectomy (Open or laparoscopic)</td>
<td>Laparoscopic procedure preferred in competent hands; For stages II and III</td>
</tr>
<tr>
<td>Partial nephrectomy (Open or laparoscopic)</td>
<td>Tumors &lt;4 cm; Limited kidney reserve; Patients with familial renal cancer syndromes</td>
</tr>
<tr>
<td>Thermal ablation</td>
<td>Can be done laparoscopically or percutaneously under imaging guidance; Higher rate of local recurrence; For patients who are high-risk surgical candidates</td>
</tr>
<tr>
<td>Radiofrequency ablation</td>
<td></td>
</tr>
<tr>
<td>Cryoablation</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 57-5

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target/Mechanism of Action</th>
<th>Mode of Administration</th>
<th>Main Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 2</td>
<td>Immune therapy</td>
<td>IV</td>
<td>Capillary leak syndrome</td>
</tr>
<tr>
<td>Interferon</td>
<td>Immune therapy</td>
<td>IV or SC</td>
<td>Flu-like syndrome, hyperglycemia, depression, suicidal ideation</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Multitargeted tyrosine kinase inhibitor</td>
<td>PO</td>
<td>Fatigue, hypertension, proteinuria, renal failure, cardiomyopathy, hypothyroidism</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multitargeted tyrosine kinase inhibitor</td>
<td>PO</td>
<td>Fatigue, hand/foot rash, hypertension, proteinuria, cardiomyopathy, cardiac ischemia, hypothyroidism</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Mammalian target of rapamycin (mTOR) inhibitor</td>
<td>IV</td>
<td>Mouth sores, hyperglycemia, hyperlipidemia, pulmonary toxicity, hypothyroidism</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR inhibitor</td>
<td>PO</td>
<td>Mouth sores, hyperglycemia, hyperlipidemia, pulmonary toxicity, hypothyroidism</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGFR inhibitor</td>
<td>IV</td>
<td>Hypertension, proteinuria, arterial and venous clots, delay in wound healing, bowel perforation</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Multitargeted tyrosine kinase inhibitor</td>
<td>PO</td>
<td>Hand/foot rash, hypertension, skin hypopigmentation</td>
</tr>
<tr>
<td>Axitinib</td>
<td>VEGFR inhibitor</td>
<td>PO</td>
<td>Fatigue, hand/foot rash, hypertension, nausea, diarrhea, dysphonia</td>
</tr>
</tbody>
</table>

**TABLE 57-5** Biologic and Targeted Therapy of Metastatic Kidney Cancer

**Metastatic Disease**

Metastatic kidney cancer is rarely curable. High-dose interleukin 2 offers durable responses and cures in 5% to 15% of patients but with significant and sometimes life-threatening toxicity. Thus, it can be offered only to relatively young patients without comorbid conditions and has to be administered in a highly monitored unit by experienced providers.15 Interferon α has also been used extensively in metastatic renal cell cancer with very limited benefit, no durable long-term complete responses, and significant toxicity.17–19 Over the past few years, however, there has been enormous progress in the field with the development of multiple targeted therapies that have been shown to prolong survival in patients with metastatic kidney cancer (Table 57-5).20–31 Many of these agents are oral and, although they have a host of systemic side effects, many patients can receive them safely. As a result, the survival of patients with metastatic kidney cancer participating in clinical trials is more than 2 years.

Debulking nephrectomy in the metastatic setting has been shown to prolong survival in patients treated with interferon and may also be beneficial in some patients treated with newer targeted agents.17,18,32 It is unfortunate that these studies did not include a nephrectomy-only arm; it remains possible that nephrectomy alone extends the survival of patients presenting with metastatic kidney cancer. Further, randomized trials will be required to resolve this issue. At present, if the bulk of the tumor can be removed surgically with an expectation of minimal morbidity, then the kidney should be removed prior to systemic therapy.

**SURVEILLANCE**

After treatment for localized disease, patients have a significant rate of recurrence (10% to 60%, depending on their risk group).33 The National Comprehensive Cancer Network (NCCN) guidelines recommend history, physical exam, and blood work (complete blood count, chemistry panel, and lactate
dehydrogenase (LDH)) every 6 months for the first 2 years and then annually for another 3 years. Chest and abdominal imaging should be performed 2 to 6 months after the primary treatment to be used as a baseline, then as clinically indicated afterward.\(^{33,34}\) We recommend imaging of the abdomen (CT or MRI in younger patients to avoid radiation exposure) every 12 months for 5 years for stage I patients and every 6 months for patients with stage II or above. Patients with T1a lesions may require a less stringent follow-up regimen consisting of an annual physical examination, chest X-ray, and liver function panel.

References


Cancers of the Testicle, Urethra, and Penis

Marisa A. Kollmeier, MD

KEY POINTS

- Early-stage seminoma has excellent cure rates regardless of management strategy.
- Later stage seminoma requires adjuvant therapy following orchietomy.
- Nonseminoma patients are managed with a combination of surgery and chemotherapy.
- Urethral cancers are rare and require multimodality management.
- Early-stage penile cancers may be managed with surgery or radiation therapy, whereas later stage cancers require a multimodality approach.

TESTICULAR CANCER

Pathology
The two main types of testicular cancers are seminoma and nonseminoma. Seminomas appear morphologically similar to undifferentiated spermatogonial cells. Nonseminomas display various morphologies similar to different stages of embryonic development and rarely contain a single histologic type. If both seminoma and nonseminomatous cells exist, the treatment is as per nonseminoma.

Clinical Manifestations
The most common presentation of testicular cancer is painless testicular swelling. Some may describe a “heaviness” of the involved scrotum. Ten percent of patients will report testicular pain. Some may have a history of infertility or azoospermia. Advanced disease may present as a neck mass, pulmonary symptoms (cough, dyspnea), or back pain. Approximately 5% of patients report gynecomastia or breast tenderness.

Diagnosis/Workup
Any solid, fixed, non-transilluminating testicular mass in a young man should be presumed to represent testicular cancer until proven otherwise. A testicular ultrasound is the initial imaging of choice. Seminomas are typically well-defined hypoechoic solid masses, whereas nonseminomas appear heterogeneous and may contain cysts and/or calcifications. Serum tumor markers (STMs) (α-fetoprotein [AFP], human chorionic gonadotropin [hCG], and lactate dehydrogenase [LDH]) are drawn. Elevations in one or more markers are seen in ~80% of nonseminomas and 15% of seminomas. AFP elevation is not seen in pure seminoma. STMs are also important during follow-up.

The diagnosis of testicular cancer is made by prompt radical inguinal orchietomy with high ligation of the spermatic cord. A transscrotal biopsy is contraindicated because of potential tumor seeding. Staging evaluation includes a computed tomography (CT) scan of the abdomen and pelvis, chest imaging, and postorchietomy STMs. For patients with preorchietomy STM elevation, these levels should normalize at a rate consistent with the expected half-lives (AFP [5 days], hCG [24 hours]). Persistent STM elevation could indicate

Incidence/Epidemiology
The incidence of testicular cancer is increasing such that in 2012, an estimated 8,590 new testicular cancers will be identified in the United States. Fortunately, mortality has decreased from 17% to 4% in the last three decades largely because of cisplatin-based chemotherapy. Although rare (1% of all cancers), testicular cancer is the most common cancer in men aged 15 to 35 years. Caucasians have a higher incidence compared to other racial groups; however, in the United States, black men have a disproportionately increased incidence compared with other races over the last several decades.

Risk Factors
Most patients with testicular cancer have no discernible risk factor. Several associated conditions include a history of cryptorchidism (undescended testicle), impaired fertility, and a prior history of testicular cancer. Genetic disorders such as Klinefelter (47, XXY) syndrome, persistent Müllerian duct syndrome, and Down syndrome (trisomy 21) have been linked to testicular cancer. Familial risk, particularly among sibling cohorts, suggests a shared environmental exposure as well as a heritable risk.

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metastatic disease requiring additional management. Sperm banking should be suggested for patients who are interested in fertility preservation prior to adjuvant therapy, if indicated.

**Staging**

The American Joint Committee on Cancer (AJCC) TNM testicular staging system was revised in 1997 to include STMs (Table 58-1). For nonseminomas, the International Germ Cell Collaborative Group (IGCCG) classification system categorizes prognostic risk based on disease extent and STMs (Table 58-2).

**Adjuvant Therapy**

Additional therapy following orchiectomy may or may not be necessary depending on the stage and histology (Table 58-3). Surveillance is an option for some early-stage patients and has the advantage of avoiding treatment-related toxicity; however, it requires a motivated patient because frequent exams, imaging, and STM evaluation are required (Table 58-4). Several important differences exist between seminomas and nonseminomas and have implications for treatment and follow-up.

- Nonseminomas tend to grow and spread faster than seminomas and are less sensitive to radiation therapy (RT). Both tumor types are sensitive to chemotherapy.
- A retroperitoneal lymph node dissection (RPLND) is indicated for nonseminomas but not for seminomas.
- STMs are less reliable indicators of disease recurrence for seminomas.
- The time to relapse is longer for seminomas; hence, long-term follow-up is essential.
- Overall cure rates for seminoma are 90% to 100%; nonseminoma cure rates vary depending on risk group (see Table 58-2).

**Treatment-Related Toxicity**

During the posttreatment follow-up period, surveillance of patients for long-term side effects of therapy and/or...
region, is not uncommon. Chest imaging should be performed because lungs are the most common site of metastasis. Bone imaging may be reserved for symptomatic patients.

**Treatment**

Early-stage, distal urethral cancers may be managed with either surgery or RT. A bilateral lymph node dissection is typically performed, although sentinel nodal sampling may minimize morbidity. More advanced or proximal cancers require multimodality approaches including surgery, RT, and chemotherapy. External beam RT with interstitial brachytherapy and radiosensitizing chemotherapy may preserve organ function and avoid the morbidity of exenterative surgery. Long-term sequelae of urethral cancer treatment may include urethral strictures, urinary incontinence, penile edema or fibrosis, vaginal stenosis or foreshortening, and rectal or bladder fistulization.

**TABLE 58-4** National Comprehensive Cancer Network Guidelines for Surveillance

<table>
<thead>
<tr>
<th>History and Physical Exam; Serum Tumor Markers</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3–4 mo × year 1–2</td>
<td>CT of the abdomen/pelvis</td>
</tr>
<tr>
<td>Every 6–12 mo × year 3–4</td>
<td>- every 6 mo × year 1–2</td>
</tr>
<tr>
<td>Annually × year 5+</td>
<td>- every 6–12 mo × year 3</td>
</tr>
<tr>
<td>Annual × year 4–5</td>
<td>- annually × year 4–5</td>
</tr>
<tr>
<td>CT of the abdomen/pelvis</td>
<td>- as clinically indicated year 1–5</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td></td>
</tr>
</tbody>
</table>

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**Treatment**

Wide local excision or circumcision (for prepuce lesions) may be diagnostic and therapeutic for small, early-stage lesions. Superficial, early-stage lesions may be treated with external beam RT or interstitial brachytherapy with penile preservation rates of 70% to 85%. Partial or total penectomy with bilateral groin dissection is indicated for larger, more advanced lesions. Postoperative RT is given for multiple positive nodes or extranodal extension. Cisplatin-based chemotherapy may be integrated in the neoadjuvant, concurrent, or adjuvant setting. Long-term sequelae after treatment may include penile edema/fibrosis, urethral strictures, and lymphedema.

**References**

Breast Cancer

Gina G. Chung, MD • Hamid Saadati, MD • Mohammad Ali Raza, MD

CHAPTER

KEY POINTS

- Breast cancer is one of the most common causes of cancer-related deaths in women in the United States.
- Numerous risk factors have been identified such as family history, estrogen-related exposure, and lifestyle factors; however, most cases diagnosed are sporadic.
- Most breast cancers are diagnosed during screening mammography, although it can also present with clinical findings such as breast mass, asymmetric thickening/nodularity, nipple discharge, or diffuse dermatologic changes.
- Prognosis is dependent on stage as well as biologic factors such as ER/PR and HER2 status, grade, and lymphovascular invasion.
- Treatment for early-stage disease involves a multimodality approach with curative intent and includes locoregional and systemic treatments.

EPIEDEMILOGY AND RISK FACTORS

Breast cancer is the most common cancer diagnosis and the second leading cause of cancer death among women in the United States. The American Cancer Society estimates that in 2011, more than 229,000 cases of breast cancer will be diagnosed and nearly 40,000 will succumb to their disease. This translates to a 1:8 lifetime risk of invasive breast cancer. Although the overall incidence of breast cancer has increased since the 1970s presumably in part secondary to more widespread screening practices, since the late 1990s the incidence has declined significantly, which some have attributed to the decreased use of exogenous hormones. Breast cancer–related mortality however, has been declining since the 1990s. This latter trend is likely because of multiple factors, including earlier detection through screening and more effective treatments, particularly in early-stage disease. Although precise etiology is usually unknown, many associated risk factors for breast cancer have been identified (Table 59-1). The strongest risk factors are age and gender. The incidence of breast cancer rises steeply with age, slowing at age 45 to 50 years perhaps because of menopause, and peaking at about age 75 years. Male breast cancers account for approximately 1% of all diagnoses. White women have the highest rates of breast cancer, followed closely by Blacks, Hispanic/Latinas, Native Americans, and Asians. Other risk factors include a personal history of invasive or in situ breast cancer or benign proliferative breast biopsies such as atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH). A lengthening list of lifestyle-related factors with a positive (e.g., higher body mass index [BMI], tobacco, alcohol, high dietary fat intake) and negative (e.g., physical activity, calcium, and vitamin D intake) association with increased breast cancer risk have been identified, although some of the data are conflicting. Although many of these variables probably have real impact on overall risk, accurately quantifying this impact has been more difficult. In addition, reproductive and estrogen-related exposure factors such as younger age at menarche, later menopause, nulliparity, older age at parity, and the use of exogenous hormones contribute to an increased risk. Perhaps most notable are the results of the Women’s Health Initiative (WHI) study, which randomized postmenopausal women to an estrogen/progestin combination versus placebo. This showed that women receiving the combination had a significantly higher risk of developing breast cancer (1.2 hazard ratio [HR] at 5.6 years of follow-up, or an extra 2 patients per 1,000 women who develop breast cancer (1.2 hazard ratio [HR] at 5.6 years of follow-up, or an extra 2 patients per 1,000 women who develop breast cancer secondary to hormone replacement therapy). Moreover, post-intervention analyses showed a decline in the risk, suggesting that discontinuation of the hormone combination lowered breast cancer risk closer to placebo. Approximately 15% to 20% of patients diagnosed with breast cancer report a positive family history. In addition, specific genetic mutations have been identified that can predispose to breast cancer, although they account for only 5% of all breast cancers. The best characterized hereditary breast cancers are associated with germline mutations in the tumor suppressor genes BRCA1 or BRCA2, inherited in an autosomal dominant fashion. These two genes have multiple functions including roles in DNA repair and cell cycle check point regulation. Patients with identified mutations have an elevated lifetime risk of developing both breast and ovarian cancer, with estimates ranging between 50% to 85% and 15% to 40%, respectively. Thus, these patients should be carefully counseled regarding prophylactic/preventative options such as chemoprevention with tamoxifen (see the following text), bilateral mastectomy, and bilateral salpingo-oophorectomy (BSO). Several studies have shown that in very high-risk patients, prophylactic mastectomies provide risk reduction of 90% or more. Some data suggest that these patients may also have increased risk of developing other cancers including melanoma, prostate cancer, and pancreatic cancer; although...
Of atypical hyperplasia or lobular carcinoma in situ (LCIS). Arguably, a referral to a specialist in the field should also be considered. Table 59-2 summarizes these recommendations.

### PREVENTION

Two main classes of chemopreventive drugs exist: selective estrogen receptor modulators (SERM) (e.g., tamoxifen, raloxifene) and aromatase inhibitors (AI) (e.g., exemestane). A decision regarding the benefit of primary prophylaxis is made by clinical judgment combined with the Breast Cancer Risk Assessment Tool, often referred to as the Gail model (www.cancer.gov/bcrisktool). This model incorporates current age, race, age at menarche, age at parity, first-degree relatives with breast cancer, number of previous biopsies, and presence of atypical hyperplasia to calculate a woman’s 5-year risk of developing breast cancer as compared to women with average risk. It should be emphasized that the Gail model does not apply to women with established invasive and/or in situ carcinoma or known BRCA mutations.

The Breast Cancer Prevention Trial (P-1) study randomized more than 13,000 women who met their inclusion criteria for increased risk of breast cancer (age older than 60 years or age 35 to 59 years, with a 5-year predicted risk for breast cancer of at least 1.66% by the Gail model) to tamoxifen versus placebo for 5 years. This study showed that tamoxifen reduced the risk of invasive breast cancer by up to 43%. In a follow-up to this study, the Study of Tamoxifen and Raloxifene (STAR) trial (P-2) randomized a similar cohort of patients to either 5 years of tamoxifen or raloxifene. Raloxifene decreased the incidence of breast cancer by a nearly similar magnitude, although with fewer thromboembolic and uterine side effects. Thus, tamoxifen and raloxifene are both approved for the prevention of breast cancer in appropriately selected high-risk women. Early data have also shown similar preventive benefits for the AI exemestane. Although in general, well tolerated, significant side effects can occur with all of these medications; hence, extensive discussion regarding the individual’s risk/benefit ratio of treatment should be conducted. Perhaps the best candidates for chemoprevention are patients at high risk (e.g., Gail model score \( \geq 1.66\% \)) who are younger (greater overall benefit and less side effects) and/or have no uterus and/or have a history of atypical hyperplasia or lobular carcinoma in situ (LCIS). Arguably, a referral to a specialist in the field should also be considered.

### SCREENING

#### Modalities

Methods of screening include self-breast examinations, clinical breast examinations, and imaging. The clinical exam includes inspection and palpation of breasts for masses, asymmetry, nipple discharge, and skin changes (e.g., erythema, peau d’orange, dimpling, nipple retraction) and locoregional areas for lymphadenopathy. Unfortunately this intervention, and more so monthly self-breast examinations, has not been consistently shown to improve outcome, likely due in part to inadequate and nonstandardized techniques.

Mammography remains the primary screening modality for all women because of irrefutable data on its beneficial effects on breast cancer–related mortality. It is important to remember, however, that approximately 10% to 30% of cancers are not identified by screening mammograms depending on variables such as age, breast density, and prior breast surgery. Many centers now offer digital mammography and computer-aided detection (CAD), which provides high resolution computer images capable of electronic review, storage, and transfer, which is then analyzed by a computer program that highlights specific areas of concern for further review by a radiologist. In general, studies have shown a small advantage in detection rates for these techniques, particularly in younger (<50 years old) women, but at a higher cost and possibly increased false-positive rate. Screening ultrasounds (US) have been studied mainly as an adjunct to screening mammograms and have shown that whereas sensitivity may be increased, the specificity is decreased. The benefit of additional routine screening US in those with dense breasts is unknown. Magnetic resonance imaging (MRI) with gadolinium contrast is being used with increasing frequency, although much variability remains in technique and interpretation of images. MRIs are associated with significantly higher sensitivity but
lower specificity compared to standard mammography. As a screening modality, MRIs are usually reserved for those at highest risk (e.g., known BRCA mutation carrier). Currently, its principal role is in patients with an established diagnosis such as in determination of locoregional extent, presence of multifocal and bilateral disease, and response to neoadjuvant chemotherapy.

**Screening Guidelines**

Numerous expert groups in the United States have outlined somewhat discordant screening recommendations for average-risk women. Undisputed is the recommendation to initiate screening at age 50 years, because randomized trials and meta-analyses have demonstrated a significant reduction in breast cancer mortality with screening mammograms for women aged 50 to 69 years. The main controversy lies in recommendations for women aged 40 to 49 years and 70 years and older as well as frequency of screening. In the younger age group, although most modern randomized studies and meta-analyses have shown a reduction of mortality similar to older women, because the incidence of breast cancer in this population is lower, the number needed to screen (and hence the cost-effectiveness) to prevent one breast cancer–related death is much greater. There is a scarcity of data for screening targeted specifically at older women. Although mammograms are likely to lead to earlier detection, the comorbidities, life expectancy, and desires of individual patients should be carefully weighed when making decisions regarding screening in this population.

**Special Populations**

Patients in a high-risk group (categorized by some as those with a lifetime risk of developing breast cancer of 25% or greater) include women who had previous therapeutic thoracic irradiation and those with documented BRCA mutations. In this high-risk group, more intense surveillance should be initiated including mammogram and possibly MRI, performed every 6 to 12 months.

**DIAGNOSIS AND INITIAL EVALUATION**

Currently in the United States, most breast cancers are diagnosed through mammographic surveillance. For all patients with a positive clinical finding or an abnormal screening mammogram, a diagnostic mammogram should be performed. This differs from a screening mammogram in that it is supervised by a radiologist who tailors the additional views to best characterize the abnormality, inclusive of spot compression and magnification views. Highly suspicious findings on mammogram and/or US warrant a breast biopsy. The methods to obtain diagnostic tissue include fine needle aspiration (FNA), stereotactic/core needle biopsy, and surgical biopsy/excision. Although the low cost and minimal invasiveness of FNA are attractive qualities, its accuracy is substantially less than the latter two approaches in inexperienced hands, often leading to a second diagnostic procedure. Furthermore, histologic evaluation is inadequate because it often cannot distinguish between in situ and invasive disease. A surgical excision is also not recommended as the initial diagnostic procedure unless core biopsy is not feasible or nondiagnostic. The initial diagnostic procedure of choice therefore is a percutaneous biopsy with image guidance (mammographic/stereotactic, US, or MRI). This has high diagnostic yield with minimal morbidity and allows appropriate histologic evaluation and surgical planning prior to the definitive therapeutic procedure.

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**TABLE 59-2 Breast Cancer Chemoprevention Considerations**

<table>
<thead>
<tr>
<th>Age</th>
<th>Comments</th>
<th>Agent (Duration 5 Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 y</td>
<td>All patients potentially eligible based on entry criteria for prevention studies, especially if other risk factors present (e.g., high Gail model score, history of ADH); however, more likely to suffer side effects and probably less overall long-term benefit</td>
<td>Tamoxifen, raloxifene, or aromatase inhibitor</td>
</tr>
<tr>
<td>35–59 y</td>
<td>With associated risk factors (e.g., high Gail model score, history of ADH) may be good candidates</td>
<td>Premenopausal: tamoxifen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postmenopausal: tamoxifen, raloxifene, or aromatase inhibitor</td>
</tr>
<tr>
<td>Gail model risk factor ≥1.66%</td>
<td>All patients aged ≥35 y potentially eligible, especially if other risk factors present (e.g., history of ADH)</td>
<td>Premenopausal: tamoxifen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postmenopausal: tamoxifen, raloxifene, or aromatase inhibitor</td>
</tr>
<tr>
<td>Atypical hyperplasia (ADH or ALH)</td>
<td>All patients potentially eligible if age ≥35 y and Gail model risk factor ≥1.66%</td>
<td>Premenopausal: tamoxifen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postmenopausal: tamoxifen, raloxifene, or aromatase inhibitor</td>
</tr>
<tr>
<td>LCIS</td>
<td>All patients potentially eligible if age ≥35 y</td>
<td>Premenopausal: tamoxifen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postmenopausal: tamoxifen, raloxifene, or aromatase inhibitor</td>
</tr>
<tr>
<td>Known genetic mutation</td>
<td>Probable benefit in those with known BRCA1 and BRCA2 mutations, although limited data available. BRCA2 carriers may have greater benefit.</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Side effect concerns</td>
<td>Presence or absence of uterus</td>
<td>Primarily: tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Risk for thromboembolism</td>
<td>Primarily: tamoxifen</td>
</tr>
<tr>
<td></td>
<td>History of or risk for osteoporosis</td>
<td>Aromatase inhibitor</td>
</tr>
</tbody>
</table>
In a young patient (e.g., ≤30 years of age) with an abnormality such as a mass, spontaneous nipple discharge, or asymmetric thickening/nodularity, the initial diagnostic modality is a breast US usually accompanied by a mammogram, except perhaps in those whose US is consistent with a cyst in which an aspiration, biopsy, or excision can be considered. Because the use of mammograms in young patients is less clear, however, patients with indeterminate or suspicious US and normal mammograms should probably still have a diagnostic procedure. For older women with a clinical abnormality, a mammogram (sometimes with a targeted US) should be performed prior to a diagnostic procedure to determine the extent of abnormality, detect other abnormal areas that may require biopsy, and to prevent any distortion of the image that may result from the procedure (e.g., hemATOMA). Of special note, a relatively uncommon form of breast cancer called inflammatory carcinoma typically presents with rapidly progressive skin changes such as nodular erythema and dermal edema (peau d’orange) with or without associated breast mass or imaging abnormalities. Early recognition is important given its aggressive behavior and sensitivity to chemotherapy. Thus, suspicion for this diagnosis should initiate urgent imaging evaluation and a referral to a breast specialist.

Once a diagnosis of invasive carcinoma is established (or after presentation of a suspicious clinical finding), referral to the appropriate treating clinician should be facilitated. In most cases, the initial referral is to a surgeon, preferably with expertise in breast oncology. A multidisciplinary team of providers including a medical oncologist and radiation oncologist would then evaluate the patient to provide a comprehensive treatment plan. Patients with higher risk disease (e.g., stage III, symptomatic) may undergo staging studies (e.g., computed tomography [CT] scan, bone scan, or positron emission tomography [PET]–CT scan) to evaluate for the presence of distant metastases. A summary of initial workup for newly diagnosed patients is provided in Table 59-3.

**TABLE 59-3**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detailed history and physical examination</td>
<td>All patients</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td>CBC, liver function tests, calcium as a minimum. Tumor marker, circulating tumor cells, etc., not recommended</td>
</tr>
<tr>
<td>Staging scans</td>
<td>For patients deemed higher risk (stage III, extensive nodal involvement, clinically symptomatic) CT scan of the chest/abdomen/pelvis and bone scan, PET–CT, symptom-directed imaging (e.g., brain CT or MRI if neurologic symptoms)</td>
</tr>
<tr>
<td>Cardiac evaluation</td>
<td>Prior to anthracycline-based chemotherapy (e.g., doxorubicin) or trastuzumab Echocardiography or multiplegated acquisition (MUGA)</td>
</tr>
</tbody>
</table>

CBC, complete blood count; CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging.

**PATHOLOGY AND PROGNOSIS**

**Benign Breast Lesions**

Benign breast lesions refer to a spectrum of pathologic changes. The management of these abnormalities depends on their histologic classification and subsequent risk for developing breast cancer. Three broad categories are generally identified: nonproliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia. Nonproliferative lesions such as breast cysts, ductal ectasia, adenosis, and mild epithelial hyperplasia of usual type do not confer increased risk of breast cancer. Proliferative breast lesions without atypia can present with a clinical abnormality or found incidentally on a biopsy and include usual ductal hyperplasia, sclerosing adenosis, intraductal papilloma, radial scar, and fibroadenomas. These lesions are associated with approximately a 1.5-fold to twofold increased risk of developing breast cancer, and in general, women with these abnormalities are not recommended for chemoprevention strategies in the absence of other significant risk factors. Usual ductal hyperplasia and sclerosing adenosis do not require further treatment after biopsy because of low risk of future breast cancer. Surgical excision is, however, usually performed after a biopsy, showing intraductal papilloma or radial scar to rule out foci of more histologically advanced lesions. Fibroadenoma is the most common benign breast neoplasm. Asymptomatic simple fibroadenomas do not necessarily require excision and can be followed with short-interval imaging. Surgical excision is indicated for complex fibroadenomas and for simple fibroadenomas observed to be increasing in size on 3- to 6-month interval US imaging.

Proliferative lesions with atypia include ADH and ALH and confer a fourfold to fivefold increased risk of developing breast cancer. Such lesions are usually found on core biopsies of mammographic or palpable breast abnormalities. Additional tissue sampling with surgical excision is indicated to exclude in situ or invasive breast cancer. Patients with atypical hyperplasia should be considered for chemoprevention.

**In situ Breast Carcinoma**

Although ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) are often discussed in parallel, in fact they have distinct incidences, presentations, biologic behavior, and management. LCIS is a relatively uncommon finding, often clinically and mammographically silent and incidentally found on a biopsy. Its primary importance stems from the fact that it is a marker of future invasive carcinoma rather than a precursor lesion, with most studies showing a subsequent risk of developing invasive breast cancer approaching 1% per year. This is highlighted by its natural history and reflected by its management. Hence, LCIS is often multicentric and/or bilateral, histology of subsequent invasive carcinoma is most commonly ductal rather than lobular, and the incidence of contralateral invasive carcinoma is similar to that of ipsilateral carcinoma. Surgical excision is usually recommended after a needle biopsy to rule out the presence of adjacent DCIS or invasive carcinoma; however, wide excision with negative margins and/or radiation does not have a role. Additional management considerations following diagnosis include close surveillance (e.g., clinical exam and mammogram every 6 to 12 months), chemoprevention (see previous text), or bilateral mastectomies (not routinely recommended).
Breast cancer screening advocacy and advances in breast imaging modalities have led to a dramatic increase in the diagnosis of DCIS. In contrast to LCIS, DCIS is considered a precursor lesion to future invasive carcinomas. Thus, treatment for DCIS is primarily targeted toward optimal local management. Mastectomy can result in cure for 99% of patients. However, most patients are excellent candidates for a lumpectomy. Multiple randomized studies have shown equivalent overall survival but slightly higher local recurrence risk when lumpectomy combined with radiation therapy is compared with mastectomy. Radiation therapy can reduce the risk of local recurrence by up to 50%; however, this must be interpreted in the context of an already excellent prognosis after surgery alone, and recent investigations have focused on the safety of omitting radiation in selected patients. Models of predictive factors for local recurrence such as grade, size, and margin width may be helpful in determining appropriate postoperative management. For patients who undergo breast lumpectomy and radiation, tamoxifen has been shown to decrease the risk of ipsilateral and contralateral DCIS and invasive disease by up to 40%, although without significant overall survival benefit. Based on results from a recently published retrospective study, DCIS that is estrogen receptor (ER) positive may predict for benefit from tamoxifen, similar to data for invasive cancer.

Invasive Breast Carcinoma

About 85% to 90% of invasive carcinomas are ductal in origin, followed in incidence by invasive lobular carcinomas. A small subset of breast cancers includes mucinous, tubular, and adenoid cystic histologies and has particularly favorable prognoses. In a newly diagnosed patient, a detailed assessment of tumor stage is essential because this has critical prognostic and therapeutic implications. The American Joint Committee on Cancer and the Union for International Cancer Control (AJCC-UICC) is a standardized staging system that uses primary tumor characteristics (T), regional nodal involvement (N), and presence or absence of distant metastases (M). Table 59-4 summarizes this staging system and the associated prognoses.

In addition to stage, pathologic assessment of the tumor’s ER, progesterone receptor (PR), and human epidermal growth factor receptor (HER2) (erbB2) status is crucial because this yields important insight into the biologic behavior and natural history of the tumor. More importantly, these factors predict response to certain therapeutic strategies such as hormonal therapy (ER, PR) and trastuzumab (HER2). Various tissue-based assays such as immunohistochemistry (IHC) and in situ hybridization (ISH) have been used to determine the ER, PR, and HER2 status, although the optimal method is still somewhat unclear. The American Society of Clinical Oncology/College of American Pathologists provides updated guidelines based on appropriately designed and validated studies, which can be used as a standard measure. Although numerous additional prognostic factors have also been studied, the most consistently used and clinically validated are tumor grade, presence of lymphatic/vascular invasion, and possibly proliferation measures such as Ki-67.

**MANAGEMENT OF INVASIVE BREAST CANCER**

### Early-Stage Disease

Standard treatment for early-stage breast cancer is composed of locoregional and systemic treatments. Locoregional treatment consists of mastectomy or breast-conserving therapy (BCT) (i.e., lumpectomy and radiation), along with sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND). Multiple randomized studies comparing BCT to mastectomy have demonstrated slightly higher local recurrence but equivalent survival rates, making BCT the standard for appropriately selected patients. For most patients, SLNB is preferable to ALND because the false-negative rates are probably less than 5%, outcomes are comparable, and it is associated with less locoregional morbidity such as decreased arm mobility and lymphedema. External beam radiation is an integral part of BCT, demonstrating a significant reduction of recurrence and breast cancer–related mortality when compared with lumpectomy without radiation.

Traditionally, systemic therapy is given after definitive surgery as adjuvant therapy and is based on the tumor’s prognostic and predictive features, estimated risk reduction obtained from treatment, and anticipated side effects from treatment. In addition, online web-based programs such as Adjuvant! Online (www.adjuvantonline.com) are also available and can serve as a guide by giving quantitative assessments of risk and treatment benefits. Newer techniques using gene expression profiling strategies have also been developed to determine a tumor’s specific molecular signature. Currently, the most extensively validated and widely used assay is the 21-gene recurrence score (Oncomtype Dx), which provides an estimated 10-year projected relapse risk and potential benefit from chemotherapy for patients with node negative, hormone receptor–positive breast cancer.

In general, hormonal therapy is indicated for most patients with ER- and/or PR-positive breast cancer irrespective

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### TABLE 59-4: AJCC-UICC TNM Classification for Breast Cancer

<table>
<thead>
<tr>
<th>Stage*</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I T1</td>
<td>N0</td>
</tr>
<tr>
<td>I T1</td>
<td>N1mi</td>
</tr>
<tr>
<td>II T2</td>
<td>N0–1</td>
</tr>
<tr>
<td>III T1</td>
<td>N2</td>
</tr>
<tr>
<td>III T2</td>
<td>N2</td>
</tr>
<tr>
<td>III T3</td>
<td>N1–2</td>
</tr>
<tr>
<td>IV T4</td>
<td>N0–2</td>
</tr>
<tr>
<td>IV T any</td>
<td>N3</td>
</tr>
<tr>
<td>IV T any</td>
<td>N any</td>
</tr>
</tbody>
</table>

* T1: Tumor ≤20 mm in greatest dimension
  T2: Tumor >20 mm but ≤50 mm in greatest dimension
  T3: Tumor >50 mm in greatest dimension
  T4: Tumor with direct extension to the chest wall and/or to the skin
  N1: Metastases to movable ipsilateral axillary lymph node
  N2: Metastases to fixed ipsilateral axillary lymph node or to ipsilateral internal mammary node
  N3: Metastases to ipsilateral infracavicular lymph node, ipsilateral internal mammary and axillary lymph node, or ipsilateral supracavicular lymph node
  N1mi: N1micrometastasis
  M1: Distant metastases

AJCC-UICC, American Joint Committee on Cancer and the Union for International Cancer Control

of stage and additional systemic treatments (Table 59-5). For premenopausal women, tamoxifen, ovarian suppression/ablation, or both are effective. The Early Breast Cancer Trials’ Collaborative Group (EBCTCG) recently updated their meta-analyses of more than 21,000 patients randomized to 5 years of adjuvant tamoxifen versus no tamoxifen. This showed that tamoxifen decreased the 15-year relative risk of recurrence by 39% and breast cancer–related death by 31%.47 For postmenopausal women, both tamoxifen and AIs (anastrozole, letrozole, exemestane) are effective. However, because studies, which have compared tamoxifen versus AI, have all shown a significant disease-free survival (DFS) benefit and a nonsignificant trend toward an overall survival (OS) benefit for AIs, AIs are now considered the preferred option for these patients.44,48 Table 59-6 compares some of the most prevalent/significant side effects of tamoxifen and aromatase inhibitors.

Adjuvant chemotherapy has also been shown to reduce the relative risk of recurrence and breast cancer–related mortality by 27% and 21% in the recent EBCTCG meta-analyses.49 However, the absolute benefits are smaller than with hormonal therapy and profoundly affected by the absolute risk of these events. For patients with lymph node–negative breast cancers with higher risk features, chemotherapy in addition to hormonal therapy may be appropriate (see Table 59-5). For most patients with lymph node–positive disease and a good performance status, adjuvant chemotherapy is considered beneficial irrespective of other risk factors. For the approximately 20% of patients with HER2-positive breast cancer, the combination of trastuzumab—the humanized monoclonal antibody targeting the HER2 protein—with chemotherapy is recommended for most patients except for those with the lowest risk (e.g., node negative and tumors ≤0.5 to 1.0 cm). For patients who are ER and PR negative, in particular those who are ER/PR/HER2 negative (triple negative) who have a poorer prognosis, chemotherapy is indicated for most patients because hormonal therapy is not effective in this group.50 Although chemotherapy is usually given after surgery, a preoperative or neoadjuvant approach is favored for patients with locally advanced tumors or inflammatory carcinoma. For patients with potentially resectable tumors who are deemed appropriate for chemotherapy, this approach can also be used because studies have shown equivalent outcome compared to adjuvant chemotherapy with a greater likelihood of successful BCT.51

Metastatic Breast Cancer

Metastatic (stage IV) breast cancer is generally not considered curative, and therapy is given with the goal of prolonging survival and preserving quality of life. Although median survival is approximately 24 months, the prognosis is highly variable for an individual patient depending on certain patient- and disease-related factors. For example, patients with ER-/PR-positive cancer tend to have initial recurrences in bone and soft tissue rather than visceral organs and often have an indolent course. These patients may have a prolonged symptom-free period on hormonal therapy only. Newer targeted therapies such as trastuzumab when combined with chemotherapy can also prolong survival significantly for those patients with HER2-positive breast cancer.

In addition to the cancer-specific treatments outlined previously, various supportive care measures should be provided. Patients with skeletal metastases are often treated proactively with osteoclast inhibitors, either bisphosphonates or...
denosumab, given on 6–12-month schedules. These interventions have been shown to decrease skeletal-related events such as pain and narcotic use, pathologic bone fractures, and requirement for palliative radiation and surgery.\textsuperscript{52}

**SURVEILLANCE AND SURVIVORSHIP**

Patients receiving multimodality treatment for breast cancer often experience a multitude of short-term and/or long-term adverse effects and toxicities. The side effects of standard hormonal therapies are well documented and are described previously and in Table 59-6. The most common side effects for both classes however are vasomotor symptoms, which can significantly worsen the quality of life. Nonpharmacologic interventions are initially encouraged (e.g., avoiding precipitating factors, exercise, and weight loss); however, for moderate-to-severe symptoms, several non–hormonally based medications such as venlafaxine or gabapentin can be considered.\textsuperscript{53} Common short-term side effects of chemotherapy include systemic symptoms such as fatigue, pain, hot flashes; gastrointestinal symptoms such as nausea, emesis, mucositis, constipation, and diarrhea; bone marrow suppression; peripheral neuropathy; and alopecia. Fortunately, most of these symptoms are nearly wholly reversible. Long-term complications of chemotherapy include potential cognitive dysfunction, ovarian failure, and secondary leukemias and myelodysplastic syndromes (less than 1%). Both anthracycline chemotherapies and trastuzumab, especially when given together, are associated with a low risk of cardiomyopathy, thus necessitating baseline assessment of cardiac function prior to initiating these treatments. Corticosteroid premedication which is routinely given prior to most chemotherapies to minimize nausea and hypersensitivity reactions also cause hyperglycemia and sleep disturbances.

Breast cancer recurrence patterns are variable. However, about 50% of distant recurrences (most commonly in the bone, lung, and liver) occur more than 5 years after diagnosis, especially for patients with ER-/PR-positive cancer.\textsuperscript{54} Locoregional recurrences in general occur earlier, with the majority occurring within the first 5 years. Routine surveillance for breast cancer survivors includes periodic clinical visits and mammograms. More intense surveillance with increased frequency of visits and/or additional tests such as CT scans, bone scans, or serum tumor markers are not routinely recommended for asymptomatic patients because studies have failed to show an improvement in overall survival or quality of life.\textsuperscript{55}

Table 59-7 outlines key components of a breast cancer surveillance program. Finally, breast cancer survivors may experience the cumulative impact of psychological and physical complications from treatment. The fear of disease recurrence, altered body image, impact on fertility and sexual function, and resultant anxiety/depression should be recognized and treated early and is often best managed with the assistance of a survivorship program if available.

### TABLE 59-7

**Surveillance Guidelines After Breast Cancer Treatment**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended routinely</strong></td>
<td></td>
</tr>
<tr>
<td>History and physical exam</td>
<td>Every 3–6 mo for the first 3 y and every 6–12 mo thereafter</td>
</tr>
<tr>
<td>Mammography</td>
<td>Annually unless otherwise indicated. Minimum of 6 mo after radiation.</td>
</tr>
<tr>
<td>Gynecologic examination</td>
<td>Annually</td>
</tr>
<tr>
<td>Osteoporosis/fracture risk</td>
<td>Baseline bone mineral density (BMD) assessment and approximately every 2 y thereafter</td>
</tr>
<tr>
<td>Screening for genetic testing</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>Not recommended routinely</strong></td>
<td></td>
</tr>
<tr>
<td>Routine lab</td>
<td>NA</td>
</tr>
<tr>
<td>Imaging</td>
<td>NA</td>
</tr>
<tr>
<td>Tumor markers</td>
<td>NA</td>
</tr>
</tbody>
</table>

\textsuperscript{4}Serial measurement (e.g., every 6–12 months) of selected labs such as liver function tests, complete blood count, and calcium often performed although not routinely recommended.  

\textsuperscript{5}MRI, magnetic resonance imaging; NA, not applicable; CT, computed tomography; PET, positron emission tomography; CEA, carcinoembryonic antigen.
Epidemiology and Risk Factors

Ninety percent of primary ovarian cancers are epithelial in origin. Epithelial ovarian cancers (EOCs) are subclassified into serous, endometrioid, mucinous, and clear cell carcinomas. Nonepithelial ovarian cancers are sex cord-stromal cell tumors and germ cell tumors. One in 71 women will develop ovarian cancer during their lifetime, with a median age at diagnosis of 63 years. The most important risk factor for EOC is family history. Germline mutations of the BRCA1 and BRCA2 genes account for 10% to 15% of EOCs, with an estimated risk of ovarian cancer by age 70 years of 16% to 44% in BRCA1 carriers and 10% in BRCA2 carriers. Also, germline mutations in the mismatch repair genes such as MSH-2, MLH-1, or MSH-6 (Lynch syndrome) are associated with increased lifetime risk of ovarian cancer (3% to 14% compared to 1.5% in the general population). Additional risk factors for EOCs are nulliparity, early age at menarche, and late age at menopause. Oral contraceptives, lactation, tubal ligation, and hysterectomy are all associated with decreased risk. In women who carry deleterious mutations of BRCA1 or BRCA2, a significant risk reduction of ovarian and breast cancer is achieved by prophylactic bilateral salpingo-oophorectomy. The U.S. Preventive Services Task Force recommends against screening for ovarian cancer in the general population because of the low positive predictive value of an abnormal screening test such as CA-125, ultrasonography, or physical examination. Screening women at high risk (i.e., with known BRCA1 or BRCA2 mutation, and Lynch syndrome) who decide not to undergo prophylactic bilateral salpingo-oophorectomy is still under investigation but reasonable. In this scenario, the National Comprehensive Cancer Network (NCCN) recommends screening with CA-125 and transvaginal ultrasound every 6 months starting at the age of 30 to 35 years (or 5 to 10 years prior to the first ovarian cancer diagnosis in the family). Women who are undergoing screening should be aware that false-positive results are very common.

Clinical Manifestation, Diagnosis, and Staging

The challenge in early diagnosis of ovarian cancer is the nonspecific nature of symptoms and signs. Symptoms may include pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size and bloating, and early satiety...
(Table 60-1). Physical examination of a patient with ovarian cancer may reveal a palpable abdominal or umbilical (Sister Joseph’s nodule) mass, ascites, or pleural effusion. Pelvic exam may reveal a palpable mass in the adnexal region and/or cul-de-sac nodularity (best appreciated on rectovaginal examination). Paraneoplastic phenomena are rare but may include hypercalcemia, subacute cerebellar degeneration with associated anti–Purkinje cell antibodies, and seborrheic keratoses (Leser-Trélat sign).

Abdominal and transvaginal ultrasound is the most sensitive test to evaluate adnexal masses (sensitivity 91% and specificity 83%). Malignant lesions usually appear as complex cysts with a solid component, septations, and internal echoes. Doppler color flow imaging can aid in detecting neovascularization, which is a distinct feature of malignant lesions. Magnetic resonance imaging (MRI) is not superior to ultrasound in differentiation of malignant from benign ovarian tumors. Once a suspicious lesion is identified by ultrasound, magnetic resonance imaging (MRI) is recommended to confirm its vascularity. It is also useful to evaluate ultrasound abnormality, especially in deep-seated lesions. Tumor differentiation is increasingly dependent on immunohistochemistry and molecular analysis; for example, CD10 is found in most endometrioid carcinomas and mesothelial cells, whereas CA125 is not consistently expressed.

Carcinoma of the Ovary

Stage Description

I Tumor limited to ovaries (one or both)  
II Tumor involves one or both ovaries with pelvic extension

III Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis

IV Distant metastasis (excludes peritoneal metastasis)

5-Year Survival

>80%  
60%–70%

30%–50%

<15%

Carcinoma of the Uterus

Stage Description

I Tumor confined to the corpus uteri

II Tumor invades cervical stroma but does not extend beyond uterus

III Tumor involves serosa and/or adnexa (IIIA), vaginal or parametrial involvement (IIIB), pelvic (IIIC1), or paraaortic lymph node involvement (IIIC2)

IV Tumor invades bladder mucosa and/or bowel mucosa (IVA), distant metastasis including intra-abdominal metastasis (IVB)

5-Year Survival

75%–90%

70%

45%–60%

15%

Carcinoma of the Cervix

Stage Description

I Cervical carcinoma strictly confined to the cervix

II Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina

III Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctioning kidney

IV Tumor invades bladder mucosa of the bladder or rectum

5-Year Survival

>80%

58%–63%

35%

15%

Postoperative Medical Management

Postoperative chemotherapy is recommended for patients with high-risk stage I disease (surface involvement or capsule rupture or positive ascites/peritoneal washings or grade 3 tumors or clear cell histology) and all patients with stage II to IV disease. Chemotherapy consists of six cycles of intravenous carboplatin and paclitaxel; the total duration of therapy
is 18 weeks. The most common side effects of this regimen are myelosuppression, including 80% moderate-to-severe neutropenia and 10% moderate-to-severe thrombocytopenia, total alopecia in more than 95% of patients, neurotoxicity (30% experience at least mild sensory neuropathy), and gastrointestinal toxicity (nausea, vomiting, diarrhea, mucositis in about 10% of patients). An important advance in the management of ovarian cancer is intraperitoneal (IP) administration of chemotherapy, which is associated with improved progression-free and overall survival in patients with optimally debulked stage III disease. The benefit of IP therapy comes at a cost of significant toxicity including catheter-related complications, abdominal pain, metabolic abnormalities, and neuropathy. Nonetheless, the benefit of IP therapy has established it as one of the postoperative standard of care treatments appropriate for newly diagnosed patients with optimally debulked stage III disease.

**Prognostic Factors and Surveillance**

The most important prognostic factor for ovarian cancer is stage. Among patients with advanced disease, poor prognostic factors include residual disease >1 cm after initial surgery (suboptimal debulking), advanced age (≥65 years), high grade, and clear cell or mucinous histology.

Standard follow-up for patients in remission is presented in Table 60-3. Laboratory studies (complete blood count [CBC], chemistry) and imaging (computed tomography [CT], MRI, positron emission tomography [PET]-CT) are only obtained if there is any clinical suspicion of disease relapse. Genetic testing for germline mutations of the BRCA1 and BRCA2 genes is a standard recommendation for all patients who are diagnosed with ovarian cancer, recognizing the fact that even among unselected patients, the possibility of a BRCA1 and BRCA2 germline mutation is as high as 10% to 15%. Finally, although CA-125 is a useful predictor of recurrence, there is no evidence that early treatment of asymptomatic patients with chemotherapy based solely on an elevated CA-125 is associated with improved outcome or quality of life (QOL). Patients should discuss the pros and cons of CA-125 monitoring and the implications for subsequent treatment and QOL with their oncologist.

**UTERINE CANCER**

**Epidemiology and Risk Factors**

Most uterine cancers arise from the epithelium of the uterine lining and are referred to as endometrial carcinomas. Endometrioid adenocarcinoma is the most common histologic type (90%); the remainder 10% of endometrial cancers are papillary serous carcinomas, clear cell carcinomas, and carcinosarcomas. The median age of diagnosis for endometrial cancer is 61 years, and 75% of patients are postmenopausal. The major risk factor for endometrial cancer (endometrioid type) is chronic unopposed estrogen exposure, as in estrogen-only replacement therapy, chronic anovulation (as in polycystic ovary syndrome), low parity, early menarche, late menopause, tumors producing estrogens, and obesity. Long-term tamoxifen use as adjuvant therapy for breast cancer and in breast cancer prevention trials has been associated with a small but significant risk of endometrial cancer. A genetic predisposition is seen in 10% of endometrial cancer; in particular, women with Lynch syndrome have a 40% to 60% lifetime risk of uterine cancer. For these women, risk-reducing total hysterectomy (with the option of concurrent bilateral salpingo-oophorectomy to also prevent ovarian cancer) is recommended after they have completed childbearing. For these women, before hysterectomy or if they choose not to undergo surgery, screening is recommended with annual endometrial sampling starting at age 30 to 35 years or 5 to 10 years prior to the earliest age of first diagnosis of Lynch-associated cancer of any kind in the family.

**Clinical Manifestation and Staging**

The hallmark symptom (see Table 60-1) of endometrial cancer is abnormal uterine bleeding. All women older than age 40 years with abnormal uterine bleeding and all women older than age 35 years with atypical glandular cells on Pap smear should undergo endometrial biopsy to rule out endometrial cancer. The cornerstone for the treatment and staging of endometrial cancer is surgery. Comprehensive surgical staging (see Table 60-2) includes simple extrafascial hysterectomy (unless there is obvious cervical invasion in which case a radical hysterectomy is required), bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. Surgical cytoreduction is performed in the case of advanced disease. Lymphadenectomy may be avoided in women with minimally invasive low-grade tumors because of the low incidence of nodal metastasis. Unlike ovarian
cancer, most patients with endometrial cancer have stage I disease at presentation, which is associated with a 5-year survival of 80% to 90% (see Table 60-2). Risk factors of extraterine spread and disease recurrence are high grade, depth of myometrial invasion, cervical stroma invasion, tumor extension beyond the uterus, histologic subtype (clear cell, papillary serous, carcinosarcoma), lymphovascular invasion, and older age.

Postoperative Management of Endometrial Cancer and Surveillance

Women with endometrioid endometrial cancer confined to the uterus with no high-risk features are treated solely with surgery because the risk of relapse is less than 5%. Radiation therapy (RT) in the form of brachytherapy or pelvic external beam radiation therapy (EBRT) is recommended in early-stage disease with high-risk features because it has been shown to decrease the risk of local relapse, but there is no evidence that RT improves overall survival. Vaginal brachytherapy is generally well tolerated with minimal acute and late toxicity, whereas pelvic EBRT may be complicated by long-term bladder and bowel toxicity. Patients with advanced (stage III or IV) disease are usually managed with a combination of postoperative chemotherapy (combination of platinum [cisplatin or carboplatin] and paclitaxel and/or doxorubicin) and tumor-directed RT, although there is currently no evidence that addition of RT to chemotherapy improves survival. The optimal sequencing of chemotherapy and radiation and the optimal chemotherapy regimen is still under investigation. Patients with nonendometrioid endometrial adenocarcinomas (serous, clear cell, carcinosarcomas) are always treated with chemotherapy even when they have stage I disease because these histologies are associated with a very high risk of lymph node, abdominal, and systemic recurrence. RT is also administered after chemotherapy to decrease the risk of local relapse.

After completion of adjuvant treatment, patients are followed as shown in Table 60-3. Referral for genetic testing should be considered in patients with significant family history. Screening for Lynch syndrome is currently recommended for all women diagnosed with endometrial cancer younger than the age of 50 years.

CERVICAL CANCER

Epidemiology, Prevention, and Screening

Most cervical carcinomas originate at the transitional zone between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. The majority are squamous cell carcinomas (80%) and adenocarcinomas. Virtually all cases (>99%) of cervical cancer are associated with human papillomavirus (HPV) infection. Fifteen of the 40 genital mucosa HPV types are oncogenic, and the subtypes 16, 18, 31, 33, 45, and 58 are most commonly associated with cervical malignancies. Infection with one of the high-risk HPV is considered necessary for the development of cervical cancer. Gardasil, a quadrivalent HPV vaccine that targets HPV types 6, 11 (responsible for 90% of genital warts), 16, and 18, received U.S. Food and Drug Administration (FDA) approval in 2006 for the prevention of cervical intraepithelial neoplasia and cervical cancer and in 2010 for the prevention of anal intraepithelial neoplasia and anal cancer. Cervarix is a bivalent vaccine that targets HPV types 16 and 18; the FDA approved its use in 2009. The Advisory Committee on Immunization Practices (ACIP) recommends HPV vaccination in females aged 11 to 12 years. The vaccine may be administered as early as the age of 9 years and between the ages of 13 and 26 years, although its efficacy in this older population is not well established. For maximum benefit, the vaccine should be administered before the onset of sexual activity; nevertheless, a history of HPV infection, abnormal Pap smear, or genital warts is not a contraindication for HPV immunization.

Clinical Manifestation and Staging

Most common symptoms of cervical cancer are intermittent spotting, postcoital vaginal bleeding, and abnormal vaginal discharge (see Table 60-1). Patients with advanced disease may complain of pelvic or low back pain radiating to the lower extremities, bowel or urinary symptoms (pressure, hematochezia, vaginal passage of urine or stools), or bone pain and/or fractures. Unlike ovarian and endometrial cancer, staging of cervical cancer is clinical. This may include physical examination (pelvic examination and examination for distant metastasis, including palpation of inguinal and supraclavicular nodes), cervical biopsy (colposcopy with biopsy, conization, endocervical curettage), endoscopy (cystoscopy, proctosigmoidoscopy), chest and skeletal X-ray, intravenous pyelography, and barium enema. Although information regarding disease extension and lymph node spread obtained from imaging studies (i.e., CT, PET, and MRI) may guide management, this information is not included in the clinical staging (see Table 60-2).

Management of Cervical Cancer and Surveillance

Microscopic cancers invading <3 mm (stage IA1) are treated with cervical conization or extrafascial hysterectomy, whereas larger tumors with no parametrial invasion (up to stage IIA disease) may be treated with surgery (radical hysterectomy or trachelectomy [removal of uterine cervix only with preservation of uterine body] if <2 cm and fertility is desired) or RT (pelvic RT and intracavitary brachytherapy) (Table 60-4). RT (pelvic radiation and intracavitary brachytherapy) is generally preferred for bulky tumors that are larger than 4 cm (stage IB2 or IIA2). Locally advanced cancers (stage IIB to IVA) are managed by RT. Whenever RT is administered for management of cervical cancer, chemotherapy is also administered for radiosensitization. Several studies have shown that addition of chemotherapy (cisplatin...
alone or in combination with fluorouracil [5-FU]) during RT decreases the risk of death by as much as 50% as compared to radiation alone.\textsuperscript{18,19} Weekly cisplatin alone is most commonly used, although a recent study showed that addition of gemcitabine to cisplatin during and after RT may further improve outcome.\textsuperscript{20} Long-term gastrointestinal and genitourinary side effects (i.e., ureteral obstruction, rectovaginal fistula, vesicovaginal fistula) are observed in up to 13% of patients treated with RT. In particular, women who received RT are prone to vaginal stenosis, which can impact sexual function. For these women, the use of vaginal dilators is recommended starting 2 to 4 weeks after completion of RT and may be used indefinitely. Surveillance after completion of the primary treatment is summarized in Table 60-3.

### References

KEY POINTS

- Warning signs of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) include lesions that bleed, itch, or continuously scab over without healing.
- The ABCDE criteria (asymmetry, border irregularity, color variegation, diameter >6 mm, evolving) are useful in identifying lesions concerning for melanoma.
- Populations most at risk for skin cancer are those with fair pigmentation and a history of substantial sun exposure.
- Treatment of BCC, SCC, and melanoma is usually surgical but depends on tumor histology, site, and size as well as individual patient comorbidities.
- Key prevention intervention is sun protection.

Pathogenesis

The pathogenesis of BCC involves UV radiation–induced mutations in PTCH1—the tumor suppressor gene of the hedgehog signaling pathway that regulates cellular growth and development. This sets in motion a cascade of events that leads to uncontrolled cellular proliferation. UV radiation in the UVB (290 nm to 320 nm) and UVA (320 nm to 400 nm) spectrum both contribute to these mutations.

Clinical Manifestations

BCC most often occur not only on sun-exposed areas of the head, neck, trunk, and arms but may also occur on sun-protected sites. The classic nodular BCC is a shiny, translucent pink papule with overlying telangiectasias and rolled edges that grows slowly over months to years (Figs. 61-1 and 61-2). BCC can often bleed or itch intermittently (Table 61-1). Blood on the pillow is a common patient observation and the event that alerts them to the need for medical attention.

Diagnosis

Diagnosis is made by skin biopsy. A shave biopsy, performed using a flexible blade that can be contoured to the skin, is sufficient to make the diagnosis.

Staging and Prognosis

There are no set staging criteria for BCC largely because the cancer rarely metastasizes. Prognosis is excellent with appropriate treatment. If neglected, untreated BCC may lead to significant morbidity such as ulceration, disfigurement, or destructive injury to the eye, ear, or other important head and neck structures. Infiltrative and micronodular histologic variants of BCC are more locally aggressive than classic nodular or superficial BCC.

Treatment

Treatment of BCC is dependent on site, size, and histologic subtype. Surgical options include standard excision, electrodessication and curettage (ED&C), and Mohs microscopically controlled surgery. ED&C is a simple office procedure in which tumor tissue is removed with a curette and the base cauterized. Mohs surgery uses horizontal frozen sections and allows for complete margin analysis, which facilitates complete clearance of the cancer in a tissue-sparing fashion. In Mohs surgery, the surgeon excises, maps, and interprets the histology. Mohs surgery is indicated for BCC on the head and
Recently, an oral medication, vismodegib, was approved for the treatment of extensive or inoperable BCC. Vismodegib inhibits the hedgehog pathway by binding to Smoothened—a transmembrane signal transduction protein whose activation leads to tumor growth.

In select cases of BCC, topical treatment is an alternative to surgery. Topical 5-flourouracil cream and topical imiquimod ointment are currently approved for use to treat superficial BCC, less than 2 cm in size, on the trunk and extremities.

### TABLE 61-1 Symptoms and Signs of Skin Cancer

<table>
<thead>
<tr>
<th>Basal Cell Carcinoma</th>
<th>Squamous Cell Carcinoma</th>
<th>Malignant Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually exhibit slow growth</td>
<td>Growth may be slow or rapid.</td>
<td>Growth may be slow or rapid.</td>
</tr>
<tr>
<td>Pruritus, bleeding, or tenderness can occur.</td>
<td>Pruritus, bleeding, or tenderness can occur.</td>
<td>Pruritus, bleeding, and tenderness can occur as more advanced symptoms.</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiny, translucent pink papule with rolled edges; many other clinical appearances</td>
<td>Erythematous, crusted hyperkeratotic papule or plaque</td>
<td>Irregular pigmentation and/or border in a macule, patch, or nodule</td>
</tr>
<tr>
<td>Overlying telangiectasias common</td>
<td>Dome-shaped nodule with central crateriform dell (keratoacanthoma type)</td>
<td>ABCDE criteria useful in raising suspicion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A—Asymmetry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B—Border irregularity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C—Color variegation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D—Diameter &gt;6 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E—Evolving</td>
</tr>
</tbody>
</table>

Recently, an oral medication, vismodegib, was approved for the treatment of extensive or inoperable BCC. Vismodegib inhibits the hedgehog pathway by binding to Smoothened—a transmembrane signal transduction protein whose activation leads to tumor growth.
SQUAMOUS CELL CARCINOMA

SCC is a malignancy derived from epidermal suprabasal keratinocytes. The prognosis of cutaneous SCC depends on its biologic and histologic behavior. Superficially invasive SCC has a very favorable prognosis. On the other hand, aggressive or neglected SCC have an increased risk of metastasis, which can lead to death.

Risk Factors

Risk factors for development of SCC are identical to those for BCC and also include immunosuppression, chronic trauma, and carcinogen exposure. Solid organ transplant patients on immunosuppression are at a dramatically increased risk of developing SCC, with rates from 65 to 250 times higher than the average population.

Pathogenesis

SCC may arise de novo or from precancerous lesions called actinic keratoses. The specific percentage of AKs that will progress to SCC is estimated to be 8%, but studies vary. Bowen disease, or SCC in situ, refers to full-thickness epidermal atypia without underlying dermal invasion and is a lower risk counterpart of SCC. UV sun exposure–induced mutations in the p53 tumor suppressor gene and the RAS proto-oncogene family have been implicated in many cutaneous SCCs.

Clinical Manifestations

SCC presents as an erythematous papule, nodule, or plaque often associated with overlying crusting or ulceration (Fig. 61-3). Patients may report pruritus, bleeding, or tenderness at the site (see Table 61-1). SCC usually occurs not only on sun-exposed skin but can also occur at special sites such as the oral and genital mucosae, the nail bed, or within long-standing burns or scars. Precancerous AKs are gritty white, pink, or tan papules that are more readily felt than seen (Fig. 61-4); Bowen disease presents as a scaly erythematous patch or plaque that may resemble eczema.

Diagnosis

Diagnosis is made by skin biopsy with histologic evaluation by a board-certified dermatopathologist. A shave biopsy must be of adequate depth to allow for proper interpretation; a superficial biopsy may miss underlying invasive SCC.

Staging and Prognosis

Prognosis of SCC is favorable if treated appropriately and if high-risk features are not present, but aggressive SCC can lead to metastasis and death. SCC is responsible for approximately 20% of skin cancer–related deaths yearly. Clinical high-risk features include anatomic location on the lip and ear, recurrent tumors, size greater than 2 cm, and underlying
occur on the head and neck (Fig. 61-5). Superficial spreading melanoma is the most common clinical subtype, presenting as a brown-black, asymmetric macule with irregular coloration and borders (see Table 61-1).7 The back and the posterior legs are the most frequent sites of occurrence in men and women, respectively. Nodular melanoma presents as a black-to-brown papule or nodule that in many cases has undergone recent change or develops de novo. Acral lentiginous melanoma occurs on the palms and soles and is the most commonly seen melanoma variant in darker skin types. Acral lentiginous melanoma may affect the nail matrix, presenting as a dark pigmented band in the nail plate with extension onto the posterior nail fold (Fig. 61-6). Melanoma may rarely occur in special sites including the ocular choroid and mucosa of the oropharynx, genitalia, and rectum.

**Diagnosis**

Diagnosis is made by skin biopsy. It is important that the biopsy encompasses the breadth and depth of the lesion to allow proper interpretation of the Breslow depth (measured in millimeters) of the tumor. Options include a deep shave biopsy, punch biopsy for small lesions, and excisional biopsy.

**Staging and Prognosis**

Once the diagnosis of melanoma has been made, a complete history and physical examination should be performed. Patient history should include a thorough review of systems for constitutional, neurologic, respiratory, gastrointestinal, musculoskeletal, hepatic, dermatologic, and lymphatic immunosuppression. Histologic high-risk features include the presence of perineural invasion, single-cell spread, and poorly differentiated tumors.5 The American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Seventh Edition, includes staging for cutaneous SCC with a TNM classification, but the use of this staging system is controversial because reliable prognostic information for any given combination of risk factors is not currently available.

**MALIGNANT MELANOMA**

Malignant melanoma is responsible for most skin cancer–related mortality and will account for an estimated 9,180 deaths in 2012.6 The incidence of melanoma has been rising over recent years, presumably because of both behavioral and environmental factors. Melanoma can occur in all ages, from childhood to the elderly, with an average age of diagnosis of 52 years.

**Risk Factors**

Risk factors for development of melanoma include fair skin, blond or red hair, light eyes, and tendency to sunburn. UV sun exposure, artificial UV such as psoralens plus UVA (PUVA), and tanning bed use have all been associated with development of melanoma. Patients with greater than 100 typical nevi, multiple atypical nevi, or a personal or family history of melanoma are at increased risk.

**Pathogenesis**

Melanoma represents an uncontrolled proliferation of atypical melanocytes, the pigment-producing cells residing in the basal layer of the epidermis. Initially, melanoma in most cases grows radially in the epidermis prior to entering a vertical phase of downward growth into the dermis. If melanoma is diagnosed prior to dermal invasion, it is referred to as a melanoma in situ. Mutations in the CDKN2A pathway have been implicated in familial melanoma, which is also associated with pancreatic cancer. BRAF and p53 mutations have also been studied in relation to melanoma pathogenesis, and BRAF is a target in a novel chemotherapy agent for advanced melanoma.4

**Clinical Manifestations**

There are four main clinical subtypes of melanoma. Lentigo maligna, which is effectively melanoma in situ, appears as an irregular “liver spot” with indistinct borders and tends to occur on the head and neck (Fig. 61-5). Superficial spreading melanoma is the most common clinical subtype, presenting as a brown-black, asymmetric macule with irregular coloration and borders (see Table 61-1).7 The back and the posterior legs are the most frequent sites of occurrence in men and women, respectively. Nodular melanoma presents as a black-to-brown papule or nodule that in many cases has undergone recent change or develops de novo. Acral lentiginous melanoma occurs on the palms and soles and is the most commonly seen melanoma variant in darker skin types. Acral lentiginous melanoma may affect the nail matrix, presenting as a dark pigmented band in the nail plate with extension onto the posterior nail fold (Fig. 61-6). Melanoma may rarely occur in special sites including the ocular choroid and mucosa of the oropharynx, genitalia, and rectum.
Signs or symptoms. Any concerning findings or symptoms must be appropriately investigated with further studies (computed tomography/positron emission tomography [CT/PET] scan) to evaluate for metastasis. Physical examination should consist of a total body skin examination as well as palpation of all lymph node basins (regional and distant) for lymphadenopathy. If a suspicious lymph node is detected, the patient should be referred for fine needle aspiration or excisional biopsy.

Baseline screening chest X-ray and blood tests (complete blood cell count [CBC], liver function tests, lactate dehydrogenase [LDH]) are not typically recommended in the asymptomatic patient, regardless of Breslow depth, because these studies have not been shown to have a high yield for detection of metastasis, and false-positive results lead to significant patient anxiety.8 One exception is patients with stage IV disease in whom an elevated serum LDH has been associated with distant metastases and a poor prognosis.

The most important predictors of survival in melanoma are Breslow depth and presence of lymph node involvement (Tables 61-2 and 61-3). Melanoma in situ has an excellent prognosis with virtually no risk of metastasis. The risk of metastasis increases with increasing Breslow depth. Whereas invasive melanoma can metastasize to almost any organ in the body, metastasis most frequently occurs to the lymph nodes, lungs, skin, liver, brain, and bone. Patients with regional metastasis have a better prognosis than those with distant metastasis in whom prognosis is guarded.

### Treatment

For melanoma in situ, wide local excision with 5 mm margins is recommended.9 For invasive melanoma, wide local excision with 1 to 2 cm margins is recommended depending

---

**TABLE 61-2**

<table>
<thead>
<tr>
<th>T Classification</th>
<th>Thickness/Breslow Depth (in mm)</th>
<th>Ulceration Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| T1               | ≤1.00                           | A: without ulceration and mitosis <1 mm²  
B: with ulceration or mitoses ≥1 mm² |
| T2               | 1.01–2.00 mm                    | A: without ulceration  
B: with ulceration |
| T3               | 2.01–4.00 mm                    | A: without ulceration  
B: with ulceration |
| T4               | >4.00 mm                        | A: without ulceration  
B: with ulceration |

<table>
<thead>
<tr>
<th>N Classification</th>
<th>No. of Metastatic Nodes</th>
<th>Nodal Metastatic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| N1               | 1                       | A: micrometastasis⁴  
B: macrometastasis⁵ |
| N2               | 2–3                     | A: micrometastasis  
B: macrometastasis |
| N3               | 4 or more metastatic nodes, or matted nodes, or in-transit metastases/satellites without metastatic nodes |

<table>
<thead>
<tr>
<th>M Classification</th>
<th>Site</th>
<th>Serum LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>N/A</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

⁴Micrometastases are diagnosed after sentinel lymph node biopsy.  
⁵Macrometastases are clinically palpable nodal metastases that are confirmed pathologically.  
N/A, not applicable; LDH, lactate dehydrogenase.  

---

**FIGURE 61-6.** Hutchinson’s sign of acral lentiginous melanoma. This figure displays a wide, dark brown streak in the nail plate with extension onto the proximal nail fold. This extension onto the nail fold is known as Hutchinson’s sign and is seen in melanoma. Note: the most proximal black marking was placed with indelible pen to confirm with the patient the lesion of concern.
on the depth of the melanoma. Sentinel lymph node biopsy is advised in higher risk invasive melanomas with a Breslow depth of >1 mm without clinically palpable lymphadenopathy. Adjuvant treatment with interferon-α2b is considered for certain cases with surgically cleared melanoma but at high risk for recurrence.

Therapeutic options for metastatic melanoma are limited but include interleukin 2, dacarbazine, temozolomide, and melanoma vaccine trials. In 2011, two new therapies, ipilimumab and vemurafenib, were U.S. Food and Drug Administration (FDA) approved for patients with advanced melanoma.10 Ipilimumab is a monoclonal antibody that blocks cytotoxic T lymphocyte antigen 4 (CTLA-4), which normally functions to downregulate antitumor immune response. The most commonly reported adverse events of ipilimumab treatment include rash, diarrhea, and hepatotoxicity. Vemurafenib, a selective BRAF inhibitor, is generally well tolerated, with reported side effects including arthralgias, rash, and development of cutaneous SCC.11

Because of the biologic behavior of melanoma and the complexity of management of advanced cases, patients should be referred to physicians or centers that specialize in the multidisciplinary care of patients with melanoma.

### SURVEILLANCE

Patients with a history of skin cancer should undergo total body skin examinations routinely (Table 61-4). In patients with a history of melanoma, there should be a low threshold to biopsy lesions of concern to either the patient or the clinician. Patients should be educated on how to monitor their skin monthly for new or changing lesions and on the importance of sun protection. Sunscreens with sun protection factor (SPF) of at least 30 and with broad-spectrum UV A/UVB coverage are recommended and must be reapplied every 2 hours when outdoors.

---

**TABLE 61-3**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>5-Year Observed Survival Ratea</th>
<th>10-Year Observed Survival Ratea</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>81%</td>
<td>67%</td>
</tr>
<tr>
<td>IIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td>IIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
<td>70%</td>
<td>57%</td>
</tr>
<tr>
<td>IIB</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>53%</td>
<td>40%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1–4a</td>
<td>N1a</td>
<td>M0</td>
<td>78%</td>
<td>68%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1–4b</td>
<td>N1a</td>
<td>M0</td>
<td>59%</td>
<td>43%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1–4b</td>
<td>N2a</td>
<td>M0</td>
<td>59%</td>
<td>43%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1–4a</td>
<td>N1b</td>
<td>M0</td>
<td>43%</td>
<td>33%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1–4a</td>
<td>N2b</td>
<td>M0</td>
<td>43%</td>
<td>33%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1–4a</td>
<td>N2c</td>
<td>M0</td>
<td>33%</td>
<td>23%</td>
</tr>
<tr>
<td>IIIC</td>
<td>T1–4b</td>
<td>N1b</td>
<td>M0</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td>IIIC</td>
<td>T1–4b</td>
<td>N2b</td>
<td>M0</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td>IIIC</td>
<td>T1–4b</td>
<td>N2c</td>
<td>M0</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td>IV</td>
<td>T any</td>
<td>N any</td>
<td>M1</td>
<td>15%–20%</td>
<td>10%–15%</td>
</tr>
</tbody>
</table>

*aSource: American Cancer Society.


**TABLE 61-4**

<table>
<thead>
<tr>
<th>Basal Cell Carcinoma</th>
<th>Squamous Cell Carcinoma (SCC)</th>
<th>Malignant Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body skin examinations</td>
<td>Total body skin examination every 6–12 mo by a dermatologist or primary care clinician</td>
<td>Total body skin examination by a dermatologist with palpation of lymph node basins every 3–6 mo for the first 2 y following diagnosis, then every 6–12 mo thereafter. Complete review of systems should be performed at each visit, and any suspicious finding must be further investigated. Surveillance imaging (CT/PET scan) can be considered every 6–12 mo in patients with stage IIB melanoma or above for up to 5 y following diagnosis.</td>
</tr>
<tr>
<td>Patient education</td>
<td>Continued emphasis on importance of self-skin exams and sun protection</td>
<td>Continued emphasis on importance of self skin exams and sun protection</td>
</tr>
</tbody>
</table>

CT/PET, computed tomography/positron emission tomography.
References


KEY POINTS

- The incidence of non-Hodgkin lymphoma (NHL) has been rising at an average rate of 2.4% per year for the past four decades.
- Most patients do not have an identified risk factor to develop lymphoma; acquired or inherited immune disorders as well as certain viral and bacterial infections may play a role in pathogenesis.
- Clinical behavior varies widely for many lymphoma subtypes; indolent lymphomas may require only observation, whereas aggressive subtypes may require emergent hospitalization for diagnosis and initial therapy. A markedly elevated LDH in a patient with suspected lymphoma is a cause for alarm.
- Excisional lymph node biopsy is typically required to determine an accurate diagnosis.
- The addition of rituximab to chemotherapy has resulted in significant improvement of overall survival even in the poorest risk groups of patients with B-cell NHL.

LYMPHOMAS

Lymphoid neoplasms are malignant tumors of lymphoid tissues derived from clonal expansion of cells of the immune system. The World Health Organization (WHO) classification of lymphoid neoplasms includes greater than 50 discrete disease entities categorized into precursor or mature neoplasms. The mature lymphoid diseases are further categorized as diseases of B-, T-, or natural killer (NK) cell origin; Hodgkin lymphoma (HL); or immunodeficiency-associated lymphoproliferative disorders. Specific disease entities are recognized on the basis of the proposed cell of origin, morphology, cell surface markers, and gene alterations. 1-3 HL, although recently discovered to be a lymphoma of B-cell origin, is distinct from an epidemiologic, treatment, and survival perspective from the other lymphoid malignancies, which are collectively known as non-Hodgkin lymphomas (NHLs). NHLs are a heterogeneous group and vary widely in clinical aggressiveness (Table 62-1). Thirteen clinical entities comprise most diagnoses rendered by pathologists (Fig. 62-1); however, two diseases, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), account for more than 50% of cases. 4

An estimated 75,190 patients (40,880 men and 34,310 women) were diagnosed with lymphoma in 2011, and 20,620 were expected to die of the disease. There were 66,360 cases of NHL and 8,830 cases of HL. 5 NHL is the seventh most common cancer in males and the sixth most common cancer in females in the United States. Incidence increases significantly with age, with a median age of 66 years old at diagnosis. The age-adjusted incidence of NHL in the United States has risen by 82.5% in the past four decades, an average of 2.4% per year. 6,7 The acquired immunodeficiency syndrome (AIDS) epidemic, posttransplantation immunosuppressive drugs, and improved diagnostic techniques do not fully account for this rise. Certain subtypes of NHL vary by geographic location; for example, Epstein-Barr virus (EBV)–associated endemic Burkitt lymphoma (BL) presents with tumors of the jaw in

<table>
<thead>
<tr>
<th>Group</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent non-Hodgkin lymphomas</td>
<td>Follicular lymphoma (FL) grade I–II</td>
</tr>
<tr>
<td></td>
<td>Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)</td>
</tr>
<tr>
<td></td>
<td>Marginal zone lymphoma (MZL)</td>
</tr>
<tr>
<td></td>
<td>Lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM)</td>
</tr>
<tr>
<td></td>
<td>Hairy cell leukemia (HCL)</td>
</tr>
<tr>
<td></td>
<td>Mantle cell lymphoma (MCL)</td>
</tr>
<tr>
<td></td>
<td>T-cell large granular lymphocytic leukemia (T-LGL)</td>
</tr>
<tr>
<td></td>
<td>Mycosis fungoides (MF)</td>
</tr>
<tr>
<td>Aggressive non-Hodgkin lymphomas</td>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
</tr>
<tr>
<td></td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Follicular lymphoma (grade III)</td>
</tr>
<tr>
<td></td>
<td>B- or T-cell prolymphocytic leukemia (PLL)</td>
</tr>
<tr>
<td></td>
<td>Peripheral T-cell lymphoma (PTCL)</td>
</tr>
<tr>
<td></td>
<td>Anaplastic large cell lymphoma (ALCL)</td>
</tr>
<tr>
<td>Highly aggressive non-Hodgkin lymphomas</td>
<td>Burkitt lymphoma (BL)</td>
</tr>
<tr>
<td></td>
<td>Precursor B-cell leukemia/lymphoma</td>
</tr>
<tr>
<td></td>
<td>Precursor T-cell leukemia/lymphoma</td>
</tr>
</tbody>
</table>
African children, whereas sporadic BL is seen in the United States and typically presents with an abdominal mass and EBV is absent.

HL comprises about 10% of all lymphomas. In the United States and Western Europe, there is a peak in young adults aged 15 to 35 years and a peak in older patients around 60 years old. Males have a slightly increased risk compared to females.9,10 HL arises from germinal center or postgerminal center B cells and contains a minority of neoplastic cells (Reed-Sternberg cells and their variants) in a background of inflammation.

Risk Factors
The risk of developing NHL is increased in individuals with first-degree relatives with NHL, HL, and leukemia.11 Most patients with lymphoma, however, have no identifiable risk factor. Nevertheless, strong evidence exists supporting the role of immune dysfunction or microbial infection in the pathogenesis of many lymphoma subtypes. Both acquired and inherited disorders of the immune system such as Sjögren disease, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Wiskott-Aldrich syndrome, ataxia telangiectasia, and common variable immunodeficiency are all associated with significantly increased risk of NHL.12–14 Viral infections are associated with multiple NHL subtypes including EBV (BL, DLBCL of the elderly, AIDS-related and transplant-related NHL), Kaposi sarcoma–associated herpesvirus (HHV-8) (AIDS-related body cavity–based lymphomas), human T-cell lymphotropic virus type I (HTLV-I) (adult T-cell leukemia/lymphoma), and hepatitis C virus (HCV) (splenic MZL and lymphoplasmacytic lymphoma [LPL]).15–21 The bacterium Helicobacter pylori, which commonly colonizes the gastric mucosa resulting in ulcers, causes chronic antigenic stimulation giving rise to malignant B-cell clones and mucosa-associated lymphoid tissue (MALT) lymphomas.22 Regression of MALT lymphomas following eradication of helicobacter with antibiotic therapy provides strong evidence for the etiologic role of the infection. Such observations suggest that genetic variation in immune response to infection may influence the risk of developing NHL. NHL has also been associated with several environmental and occupational exposures such as high levels of nitrates in drinking water, solar ultraviolet light, pesticides, as well as dark and permanent hair dyes used before 1980. An increased risk is seen with a high-fat diet and meat intake. In addition, tobacco use has been associated with increased risk in some studies.7

Risk factors for the development of HL include growing up in single-family homes, with small family size, and lack of exposure to childhood viral illnesses. The risk of developing HL is threefold to fivefold higher in family members of patients with HL. This may be a result of genetic susceptibility or common environmental exposure. The risk in identical twins is increased about 100-fold.3,23

Pathogenesis
It is believed that the lymphoid neoplasms arise from B or T cells, which have arrested at specific stages of differentiation and have undergone lymphoma-specific oncogene rearrangements.24 Chromosomal translocations resulting in activation of oncogenes or inactivation of tumor suppressor genes are typical of NHL and provide malignant cells with a growth and survival advantage. For example, the translocation t(8;14) (q24;q32) is characteristic of BL and juxtaposes the c-MYC gene on chromosome 8 to the immunoglobulin (Ig) heavy chain promoter on chromosome 14 (IGH locus at 14q32), resulting in overexpression of the transcription factor c-MYC. In contrast, in anaplastic large cell lymphoma, translocation t(2;5)(p23;q35) results in oncogenic fusion of two genes (nucleophosmin/anaplastic lymphoma kinase [NPM/ALK]) and activation of the tyrosine kinase ALK. Although recurrent translocations involving oncogenes are lacking in HL, multiple chromosomal abnormalities have been described, and overall genomic instability may play a role in pathogenesis.25

Clinical Manifestations
Patients with NHL usually present with painless swelling of lymph nodes (Table 62-2). Nodes greater than 1 cm in short-axis diameter are considered enlarged. Because most patients with adenopathy will not have NHL, other causes of lymph node enlargement should be excluded. Considerations include bacterial, viral (including HIV and HTLV-1 in patients from endemic regions), mycobacterial, protozoal, spirochete, as well as autoimmune conditions such as lupus, RA, and Still disease. Among malignant etiologies, squamous cell carcinoma of the head and neck, melanoma, and leukemia should be considered. A diagnosis of lymphoma should be suspected in patients who are experiencing B symptoms (defined in Table 62-2). These may occur in up to 40% of patients. Indolent lymphomas may present with waxing and waning of lymphadenopathy of several months’ duration and even spontaneous regression. At the time of diagnosis, indolent lymphomas are often stage IV, involving the bone marrow. On the contrary, highly aggressive lymphomas present with rapid lymph node enlargement, and death may occur within weeks if left untreated. Important history points to elicit from patients are the location of the lymph nodes, the pace of lymph node enlargement, and symptoms referable to specific organs. Rapidly growing nodes require immediate referral to a surgeon and should be biopsied without delay. A hematologist–oncologist should be consulted for prompt institution of therapy.

More than half of patients with aggressive lymphomas will have involvement of organs outside of lymph nodes (extranodal)
table 62-3

<table>
<thead>
<tr>
<th>Symptoms and Signs of Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Swollen lymph nodes</td>
</tr>
<tr>
<td>Fever &gt;38°C, night sweats, weight loss &gt;10% of body weight in the 6 mo preceding the diagnosis (B symptoms) and fatigue</td>
</tr>
<tr>
<td>Early satiety (splenomegaly)</td>
</tr>
<tr>
<td>Headaches, visual changes, lethargy, seizures</td>
</tr>
<tr>
<td>Pain (bone lesions, pathologic fracture, or spinal cord compression)</td>
</tr>
<tr>
<td>Chest pain and shortness of breath (mediastinal masses, pleural effusions)</td>
</tr>
<tr>
<td>Abdominal pain, diarrhea, blood in the stools (bowel involvement)</td>
</tr>
<tr>
<td>Recurrent infections (hypogammaglobulinemia or functional hypoplasminemia)</td>
</tr>
<tr>
<td>Peripheral neuropathy (monoclonal protein production in lymphoplasmacytic lymphoma/Waldenström macroglobulinemia)</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Asymmetric enlargement of tonsils, base of tongue, nasopharynx (Waldeyer's ring)</td>
</tr>
<tr>
<td>Orbital swelling (mucosa-associated lymphoid tissue lymphoma, primary CNS lymphoma)</td>
</tr>
<tr>
<td>Papilledema, hemorrhages, retinal vein thrombosis (hyperviscosity in Waldenström macroglobulinemia)</td>
</tr>
<tr>
<td>Splenomegaly and/or hepatomegaly</td>
</tr>
<tr>
<td>Abdominal and testicular masses</td>
</tr>
<tr>
<td>Face/neck swelling (superior vena cava syndrome), ascites, lower extremity edema (venous obstruction)</td>
</tr>
<tr>
<td>Skin rashes (extranodal marginal zone lymphoma, primary cutaneous follicle center lymphoma, primary cutaneous diffuse large B-cell lymphoma leg type)</td>
</tr>
<tr>
<td>Cranial nerve abnormalities</td>
</tr>
<tr>
<td>Bone fractures</td>
</tr>
<tr>
<td>Raynaud’s phenomenon, urticaria, purpura, acral cyanosis (cryoglobulin precipitation in Waldenström macroglobulinemia)</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

such as the gastrointestinal (GI) tract, the skin, the central or peripheral nervous system, bones, or genitourinary system. About 10% to 35% of patients will have primary extranodal disease at presentation. The GI tract is the most common site of involvement, followed by skin. Skin may be the only organ involved or a manifestation of systemic disease. Neurologic manifestations may include spinal cord compression or radiculopathy resulting from leptomeningeal disease or epidural extension of tumor from involved vertebrae or paraspinal adenopathy. Primary central nervous system (CNS) lymphoma constitutes 1% of all NHL. A testicular exam should be performed in men, especially those who are older than the age of 60 years because NHL is the most common malignancy involving the testicle in this age group.

Hyperviscosity and neuropathy may result from monoclonal protein production in LPL/Waldenström macroglobulinemia. Macroglobulins that precipitate in the blood (cryoglobulins) may result in Raynaud’s phenomenon, urticaria, purpura, and acral cyanosis. For patients with headaches, visual changes, and suspected hyperviscosity, fundoscopic examination is indicated looking for hemorrhages, papilledema, and retinal vein thrombosis. Dilated and tortuous retinal veins have a characteristic “sausage-link” appearance.

HL involves primarily cervical, supraclavicular, and axillary nodes. It tends to spread in a contiguous fashion along lymphatic channels, although exceptions occur. About one-third of patients present with B symptoms, and this denotes a poorer prognosis. Some patients experience pruritus or, rarely, pain in enlarged nodes with alcohol ingestion. Dermatologic manifestations include eczema, erythema nodosum, acrokeratosis (Bazex syndrome), and ichthyosis.

**Laboratory Abnormalities**

Cytopenias may be related to marrow infiltration by disease, hypersplenism, or may be immune mediated such as immune thrombocytopenia or autoimmune hemolytic anemia. The peripheral smear in these cases may show large platelets, schistocytes, or spherocytes. Peripheral smear findings may suggest a diagnosis, such as hairy projections in hairy cell leukemia, villous projections related to splenic MZL, and smudge cells seen in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). A comprehensive metabolic panel may reveal elevations in uric acid, potassium, and phosphate as well as secondary hypocalcemia, which should raise suspicion for tumor lysis syndrome (TLS). Hypercalcemia may occur with aggressive lymphoma subtypes as a result of either bone destruction or excess vitamin D production by the lymphoma.

Elevations in lactate dehydrogenase (LDH) reflect either rapidly proliferating disease that requires prompt treatment such as in the case of BL, extensive tumor burden, liver infiltration by disease, or red cell destruction such as in immune-mediated hemolytic anemia. When greater than normal, LDH is associated with a poorer prognosis. It is in fact one of the five contributing risk factors to the predictive model of 5-year relapse-free survival and overall survival (OS) in patients with aggressive lymphomas (Table 62-3).

**Table 62-3**

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>Risk Group</th>
<th>4-Year Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Very good</td>
<td>94%</td>
</tr>
<tr>
<td>1–2</td>
<td>Good</td>
<td>79%</td>
</tr>
<tr>
<td>3–5</td>
<td>Poor</td>
<td>55%</td>
</tr>
</tbody>
</table>


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Abnormal viral serologies may be encountered and impact treatment decisions. Viral treatment or prophylaxis against reactivation may be required prior to initiation of chemotherapy and lymphocyte-depleting monoclonal antibodies such as rituximab. In addition, some malignancies are cured with treatment of the underlying infection alone such as in the case of HCV and splenic MZL or H. pylori and gastric MALT. Serum protein electrophoresis (SPEP) may detect a small monoclonal spike, such as in LPL. If this is an IgM spike, a diagnosis of Waldenström macroglobulinemia is suggested. If the IgM spike is greater than 4 g per dL, serum viscosity should be determined. β2-Microglobulin is also elevated in certain lymphomas and may be associated with worse prognosis. Quantitative serum immunoglobulins are often low in patients with CLL/SLL, resulting in recurrent infections, and can be repleted intravenously.

In patients with HL, abnormalities include leukocytosis, lymphopenia, thrombocytosis, normocytic normochromic anemia, elevated erythrocyte sedimentation rate (ESR), and hypalbuminemia, which are often associated with more advanced disease. Eosinophilia may be seen related to production of chemokines. There may be hypercalcemia related to excess calcitriol production or bone involvement.

HIV serology should be obtained in newly diagnosed patients with either NHL or HL.

### Oncologic Emergencies

Emergencies that require immediate hospitalization and treatment include cranial nerve palsies, lymphomatous meningitis, spinal cord compression, airway obstruction, superior vena cava syndrome, TLS, symptomatic hypercalcemia, hydronephrosis related to ureteral obstruction by tumor, severe autoimmune hemolytic anemia, and immune-mediated thrombocytopenia. TLS is common not only in patients with BL and precursor lymphoblastic leukemias/lymphomas but can also occur in patients with other aggressive lymphomas, such as DLBCL and mantle cell lymphoma (MCL), when there is large tumor burden, bulky disease (greater than 10 cm in diameter), and elevated LDH levels. Patients with CLL/SLL and white blood cell (WBC) count greater than 500,000 per µL are at increased risk as well. TLS can be spontaneous in the setting of rapidly dividing tumor cells with high turnover rates producing uric acid, or can be seen up to 7 days following chemotherapy from ongoing cell destruction. TLS has also been described following radiation therapy, treatment with steroids alone, or monoclonal antibodies such as rituximab. Patients with preexisting renal dysfunction, oliguria, and dehydration are at increased risk. Precipitation of uric acid and calcium phosphate crystals may result in renal failure. Other clinical features of TLS are cardiac arrhythmias and seizures related to electrolyte abnormalities. Patients with risk factors for TLS should receive intravenous hydration and allopurinol, which blocks new uric acid production. Patients in the very high-risk group, with already elevated uric acid levels and/or renal dysfunction, are generally treated with rasburicase, a recombinant urate oxidase, which oxidizes preformed uric acid to allantoin. Allantoin is significantly more soluble in acidic urine. This results in rapid decrease in serum and urine uric acid levels.

### Diagnosis

Lymphoma is usually diagnosed with a lymph node biopsy (Table 62-4). Lymph nodes that persist for more than 4 weeks in the absence of infectious symptoms, nodes that measure greater than 1.5 cm × 1.5 cm in perpendicular diameter, and those that grow rapidly should be biopsied. Location matters, as enlarged supraclavicular nodes, for example, are more often involved with malignancy, followed by axillary nodes, and less likely inguinal lymph nodes. Large or rapidly increasing nodes give better diagnostic yields. If peripheral nodes are present, those should be biopsied first. An excisional lymph node biopsy is the optimal procedure. If no peripheral nodes are accessible, a computed tomography (CT)-guided core biopsy or even a laparoscopic biopsy can be used. Fine needle aspiration (FNA) samples are generally inadequate because such specimens do not allow for accurate diagnosis of the lymphoma subtype, which is required for treatment decisions and prognosis. Adequate tissue obtained through excisional lymph node biopsy allows the pathologist to examine the morphology of tumor cells (i.e., small, intermediate, large) and patterns of involvement of the lymph node (i.e., nodular vs. diffuse). Furthermore, immunohistochemistry, flow cytometry, cytogenetics, fluorescence in situ hybridization (FISH), and molecular studies commonly used to classify the lymphoma can be performed. Examination of the bone marrow is also an important part of staging for lymphoma can be performed. Other sites may require evaluation based on symptoms and exam findings (Table 62-4).

### Staging and Prognostic Systems

To assess the extent of disease involvement in lymphoma, a contrast-enhanced CT scan of the chest, abdomen, and pelvis should be performed in all newly diagnosed patients. Positron emission tomography (PET) scan before treatment should be

### TABLE 62-4 Lymphoma—Initial Workup

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node biopsy (preferably excisional biopsy)</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood flow cytometry for indolent lymphomas (often negative in diffuse large B-cell lymphoma and HL)</td>
<td></td>
</tr>
<tr>
<td>CT chest/abdomen/pelvis with oral and IV contrast for staging</td>
<td></td>
</tr>
<tr>
<td>PET/CT whole body for diffuse large B-cell lymphoma and HL</td>
<td></td>
</tr>
<tr>
<td>MRI spine if cord compression is suspected</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram or nuclear study to evaluate cardiac ejection fraction</td>
<td></td>
</tr>
<tr>
<td>Bone marrow aspiration and biopsy for staging, with flow cytometry, cytogenetics, molecular studies</td>
<td></td>
</tr>
<tr>
<td>Spinal fluid evaluation with cytology and flow cytometry for highly aggressive lymphomas or symptomatic patients</td>
<td></td>
</tr>
<tr>
<td>Testicular exam and ultrasound if abnormal</td>
<td></td>
</tr>
<tr>
<td>Endoscopy with biopsy if GI involvement is suspected</td>
<td></td>
</tr>
<tr>
<td>Central venous access</td>
<td></td>
</tr>
<tr>
<td>Early referral to reproductive endocrinologist for patients who desire fertility</td>
<td></td>
</tr>
<tr>
<td>Hydration to prevent/treat tumor lysis</td>
<td></td>
</tr>
<tr>
<td>Allopurinol or rasburicase to prevent/treat hyperuricemia</td>
<td></td>
</tr>
</tbody>
</table>

CBC, complete blood count; LDH, lactate dehydrogenase; PT/PTT, prothombin time/partial thromboplastin time; ESR, erythrocyte sedimentation rate; HL, Hodgkin lymphoma; HIV, human immunodeficiency virus; CT, computed tomography; HL, intravenous; PET, positron emission tomography; MRI, magnetic resonance imaging; GI, gastrointestinal.
obtained in patients with typically FDG-avid, potentially curable lymphomas such as DLBCL and HL. PET scan can detect otherwise occult splenic involvement in HL and has replaced the role of surgery for staging. In indolent lymphomas, significant uptake on PET may raise concern for transformation to more aggressive disease. Several studies have demonstrated that PET negativity following the first few cycles of chemotherapy for HL is of prognostic importance. Complete disease response by PET at the end of treatment is required for DLBCL and HL.

The Ann Arbor staging system was initially developed for HL but has also been applied to NHL (Table 62-5). Four stages are based on anatomic sites of disease involvement, extent of disease, and presence or absence of B symptoms. Bone marrow, liver, or extralymphatic organ involvement prior to initiation of therapy indicate stage IV disease.33 The International Prognostic Index (IPI) for DLBCL identifies five risk factors, which independently predict survival.34 The addition of rituximab to anthracycline-based combination chemotherapy has almost doubled 4-year OS even for patients in the highest risk category (see Table 62-3).35 IPI has less predictive power in FLs. For this reason, an alternative index, FLIPI (Follicular Lymphoma Prognostic Index), was developed, which, in addition to age, Ann Arbor staging system, and elevated LDH, also takes into account hemoglobin levels less than 12 g per dL and involvement of more than four nodal areas. Five-year OS rates for the low-risk FL group were 91% compared to 78% for the intermediate-risk group and 53% for the high-risk group.36

The staging system in use for HL is the Ann Arbor staging system with Cotswolds modifications. In addition to the designations “E” and “X,” clinical stage was added, whereby involvement of the spleen and liver is accepted if detected with two imaging techniques.37 Patients with HL with early-stage disease are further stratified into favorable and unfavorable prognosis. Patients with favorable risk factors may have equivalent outcomes with less toxicity if lower intensity treatments are used compared to patients with early-stage disease and unfavorable risk factors or patients with advanced-stage disease. Several research groups have attempted to define favorable prognosis, but two of the most commonly used sets of criteria are those proposed by the German Hodgkin Study Group and the European Organization for Research and Treatment of Cancer (Table 62-6). Patients with Stage I and non-bulky Stage II disease without unfavorable risk factors have overall survival rates of greater than 95%.38,39 For patients with advanced HL, the International Prognostic Score (IPS) is used, which places in a higher risk category patients who are male, older than 45 years, with stage IV disease, anemia, leukocytosis with relative lymphopenia, and hypoalbuminemia. Treatment with combination chemotherapy in advanced disease, with or without radiotherapy, results in 5-year OS of 89% in the lowest risk group to 56% in the highest risk group.40

### Table 62-5

<table>
<thead>
<tr>
<th>Stage</th>
<th>Area of Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)</td>
</tr>
<tr>
<td>II</td>
<td>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 and of one or more lymph node regions on the same side of the diaphragm (IIIE)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localized involvement of extralymphatic organ or site (IIIIE), by involvement of the spleen (IIIS), or both (IIISIE)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement. Bone marrow and liver involvement are always stage IV.</td>
</tr>
</tbody>
</table>

Lymphoma Subtypes and Treatment Considerations

Treatment goals in NHL depend on the clinical course of disease, that is, indolent versus aggressive, stage of disease at diagnosis, performance status of the individual patient, and comorbidities. Indolent lymphomas, despite advanced stage at presentation, may have a more benign clinical course. Early initiation of therapy in asymptomatic patients does not improve survival, and such patients may therefore be offered a “watch-and-wait” approach. Treatment is reserved until symptoms develop or end-organ function is threatened. Goals of treatment for this group of patients include prolonging...
The amount of chemotherapy and dose of radiation differs for patients with favorable and unfavorable prognosis disease, and studies are ongoing to minimize toxicities without affecting therapeutic outcomes. Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) has become the standard of care for treatment of both early and advanced-stage HL largely because of high cure rates and reduced long-term toxicity compared to other regimens. Patients with advanced disease receive six cycles of ABVD without radiation therapy. Patients with relapsed disease may be treated with brentuximab, an anti–cluster of differentiation (CD) 30 monoclonal antibody.

**T-cell lymphomas** account for about 15% of NHL in the United States. Several subtypes are rare, with few patients diagnosed per year throughout the world. There are several major categories: extranodal T-cell lymphomas (i.e., NK/T-cell lymphoma nasal type, enteropathy-associated T-cell lymphoma, hepatosplenic T-cell lymphoma), cutaneous T-cell lymphomas (i.e., Sézary syndrome and mycosis fungoides), peripheral T-cell lymphoma not otherwise specified (NOS), anaplastic large cell lymphoma (ALK positive or negative), and angioimmunoblastic T-cell lymphoma. Cutaneous T-cell lymphomas and large granular lymphocyte leukemia are associated with a good prognosis. Many T-cell lymphomas, however, are aggressive and do not respond as well to conventional chemotherapy as B-cell lymphomas. Consolidation with high-dose chemotherapy and stem cell transplantation may be incorporated earlier in the treatment algorithm to reduce the risk of relapse.

Patients with relapsed HL and NHL receive second-line alternate “salvage” chemotherapy. Patients achieving a second partial or complete remission (CR) may be cured with subsequent high-dose chemotherapy followed by autologous stem cell rescue (using patient’s own stem cells). For more refractory cases, allogeneic stem cell transplantation is considered (using donor stem cells), with the added benefit of the donor’s immune system providing antilymphoma activity.

**Surveillance**

Patients with a history of lymphoma should be monitored for relapse and complications of treatment including secondary malignancies. Most relapses for aggressive NHL occur during the first 2 years after completion of treatment and are rare beyond 5 years. In HL, most relapses occur within the first 3 years after diagnosis, but a smaller fraction develop even after 10 years. Patients with indolent lymphomas on the other hand may relapse after many years of remission and are usually followed indefinitely. Relapses are detected more frequently based on symptoms rather than surveillance imaging studies. A biopsy should always be performed to document relapse before proceeding to salvage therapy. Aggressive screening is limited to those high-risk patients eligible for potentially curative salvage therapy. A thorough physical exam, complete blood count (CBC), chemistries, and LDH are performed as well as CT scans of the chest, abdomen, and pelvis when indicated. The National Comprehensive Cancer Network (NCCN) has published guidelines for follow-up of patients with HL and NHL. Patients with HL in complete remission should be followed with interim history and physical examination every 2 to 4 months for 1 to 2 years, then every 3 to 6 months for the next 3 to 5 years, with annual monitoring for late effects after 5 years. Patients with DLBCL should be followed every 3 months for 2 years then every 6 months for 3 years. Patients...
with indolent lymphoma should be followed every 3 months for a year then every 3 to 6 months.\textsuperscript{50,51}

Second malignancies have been reported for at least 30 years after treatment for HL, emphasizing the need for continued follow-up.\textsuperscript{52} These include chemotherapy-related myelodyplasia and acute nonlymphocytic leukemias, NHL, and solid tumors such as in lung, breast, and GI tract, which are usually related to radiation therapy. Secondary myelodyplasia and leukemias can be seen starting at 2 years following anthracyclines and topoisomerase inhibitors and 7 to 10 years later following alkylating agent–based chemotherapy. The rates of secondary malignancy with the narrowed fields of radiation currently in use are predicted to be lower than those previously seen with mantle fields. As the number of long-term disease-free survivors is increasing, mortality rates from causes other than HL in the 15 to 20 years posttreatment are exceeding those from HL.\textsuperscript{53}

In addition to routine age-appropriate cancer surveillance, more proactive screening is advocated in certain clinical scenarios. For example, females should undergo screening for breast cancer starting no later than the age of 40 years. If they have received mediastinal radiation, screening should begin 8 years after radiation or at the age of 25 years. For women who have received chest radiation between the ages of 10 and 35 years, screening should be with both mammography and magnetic resonance imaging (MRI).\textsuperscript{54} Annual complete skin exams should be performed to monitor for development of skin cancer. Unprotected sun exposure should be avoided. Cardiac risk factors (smoking, hypertension, hyperlipidemia, obesity) should be minimized. Cardiac evaluation should be performed in late survivors of chest radiation, especially beyond 10 years. Patients who have received radiation to the neck region or mediastinum should undergo yearly measurements of thyroid stimulating hormone (TSH) to diagnose hypothyroidism. These patients are also at risk for developing thyroid cancer. Risk of infertility is higher in patients who have received multiple chemotherapy regimens and high-dose chemotherapy followed by hematopoietic stem cell transplantation. Screening for depression or posttraumatic stress disorder should be performed annually. Patients should always be referred back to the treating hematologist/oncologist if questions or concerns arise.

References


and multiple myeloma. Although a cardinal feature of plasma cell disorders is the presence of clonal excess immunoglobulin production, it should be noted that both alternate malignancies and nonmalignant immune disorders may occasionally result in overproduction of clonal immunoglobulin molecules and must be distinguished from primary plasma cell disorders. Chronic lymphocytic leukemia and lymphoplasmacytic lymphoma are two such examples.

**RISK FACTORS**

Most patients diagnosed with a plasma cell disorder have no identifiable risk factor such as genetic predisposition or exposure to an etiologic agent. The risk to acquire these disorders is generally increased in first-degree relatives of affected individuals supporting a genetic predisposition, although the genetics of inheritance are in the early stages of investigation. Associations have been noted for occupational exposure to pesticides, petroleum products, organic solvents, and ionizing radiation; however, most patients have had no such exposures. Multiple myeloma occurs more frequently in men than women and in African Americans compared to Caucasians. Multiple myeloma is almost always preceded by MGUS, based on retrospective studies of stored blood samples from individuals who ultimately develop myeloma, wherein a monoclonal protein is found many years prior to the development of overt disease.

**PATHOGENESIS**

In MGUS and multiple myeloma, genetic translocations in immunoglobulin genes in B lymphocytes play a role in tumor development. Interactions between tumor cells and the bone marrow microenvironment mediated by cell surface molecules, adhesion molecules, and cytokines result in tumor growth and survival, promoting drug resistance and metastatic potential. Bone lesions are the result of both inhibition of osteoblastic activity as well as enhanced osteoclastic activity through the receptor activator of nuclear factor κB (RANK) pathway. Genetic aberrations may accumulate in persistent tumor cells, resulting in tumor progression, extramedullary spread, and plasma cell leukemia. In primary light chain amyloidosis mutations in immunoglobulin light chains allow for misfolding, resulting in protein aggregation and deposition in tissues causing injury to affected cells.
light chain molecules may have a normal total serum protein, normal serum protein electrophoresis (SPEP), and a negative urine dipstick for protein and may therefore elude diagnosis unless analysis of the serum and urine for free light chains (FLCs) are performed with an FLC assay and urine protein electrophoresis. The FLC assay measures FLCs in the serum and is the most sensitive test to detect light chain disease.9–12 FLCs are freely filtered by the kidney and accumulate in the urine and are termed Bence-Jones (B-J) protein. A small percentage of patients with multiple myeloma will have small quantities of FLCs in the blood with no B-J protein in the urine and would otherwise be considered nonsecretory if not for the availability of the FLC assay. FLCs have a relatively short half-life in the circulation, 2 to 6 hours, in comparison to weeks for intact immunoglobulin molecules and may therefore be used to obtain a more rapid assessment of disease response for patients receiving therapy.

**CLINICAL MANIFESTATIONS, TREATMENT, AND PROGNOSIS**

**Monoclonal Gammopathy of Uncertain Significance**

MGUS is by definition an asymptomatic disorder. A monoclonal protein is typically discovered by chance as the result of further investigation of an elevated total protein on routine chemistry screening. SPEP reveals a clonal protein in the absence of any laboratory or clinical evidence of a plasma cell dyscrasia. Additional testing is required to rule out multiple myeloma or other lymphoproliferative disease (Table 63-2). MGUS is defined by the presence of low levels of serum M protein (<3 g per dL), less than 10% clonal bone marrow plasma cells, and absence of anemia, hypercalcemia, renal failure, and lytic bone lesions. MGUS is more common than myeloma and increases in frequency with aging, occurring in 3% of the population older than age 50 years.13,14 MGUS is considered a premalignant condition and affected patients are at increased risk of developing overt multiple myeloma or a related plasma cell or lymphoproliferative neoplasm.
Solitary Plasmacytoma

Plasmacytomas are localized tumors of plasma cells that may be associated with discomfort in the area of involvement. A diagnosis of solitary plasmacytoma is rendered only after a negative workup for systemic myeloma is completed. Plasmacytomas typically arise from bone but may involve soft tissue, may be palpable, and may be mistaken for adenopathy. Plasmacytomas of bone may result in fracture or local effects such as spinal cord compression or radicular nerve compression. Rarely, patients may have multiple plasmacytomas, synchronously or metachronously, without evidence of progression to systemic myeloma.

Solitary plasmacytomas may be treated effectively with radiation therapy to the involved site. Plasmacytomas involving the soft tissues of the head and neck region may be cured through this approach. Solitary plasmacytomas involving other sites are also typically treated with radiotherapy but are associated with a higher rate of subsequent development of systemic myeloma and therefore more intensive surveillance is required.

Multiple Myeloma

Multiple myeloma is characterized by neoplastic plasma cell infiltration of the bone marrow and bone and the overproduction of monoclonal immunoglobulin proteins or FLCs. Patients with no end-organ impairment are characterized as having asymptomatic myeloma (formerly “smoldering myeloma”), if plasma cells are present in >10% of the bone marrow and/or clonal immunoglobulin exceeds the limits that define MGUS (Fig. 63-2). The distinction between MGUS and asymptomatic myeloma is quite important because patients with the latter diagnosis have a much higher rate of progression to myeloma requiring therapy, particularly in the first 5 years following diagnosis.15,16

Patients are said to have symptomatic myeloma when there is evidence of end-organ impairment.17 The mnemonic “CRAB” (calcium/renal/anemia/bone) is used to recall the compared to the general population. Progression of MGUS to a frank plasma cell neoplasm occurs in about 1% to 2% of patients per year.13,14 Survival for patients with MGUS is excellent because most patients with this diagnosis do not develop frank malignancy.

### TABLE 63-2

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MGUS</strong></td>
</tr>
<tr>
<td>CBC</td>
</tr>
<tr>
<td>Comprehensive chemistry panel including calcium</td>
</tr>
<tr>
<td>SPEP, SIFE</td>
</tr>
<tr>
<td>Serum free light chains</td>
</tr>
<tr>
<td>Quantitative immunoglobulins</td>
</tr>
<tr>
<td>24-h urine for UPEP/UIFE, spot urine protein/creatinine ratio</td>
</tr>
<tr>
<td>Skeletal survey</td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>Multiple myeloma or plasmacytoma</td>
</tr>
<tr>
<td>All of the above plus</td>
</tr>
<tr>
<td>Bone marrow biopsy with cytogenetics and FISH</td>
</tr>
<tr>
<td>β2-Microglobulin, albumin, uric acid, LDH</td>
</tr>
<tr>
<td>MRI</td>
</tr>
<tr>
<td>PET–CT</td>
</tr>
</tbody>
</table>

*Lytic lesions appear on plain radiographs but are not well visualized on bone scans.

May not be required for low-risk patients

May add useful information in patients with negative X-rays

May be useful in patients with nonsecretory myeloma

MGUS, monoclonal gammopathy of uncertain significance; CBC, complete blood count; SPEP, serum protein electrophoresis; SIFE, serum immunoelectrophoresis; UPEP, urine protein electrophoresis; UIFE, urine immunoelectrophoresis; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET–CT, positron emission tomography–computed tomography.

**FIGURE 63-2.** Features of monoclonal gammopathy of uncertain significance (MGUS), asymptomatic or “smoldering” myeloma, and symptomatic myeloma. Monoclonal immunoglobulin proteins typically migrate to the gamma region on the electrophoresis gel and are quantified for monitoring. MGUS is distinguished from myeloma by the quantity of plasma cells in the bone marrow and the amount of monoclonal immunoglobulin present. (Reprinted from Kyle RA, Pharmstead TD, Therneau TM, et al. Clinical course and prognosis of smoldering [asymptomatic] multiple myeloma. New Engl J Med. 2007;356[25]:2582–2590, with permission.)

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most common features defining symptomatic myeloma (Table 63-3). Bone pain and fatigue are the most frequent presenting symptoms, related to lytic bone disease and anemia, respectively. Bone radiographs typically show pure lytic lesions and may be associated with pathologic fractures (Fig. 63-3). Vertebral lesions may present as expansile masses associated with spinal cord compression. Anemia occurs as a result of marrow infiltration and may be compounded by renal insufficiency and low erythropoietin production. Hypercalcemia is common at presentation and may contribute to renal injury. Renal insufficiency occurs in about 25% of patients with myeloma, and the cause is often multifactorial; injury from excess light chain delivery to the renal tubules is compounded by hypercalcemia, hyperuricemia, and volume depletion. Nonsteroidal anti-inflammatory use for bone pain will also worsen the problem. Renal injury at presentation is typically reversible with prompt supportive care; however, direct tubular damage from excess light chain excretion may cause permanent injury or end-stage renal disease if prolonged. Patients with myeloma typically have impaired production of normal immunoglobulins and are at increased risk of infection with encapsulated organisms. Patients with greater than 20% circulating plasma cells in the peripheral blood or >2 × 10⁹ per L are classified with plasma cell leukemia and have a particularly poor prognosis.¹⁸

Most patients with myeloma present with symptomatic, advanced-stage disease and require therapy. Hospitalization is advisable for supportive care and expedited workup for patients with significant renal insufficiency or suspicion of spinal cord compression. The goals of initial therapy are to achieve remission of disease while limiting the side effects of therapy and preventing clinical complications such as bone fracture and renal insufficiency. Virtually all patients are treated with dexamethasone in combination with one of the novel targeted agents thalidomide, lenalidomide, or bortezomib (Table 63-5).¹⁹⁻²³ Chemotherapy agents such as cyclophosphamide and melphalan may also be incorporated into combination treatment regimens with the targeted agents. High-dose chemotherapy and autologous stem cell rescue is typically considered for patients in first or second complete or partial remission. The choice of initial therapy is based on

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**TABLE 63-3** Myeloma-Related Tissue or Organ Impairment Defining Symptomatic Myeloma

| Calcium levels increased: serum calcium >11.5 mg/dL |
| Renal insufficiency: creatinine >2 g/L |
| Anemia: hemoglobin 2 g/dL below the lower limit of normal or hemoglobin <10 g/dL |
| Bone lesion: lytic lesions or osteoporosis with compression fractures |
| Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 mo) |

**TABLE 63-4** Symptoms and Signs of Plasma Cell Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>Asymptomatic</td>
<td></td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>Localized pain</td>
<td>Palpable mass</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Neuropathy</td>
<td>Hepatosplenomegaly</td>
</tr>
<tr>
<td></td>
<td>Diarrhea/obstipation</td>
<td>MacroGLOSSIA</td>
</tr>
<tr>
<td></td>
<td>Dyspnea/fatigue</td>
<td>CHF/edema</td>
</tr>
<tr>
<td>POEMS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Neuropathy</td>
<td>Organomegaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Papilledema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Volume overload</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gonadal changes</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Fatigue/dyspnea</td>
<td>Pallor</td>
</tr>
<tr>
<td></td>
<td>Bone pain</td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Neuropathy</td>
<td>Tender bone lesions</td>
</tr>
<tr>
<td></td>
<td>Polyuria/polydipsia/constipation</td>
<td></td>
</tr>
</tbody>
</table>

>**FIGURE 63-3**. Multiple lytic lesions and radial bone fracture in a 56-year-old woman with multiple myeloma presenting with bone pain at multiple sites.


MGUS, monoclonal gammopathy of uncertain significance; CHF, congestive heart failure; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

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produces the toxic light chains, but the malignant cells do not proliferate and infiltrate bone or tissue such as in myeloma. Target organs include the kidneys, heart, liver, spleen, peripheral nerves, and gastrointestinal tract. Symptoms of amyloidosis may be both profound and nonspecific, and the diagnosis may be missed unless tissue biopsy of affected organs is performed to demonstrate amyloid protein by Congo red staining or electron microscopy. Symptoms suggestive of heart failure, autonomic neuropathy, bowel dysfunction, peripheral neuropathy, and hepatosplenic enlargement may be present. Amyloidosis may also occur consequent to myeloma if the light chains produced by the myeloma clone can form amyloid protein. Amyloidosis is not always the result of abnormal light chain deposition in tissues, and management will depend on the source and type of protein present. The absence of a plasma cell clone and abnormal FLCs raises this possibility and may require specialized techniques to identify the source of the abnormal protein.

Therapy for systemic light chain amyloidosis is aimed at eliminating production of the toxic light chains as completely as possible. The novel agent bortezomib has been associated with the most rapid and complete responses. High-dose therapy and autologous stem cell transplantation may more effectively eliminate light chain production; however, patients with amyloidosis are at high risk for morbidity, and patient selection is critical. The prognosis for patients with primary light chain amyloidosis is generally poor but varies with the degree of organ involvement. Patients with multiorgan involvement and cardiac involvement, in particular, have a poor prognosis.

**SURVEILLANCE**

A knowledge of the natural history and surveillance program for patients with MGUS is essential to the primary care provider. The risk of development of myeloma or another plasmacytic or lymphoproliferative disorder is approximately 1% per year for patients with MGUS. The risk of progression of MGUS to multiple myeloma is greater in patients with IgA or IgM proteins, in patients with initial concentrations of monoclonal protein in excess of 1.5 g per dL and in patients with an abnormal FLC ratio. Patients should be monitored without therapy, provided signs or symptoms suggestive of progression to neoplasm such as anemia, bone pain, or unexplained renal insufficiency have not developed. For low-risk patients, a reevaluation with SPEP in 6 months then every 2 years thereafter is adequate in the absence of clinical signs or symptoms.

**TABLE 63-5** Common Agents for Treatment or Support of Multiple Myeloma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Immunomodulatory agent</td>
<td>Sedation, neuropathy, constipation</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Immunomodulatory agent</td>
<td>Myelosuppression, rash</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteosome inhibition</td>
<td>Neuropathy, thrombocytopenia</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Alkylating agent</td>
<td>Myelosuppression, mucositis*</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylating agent</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Bisphosphonate</td>
<td>Bone pain, osteonecrosis</td>
</tr>
<tr>
<td>Zoledronic Acid</td>
<td>Bisphosphonate</td>
<td>Bone pain, osteonecrosis</td>
</tr>
</tbody>
</table>

*Melphalan is commonly used in high doses for autologous stem cell transplant and causes significant temporary mucosal injury.

**TABLE 63-6** International Prognostic Scoring System for Multiple Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B2M &lt;3.5</td>
<td>62</td>
</tr>
<tr>
<td>II</td>
<td>Albumin &gt;3.5</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>B2M &gt;5.5</td>
<td>29</td>
</tr>
</tbody>
</table>

B2M, β2-microglobulin.

patient age and risk factors as well as eligibility for autologous stem cell transplantation. Virtually all patients are expected to respond to initial therapy with at least a 50% reduction in tumor burden, although complete remissions are not common.

Supportive care directed toward the anticipated complications of myeloma is an important aspect of management. Bone fracture risk can be reduced with regular injections of the bisphosphonates zoledronic acid or pamidronate. Care must be taken to avoid invasive dental procedures while receiving bisphosphonates because of the increased risk of osteonecrosis. Bony lesions, particularly those involving weight-bearing bones, may require orthopedic evaluation and palliative radiation for pain control and prevention of pathologic fractures. Symptoms suggestive of spinal cord compression require prompt evaluation with spinal magnetic resonance imaging, empiric corticosteroid therapy, and radiation therapy consultation for considerations of radiation to involved areas. Avoidance of nephrotoxins, including nonsteroidal drugs and intravenous contrast agents, is important to prevent renal failure. All patients should receive pneumococcal and *Haemophilus influenzae* vaccine given the high prevalence of hypogammaglobulinemia.

Although still considered an incurable malignancy, survival for patients with multiple myeloma has improved significantly in the past decade with the advent of more effective therapies and better supportive care. Median survival from diagnosis as reported by the Mayo Clinic, for example, increased from 25 to 40 months for patients diagnosed after 1996 compared to those diagnosed earlier. A simplified prognostic scheme, the International Staging System for Myeloma, is commonly employed for staging based on only two variables present at diagnosis: β2-microglobulin and albumin levels (Table 63-6). Abnormal cytogenetic findings are also important prognostic factors.

**Primary Light Chain Amyloidosis**

Primary light chain amyloidosis results from tissue deposition of light chains capable of forming β-pleated sheets that stain with Congo red dye. A small population of clonal plasma cells
suggesting disease. Patients at higher risk should have repeat tests 6 months following diagnosis and then annually thereafter. Patients should be counseled to report undue fatigue, bone pain, or infectious symptoms promptly. Patients with asymptomatic myeloma have a high risk for progression, requiring therapy of about 10% per year for the first 5 years from diagnosis. Monitoring should be repeated initially at 2 to 3 months after diagnosis and then every 4 to 6 months for the first year. Stable patients may be monitored subsequently every 6 to 12 months provided symptoms remain absent. Patients with symptomatic multiple myeloma require individualized monitoring dependent on disease features and therapeutic history.

References

KEY POINTS

- Acute leukemia is a medical emergency requiring care at a tertiary cancer center.
- Prognosis is largely determined by chromosomal and molecular studies.
- Patients with acute promyelocytic leukemia present critically ill with bleeding and have a high cure rate with the immediate use of all-trans-retinoic acid (ATRA) with chemotherapy.
- Imatinib, dasatinib, and nilotinib are effective for Philadelphia chromosome-positive acute lymphoblastic leukemia.
- The myelodysplastic syndromes are heterogeneous disorders for which effective therapy can offer significant benefit even in the elderly.

ACUTE LEUKEMIA

The acute leukemias are malignant disorders of the bone marrow in which the normal marrow is replaced by immature, clonal, dysfunctional hematopoietic cells called blasts. In acute myeloid leukemia (AML), the blasts have characteristics of monocytes, neutrophils, red blood cell precursors, or megakaryocytes (the myeloid lineage). In acute lymphoid leukemia (ALL), the blasts have characteristics of B, T, or natural killer cells. In 10% to 20% of acute leukemias, the blast cells have characteristics of both the myeloid and lymphoid lineages. Untreated, acute leukemia leads to a rapid death in most patients. However, many patients can be cured with aggressive chemotherapy and stem cell transplantation.

An estimated 13,780 people in the United States were diagnosed with AML in 2012 and an estimated 6,050 people were diagnosed with ALL. The incidence of acute leukemia is somewhat higher in men, with 53% of patients with AML and 60% of patients with ALL being male. The incidence is highest among Whites and lowest among American Indians, Alaska Native populations, and Asian and Pacific Islander populations. The age-specific incidence rates of AML increases sharply after the age of 55 years from 7.2 per 100,000 for ages 55 to 59 years to 35 per 100,000 for ages 80 years and older. In contrast, most new ALL cases occur in children, with 60% of new cases of ALL diagnosed younger than the age of 20 years.

Risk Factors

The etiology of the leukemia in an individual patient is usually unknown. Several genetic syndromes are associated with the development of both AML and ALL, including Down syndrome (trisomy 21) and Li-Fraumeni syndrome (mutations in the p53 tumor suppressor gene) (see Chapter 3). Hematologic disorders such as the myeloproliferative and myelodysplastic syndromes are known pre-AML states. Carcinogens known to be leukemogenic include ionizing radiation, benzenes, and chemotherapy agents such as alkylating agents and topoisomerase II inhibitors.

Pathogenesis

In acute leukemia, a mutated hematopoietic stem cell undergoes malignant transformation, which provides it with a survival advantage, impairs its ability to differentiate, and enhances its ability for self-renewal. As a result, immature cells proliferate and replace the normal bone marrow cells. The identification of mutations and chromosomal translocations in leukemic cells has greatly enhanced our ability to classify and prognosticate the leukemias and, in some cases, has led to the development of targeted therapy.

Clinical Manifestations

Most patients with acute leukemia present with symptoms related to low blood counts (Table 64-1). In younger patients, the presentation is usually acute, with a febrile illness and bleeding. In older patients, the diagnosis can be subacute or on occasion even an incidental diagnosis made on routine blood work. Most patients will report several weeks or months of fatigue. Other symptoms of anemia, including poor exercise tolerance, shortness of breath, and chest pain, are also often present, especially in older patients. Bleeding manifestations include gum bleeding, bruising, epistaxis, and menorrhagia in women. Patients will often experience recurrent infections in the months prior to the diagnosis, and fever and infection are usually present on presentation.
Headaches, cranial nerve palsies, and visual disturbances may indicate central nervous system (CNS) involvement. Bone pain and tenderness are found in 25% of patients and are secondary to rapid expansion of the leukemia in the bone marrow compartment. Patients with gingival involvement may present to the dentist with painful, swollen, bleeding gums. A myeloid sarcoma (chloroma) is an uncommon manifestation of AML in which conglomerates of leukemic blasts cause a mass. A myeloid sarcoma can involve any organ including the spine, skin, gastrointestinal, or urinary tracts and cause localized symptoms such as pain, neurologic deficits, bleeding, or obstruction.

On examination (see Table 64-1), common findings include pallor, tachycardia, tachypnea, ecchymoses, and petechia. Examination of the mouth may show evidence of mucosal bleeding, gingival hypertrophy and bleeding secondary to leukemic infiltration (especially common in monocytic leukemias), and evidence of thrush or herpetic lesions. Fundoscopic examination may demonstrate evidence of retinal bleeding. The perianal region may show signs of infection and mucosal tears. Organomegaly, especially splenomegaly, is more common in ALL than AML and is usually mild. Lymphadenopathy is uncommon in AML but can be found in patients with ALL. Skin involvement is rare in ALL but is found in approximately 10% of patients with AML and usually appears as nodular violaceous lesions.9,10

### Hyperleukocytosis and Leukostasis

Patients with circulating blast counts greater than 50,000 per μL have hyperleukocytosis. These patients are at risk for leukostasis, a medical emergency caused by the widespread occlusion of small blood vessels by leukemic cells. Leukostasis is more common in AML, especially in monoblastic leukemia and the microgranular variant of acute promyelocytic leukemia (APL), compared with ALL, in which symptoms of leukostasis usually occur only when the blast count approaches or exceeds 100,000 per μL. Patients develop fever, shortness of breath and hypoxemia, and have tachypnea and diffuse rales on physical exam. The chest X-ray demonstrates bilateral lung infiltrations typical for noncardiogenic pulmonary edema. CNS manifestations include headaches, confusion, somnolence, and, if left untreated, patients sink into a coma. Visual disturbances are common and patients may report blurry vision and unilateral or bilateral vision loss. Priapism can occur from stasis of blood in the circulation.

Leukostasis must be treated immediately with hydration, correction of thrombocytopenia and coagulopathy, and avoidance of red blood cell transfusions, which increase blood viscosity. Immediate measures to reduce the circulating blast count using rapidly acting chemotherapy agents such as hydroxyurea and/or leukapheresis must be instituted. Dexamethasone may also have a role in the treatment of pulmonary leukostasis.11

### Metabolic Abnormalities and Tumor Lysis Syndrome

Metabolic abnormalities are common at diagnosis in patients with acute leukemia. Hyperuricemia secondary to the rapid nucleic acid turnover in the malignant cells is often present and worsens when treatment is initiated. The deposition of uric acid in the renal tubules and ureters can lead to acute renal failure. This can be prevented by hydration and treatment with allopurinol, a xanthine oxidase inhibitor, or rasburicase, an intravenous drug that converts uric acid to allantoin. Other manifestations of tumor lysis include hyperkalemia, hyperphosphatemia, and hypocalcemia. In most patients, these metabolic abnormalities can be managed by identifying the patients at risk and prophylactic hydration. However, some patients require urgent dialysis.12 Hypokalemia can also occur in patients with AML, especially in the myelomonocytic and monocytic subtypes. Its main cause is thought to be the release of lysozyme from leukemic cells, which is toxic to the renal tubules and causes renal potassium wasting. Hypercalcemia can also be found in patients with acute leukemia, especially in patients with T-cell leukemia/lymphoma.

### Spurious Laboratory Abnormalities

High white blood cell counts can result in spururious hypoglycemia, hypokalemia, and hypoxemia if the sample is not analyzed promptly because the metabolically active leukemic cells consume glucose, potassium, and oxygen in the tube. Spurious serum hyperkalemia is also common in patients who have a high white blood cell count and result from lysis of cells during the coagulation of the blood in the tube prior to processing. When spurious hyperkalemia is suspected, a plasma potassium measurement should be obtained on a blood sample that has been anticoagulated with heparin.13

### Diagnosis

The diagnosis of acute leukemia is straightforward in most patients and can often be made by examination of a peripheral blood smear, although a bone marrow aspirate and biopsy is recommended to ensure adequate material for diagnosis and prognostication. The current classification of the acute leukemias uses information obtained from multiple modalities, including morphology, immunohistochemistry, cytogenetic analysis, flow cytometry, and molecular techniques such as fluorescent in situ hybridization (FISH) and polymerase chain reaction (PCR). Lymphoblasts tend to be small with scant agranular cytoplasm and a round or mildly clefted nucleus. Myeloblasts tend to be larger, have more cytoplasm, a nucleus
with prominent nucleoli, and visible granules. Auer rods, which are elongated cytoplasmic inclusions, are pathognomonic for AML blasts and are especially abundant in acute promyelocytic leukemia (Fig. 64-1). However, distinguishing AML from ALL and identifying the subtypes of these two leukemias on morphologic grounds alone is difficult in patients with less differentiated blasts. Flow cytometry, which uses fluorescent-tagged antibodies against proteins expressed on the cell surface, the cytoplasm, and/or in the nucleus, allows the laboratory to confirm the subtype of leukemia within hours of receiving the specimen.14–16

**Prognosis**

Chromosomal abnormalities of the leukemic cells are the most important determinants of prognosis in leukemia (Table 64-2). Routine chromosome analysis requires culturing of the malignant cells and takes in total 7 to 14 days. Molecular techniques such as FISH and PCR are rapid and can identify mutations and translocations of known prognostic and therapeutic significance within hours. Furthermore, molecular techniques can identify cryptic abnormalities that are not visible on traditional chromosome analysis. Prognosis in AML is also determined by the patient’s age and the rapidity in which initial remission is obtained.14–16

Poor prognostic features in ALL include older age, a high white blood cell count (>50,000 per μL for B-cell ALL and >100,000 per μL for T-cell ALL), and specific cytogenetic abnormalities. The Philadelphia chromosome (Ph+, t[9;22]) is a poor prognosis cytogenetic abnormality, which is found in 30% of adult patients with B-cell ALL. Targeted therapy (imatinib, nilotinib, dasatinib) has improved survival for this leukemia but remains incurable without the use of allogeneic transplant. Patients with Ph−negative ALL can be cured with chemotherapy alone, with a survival of 42% for patients 65 years of age and younger, which declines steadily with age.17–19

**Treatment**

Most patients with acute leukemia require aggressive multiagent chemotherapy delivered in a hospital with physicians and nurses experienced in the management of this condition and excellent blood bank, infectious disease, and interventional radiology support. However, elderly patients with a smoldering course can sometimes be managed in the outpatient setting and in some instances should be referred at diagnosis directly to hospice and palliative care services.

**General Measures**

All patients who are offered therapy with curative intent should be admitted to the hospital in a private room with specialized nurses. Psychosocial support should be offered, and patients and their caregivers should be educated extensively about the severity of their disease, the therapeutic plan, and the prognosis. Patients should be informed that their first hospitalization will likely be at least 4 to 6 weeks in length.

Hand washing must be enforced, and contact with staff and visitors who have infectious symptoms should be avoided. Baseline laboratory examination should include, in addition to the diagnostic workup described previously, a full chemistry panel, which includes renal and liver function, uric acid, lactic dehydrogenase, phosphate, calcium, magnesium, and albumin levels. Coagulation profile including prothrombin time and partial thromboplastin time should also be obtained, and in patients who are coagulopathic or have abnormalities in their baseline coagulation profile, workup for disseminated intravascular coagulation is indicated. Patients who are candidates for allogeneic stem cell transplant should undergo HLA typing at diagnosis. Sperm banking should be offered to younger men because approximately 50% will develop prolonged azoospermia if they undergo stem cell transplant. Unfortunately, although most women will develop ovarian failure after stem cell transplant, methods of ovarian cryopreservation are still experimental.19

The patient should undergo urgent dental evaluation if he or she does not see a dentist regularly, with immediate teeth extractions, if necessary, to avoid infections. The heart ejection function should be evaluated in anticipation of the use of cardiotoxic chemotherapy agents. Vascular access either in the form of a tunneled catheter or a peripherally inserted central catheter must be obtained. All patients at risk for tumor lysis syndrome if a tunneled catheter or a peripherally inserted central catheter must be obtained. All patients at risk for tumor lysis should receive prophylactic hydration with normal saline. Patients with elevated uric acid levels and/or a circulating
blast count of 20,000 per μL or higher should be started on allopurinol, and rasburicase should be available for patients at high risk for tumor lysis (Table 64-3).

The goal of chemotherapy in acute leukemia is to suppress the malignant clone in the bone marrow to the point that it is undetectable while enabling the normal hematopoiesis to repopulate the bone marrow. A remission is usually defined as less than 2% blasts in the bone marrow, normalization of cytogenetic abnormalities, an absolute neutrophil count greater than 1,000 per μL, and a platelet count greater than 100,000 per μL. In some subtypes of leukemia, more sensitive techniques such as FISH and PCR are used to detect minimal residual disease and to guide postremission therapy.

**Chemotherapy for Acute Myeloid Leukemia**

All subtypes of AML in younger patients (usually defined as age younger than 60 years) with good functional status, except APL, are treated similarly with an anthracycline (usually either daunorubicin or idarubicin) and cytarabine. The most commonly used initial (induction) regimen is cytarabine given for 7 days and an anthracycline given for 3 days (“3 + 7”). Bone...
marrow evaluations are performed every few weeks to determine response to therapy. Patients who have persistent disease after induction receive a second dose of a similar regimen. If a remission is not achieved, a salvage chemotherapy regimen is administered. Once patients achieve remission, they still harbor a significant burden of undetectable leukemic cells and therefore benefit from additional chemotherapy (consolidation). Given the high doses of chemotherapy and the need for intensive supportive care with transfusions of red blood cells and platelets and broad-spectrum antibiotics and antifungal agents, most chemotherapy for acute leukemia must be given in the inpatient setting. Toxicities of the anthracyclines (idarubicin and daunorubicin) include a dose-dependent cardiomyopathy (see also Chapter 39). High doses of cytarabine cause mucositis, diarrhea, fever, rash, corneal damage, and cerebellar dysfunction. Patients receive prophylaxis with steroid eye drops and must undergo a cerebellar exam prior to the administration of every dose of high-dose cytarabine.

The patients’ age, comorbid conditions, prognostic category at diagnosis, response to chemotherapy, and stem cell donor availability will determine whether they will be considered for allogeneic stem cell transplant once remission is achieved. Patients who do not achieve a remission have a poor prognosis and can seldom be salvaged by an allogeneic stem cell transplant.20,21

**ACUTE PROMYELOCYTIC LEUKEMIA**

APL is a unique, favorable subclass of AML in which the leukemic cells contain a translocation involving the retinoic acid receptor α (most commonly t(15:17)). APL accounts for 5% to 8% of AML cases and tends to affect younger adults. It has an increased incidence in Hispanics and in patients who have received topoisomerase II inhibitors. Disseminated intravascular coagulation is very common at diagnosis, and patients often present with gum bleeding, bruising, and menorrhagia in women. Patients are at high risk for early death secondary to bleeding complications and require intensive supportive care with blood products. It is critical to establish the diagnosis emergently so that specific therapy in the form of all-trans-retinoic acid (ATRA) and/or arsenic trioxide can be initiated. With this targeted therapy in combination with conventional chemotherapy and with intensive supportive care during induction, more than 80% of patients with APL can be cured.20-22

**CHEMOTHERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA**

Induction regimens for adult ALL contain multiple chemotherapeutic agents, which usually include an anthracycline such as doxorubicin or daunorubicin, vincristine, and corticosteroids. Methotrexate, cytarabine, cyclophosphamide, and/or asparaginase are also components of some of the commonly used protocols. Patients with Ph+ ALL also receive targeted therapy in the form of imatinib, dasatinib, or nilotinib. Given the high incidence of CNS involvement in ALL, all induction regimens include intrathecal chemotherapy.

More than 80% of adults with ALL will achieve a remission with intensive induction chemotherapy; however, as in AML, these patients require postremission therapy to prevent relapse, and patients at high risk for relapse need to be considered for allogeneic stem cell transplant. Most regimens include several months of intensive chemotherapy after remission is achieved, and then maintenance, lower intensity chemotherapy with agents such as methotrexate, 6-mercaptopurine, vincristine, and prednisone for up to 24 months from diagnosis. During this maintenance period, patients continue to be at significant risk of infections, require prompt workup of fever, and remain on prophylaxis for *Pneumocystis jiroveci* infection.10,20,23

**LEUKEMIA IN THE ELDERLY**

The incidence of both AML and ALL increase with age, and acute leukemia in the elderly deserves special mention because older adults tend to develop poor-prognosis acute leukemia, are less able to tolerate the toxicities of aggressive chemotherapy, and are often not candidates for allogeneic stem cell transplant. Older patients often present with pancytopenia and do not have a high number of blasts in their peripheral blood. The incidence of good prognosis chromosomal abnormalities in AML decreases with age, whereas the incidence of poor prognosis chromosomal abnormalities increases. However, older patients without significant comorbidities may still benefit from curative intent chemotherapy, and treatment decisions in this age group must be individualized. Older patients with AML transformed from myelodysplastic syndrome (MDS) benefit from hypomethylating agents (see the following section on MDS). Occasionally, AML has a more indolent course in older adults, and patients can survive for months with transfusions and other supportive care.24,25 Older patients with Ph+ ALL can be treated with imatinib, dasatinib, or nilotinib with a 1-year survival of approximately 50%.23,26

**SURVEILLANCE**

Acute leukemia survivors in remission are at significant risk of relapse, especially in the first 3 years. In one single institution study of 1,069 patients with AML in first remission who did not undergo allogeneic transplant, the risk of relapse was 69.0%, 37.7%, 17.0%, 7.6%, and 6.6% in years 1 to 5 after achieving remission, respectively.27 In a study of 378 adults with ALL, leukemia-free survival was 30%, 26%, and 24% at 3, 5, and 8 years from remission, respectively.28 The relapse rate is decreased in higher risk patients who undergo allogeneic stem cell transplant, and patients without leukemia recurrence 2 years after transplant have an overall chance of long-term survival of 82%.29 Patients should be monitored with physical exams, blood counts, bone marrow evaluations, and molecular studies when appropriate every 3 to 6 months after completing therapy. Patients who develop a decline in their blood counts need to undergo a prompt workup with a bone marrow evaluation (Table 64-4).

Patients are also at risk for second malignancies including MDS, secondary AML, and, in patients who received

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**TABLE 64-4**

**Surveillance for Patients with Acute Leukemia in Remission**

- Physical exam, blood counts, molecular studies, bone marrow evaluation q3–6 mo after completing therapy
- Vaccinations (inactivated while patients on chemotherapy)
- Prompt treatment of infections

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cranial radiation, meningiomas and malignant brain tumors. Anthracyclines cause a dose-dependent cardiomyopathy (see also Chapter 39). Intrathecal chemotherapy and especially brain radiation can result in cognitive decline. Survivors of acute leukemia remain at increased risk of infection for many years, and special attention should be paid to appropriate vaccinations and prompt treatment of infections. Many patients with acute leukemia undergo stem cell transplant, and a detailed discussion of survivorship issues related to this procedure can be found in Chapter 46.

THE MYELODYSPLASTIC SYNDROMES

Similarly to the acute leukemias, in MDS, a clone of malignant hematopoietic cells accumulates in the bone marrow. Patients typically have, however, low circulating blood counts; and the clinical course is more indolent and variable, with only a minority of patients transforming to acute leukemia. The risk factors for MDS include exposure to benzenes, ionizing radiation, and chemotherapeutic agents. The incidence of MDS increases with age, with a median age at diagnosis of 76 years and an annual incidence increasing from 1.5 per 100,000 for patients aged 50 to 54 years to 36 per 100,000 for patients older than 80 years.30–32 Approximately 54% of patients are men. Presenting signs and symptoms may include symptomatic anemia, recurrent infections, and/or abnormal bleeding, and many patients are diagnosed because of an incidental finding of low blood counts. Immunologic manifestations such as arthritis, vasculitis, myositis, neuropathies, and lupus-like symptoms can also be associated with MDS. On physical exam, patients may be pale and may have evidence of skin and mucosal bleeding. Hepatosplenomegaly and lymphadenopathy are absent in the classic forms of MDS, and the presence of splenomegaly suggests a myeloproliferative disorder or chronic myelomonocytic leukemia (see Chapter 65). More than 90% of patients will have a macrocytic anemia and approximately half will have thrombocytopenia and/or neutropenia. The bone marrow biopsy and aspirate are usually hypercellular with dysplastic changes. Iron stain of the bone marrow can reveal ringed sideroblasts, which are red cell precursors containing a ring of iron-filled mitochondria around the nucleus.31,32

Similar to AML, the prognosis of MDS is determined by the presence of chromosomal abnormalities in the malignant cells. Other prognostic factors include the percentage of blasts in the bone marrow, the degree of transfusion dependence, and the morphologic subtype. The median survival ranges from 141 months in the very low-risk group to 9 months in the very high-risk group33 (Table 64-5).

Most patients with MDS have an increased risk of infections and should be evaluated promptly when they develop a fever, even when their neutrophil count is normal or near normal because their neutrophils often have functional abnormalities. Similarly, patients may have a bleeding tendency out of proportion to their thrombocytopenia because of dysfunctional platelets. Aspirin and other antiplatelet agents may be poorly tolerated in these patients.31,32

All patients with MDS should be evaluated for conditions that may exacerbate their low blood counts such as nutritional deficiencies (iron, vitamin B12, folic acid), hypothyroidism, alcohol consumption, and marrow suppressive medications. Some patients with MDS are asymptomatic and can be observed without treatment. Patients with low-risk MDS (see Table 64-5) may benefit from growth factors including erythropoietin and colony-stimulating factor. Chemotherapy with hypomethylating agents such as 5-azacitidine and decitabine has been shown to delay progression to acute leukemia, decrease transfusion requirements, improve quality of life, and prolong survival. Lenalidomide induces transfusion independence in 67% of patients with MDS and deletion of the long arm of chromosome 5 (5q−).34 Allogeneic stem cell transplant remains the only curative modality in MDS and should be considered in younger, otherwise healthy patients.31,32
References


KEY POINTS

- Myeloproliferative neoplasms (MPNs) are characterized by high circulating blood counts, splenomegaly, and a propensity to progress to myelofibrosis and acute leukemia.
- MPNs are associated with thrombosis in unusual places and should be considered in patients with thrombosis of intra-abdominal veins.
- The treatment of chronic myelogenous leukemia has been revolutionized by the development of imatinib mesylate and other oral tyrosine kinase inhibitors.
- Hydroxyurea and aspirin are used to treat polycythemia vera and essential thrombocythemia with a primary goal of reducing thrombotic and hemorrhagic complications.

The myeloproliferative neoplasms (MPNs) are a group of clonal stem cell disorders characterized by a malignant growth of at least one myeloid (i.e., granulocytic, erythroid, megakaryocytic, or mast cell) cell lineage. The four most common MPNs are chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), which will be discussed in this chapter. Rare subtypes include chronic eosinophilic leukemia and systemic mastocytosis. MPNs as a group are diagnosed in approximately 2.3 per 100,000 people in the United States each year. They usually present with either asymptomatic abnormal blood counts, constitutional symptoms, and/or arterial and venous thrombosis (Table 65–1). Patients with MPNs have a life expectancy measured in years and are readily managed with oral agents. Thus, most primary care clinicians (PCCs) will encounter these patients in their practice and will play important roles in their diagnosis and long-term management.

CHRONIC MYELOGENOUS LEUKEMIA

CML is a MPN caused by the breakpoint cluster region–Abelson (BCR–ABL) fusion gene, a result of a translocation between the ABL gene on chromosome 9 and the BCR gene on chromosome 22 (t[9;22], the Philadelphia [Ph] chromosome). The peak incidence of CML is in the fifth decade of life, but it can occur at any age. If affects slightly more males than females. The etiology for most CML patients is not known. The malignant transformation occurs in an early hematopoietic precursor from the overexpression of the oncogene ABL on chromosome 9, which results in proliferation and suppression of apoptosis.

Diagnosis

CML should be suspected when a blood count reveals leukocytosis with a differential showing granulocytes in all stages of maturation. Basophilia, eosinophilia, anemia, and

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**TABLE 65-1**

Clinical Manifestations of the Myeloproliferative Neoplasms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional (weight loss, fever, sweats)</td>
<td>Pallor</td>
</tr>
<tr>
<td>Headaches, visual disturbances</td>
<td>Petechia, ecchymosis, other bleeding</td>
</tr>
<tr>
<td>Left upper quadrant pain (from splenomegaly)</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Early satiety</td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Gout attacks</td>
<td>Plethora (PV)</td>
</tr>
<tr>
<td>Pruritus (especially after water exposure)</td>
<td>Thromboembolic disease (including portal, mesenteric, hepatic veins)</td>
</tr>
<tr>
<td>Erythromelalgia (painful burning and erythema of hands and feet)</td>
<td>Arterial events</td>
</tr>
<tr>
<td>Pica (PV, associated with severe iron deficiency, rare)</td>
<td>Hyperleukocytosis (CML, rare)</td>
</tr>
</tbody>
</table>

PV, polycythemia vera; CML, chronic myelogenous leukemia.
thrombocytosis are often present. The diagnosis is established by demonstrating either the Ph chromosome or molecular evidence of the BCR–ABL translocation. A bone marrow examination is usually performed in younger patients because it may help determine prognosis.

**Treatment**

Untreated patients with CML transform after a median of 3.5 to 5.0 years to acute leukemia.\(^3\)\(^4\) There are three highly effective oral tyrosine kinase inhibitors (TKIs) currently approved in the United States to treat CML in the front line setting, imatinib mesylate, dasatinib, and nilotinib, and there are several more compounds in advanced stages of clinical trials.\(^5\)\(^–\)\(^9\) Ponatinib, an oral pan-BCR-ABL inhibitor, recently received approval for patients with CML who are resistant or intolerant to prior tyrosine kinase therapy. Up to 95% of patients will normalize their blood counts and achieve a complete cytogenetic remission (disappearance of the Ph chromosome) with these drugs. These TKIs are generally well tolerated, and less than 5% of patients discontinue the drugs for intolerance (Table 65-2).\(^5\)\(^–\)\(^9\) Drug interactions are a concern, especially when these drugs are administered to older patients with comorbid conditions.\(^9\) Patients are treated indefinitely, although studies are underway to see if some patients with sustained remissions may stop therapy.\(^10\) Allogeneic transplant is reserved for the rare patient with resistant leukemia.

**Surveillance**

Patients with CML should be monitored periodically by blood counts and quantitative polymerase chain reaction (PCR) for the BCR–ABL transcript (Table 65-3). Rising levels of BCR–ABL should prompt further workup including a bone marrow evaluation and mutational analysis. Patients on long-term TKIs should have monitoring of their thyroid function. Hypophosphatemia, osteomalacia, and cardiac toxicities have also been described. Lack of adherence to treatment is a major cause of treatment failure, and all patients should be educated about the importance of avoiding treatment interruptions.\(^9\)

**Prognosis**

The TKIs have had a major positive impact on the survival of patients with CML, and clinical trials are reporting an 8-year survival of 85% to 87%.\(^11\)\(^12\)

### TABLE 65-2

<table>
<thead>
<tr>
<th>Side Effects of the Tyrosine Kinase Inhibitors for CML (Imatinib Mesylate, Dasatinib, and Nilotinib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatigue</td>
</tr>
<tr>
<td>• Peripheral and peri orbital edema (imatinib)</td>
</tr>
<tr>
<td>• Pleural effusion (dasatinib)</td>
</tr>
<tr>
<td>• Musculoskeletal pain, cramps</td>
</tr>
<tr>
<td>• Abdominal pain, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td>• Pancreatitis (nilotinib)</td>
</tr>
<tr>
<td>• QT prolongation, sudden death</td>
</tr>
<tr>
<td>• Platelet function inhibition (dasatinib)</td>
</tr>
</tbody>
</table>

\(\text{CML, chronic myelogenous leukemia.}\)

### TABLE 65-3

<table>
<thead>
<tr>
<th>Long-term Follow-up of Stable Patients with Chronic Myelogenous Leukemia on Tyrosine Kinase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Every 3–6 mo</strong></td>
</tr>
<tr>
<td>• History and physical exam</td>
</tr>
<tr>
<td>• Assessment of patient compliance</td>
</tr>
<tr>
<td>• Quantitative PCR of BCR–ABL</td>
</tr>
<tr>
<td>• Complete blood count with white blood cell differential</td>
</tr>
<tr>
<td>• Liver function tests</td>
</tr>
<tr>
<td>• K(^+), Mg(^2+), Ca(^2+)</td>
</tr>
<tr>
<td>• Amylase and lipase (for nilotinib)</td>
</tr>
<tr>
<td><strong>Yearly</strong></td>
</tr>
<tr>
<td>• TSH</td>
</tr>
<tr>
<td>• Bone marrow cytogenetics (in younger patients)</td>
</tr>
<tr>
<td>• ECG</td>
</tr>
<tr>
<td><strong>Every 2–3 y</strong></td>
</tr>
<tr>
<td>• Bone density (for patients with other risk factors for osteoporosis)</td>
</tr>
<tr>
<td>• Cardiac function (for patients with other risk factors)</td>
</tr>
</tbody>
</table>

\(\text{PCR, polymerase chain reaction; BCR–ABL, breakpoint cluster region–Abelson; TSH, thyroid-stimulating hormone; ECG, electrocardiogram.}\)

### POLYCYTHEMIA VERA

PV is an MPN characterized by overproduction of the red cell lineage. It is usually diagnosed in the sixth decade of life with a slightly higher incidence in males. The etiology of PV is not known. Most patients carry an acquired gain-of-function mutation in the Janus kinase 2 (JAK2) gene. This mutation contributes to the malignant phenotype of the disease, but it is not the primary event causing the transformation.\(^13\) Approximately 9% of cases are familial.\(^14\)

**Diagnosis**

The diagnosis of PV is usually established by the demonstration of a mutation in either exon 14 (V617F; 95% to 97% of patients) or exon 12 (four different mutations; 3% of patients) of the JAK2 gene in a patient with a high hemoglobin and hematocrit. Occasionally, patients will have normal or near-normal hemoglobin and hematocrit levels because of concomitant iron deficiency. Clues to the diagnosis in these patients may include elevated leukocyte and platelet counts, a macrocytosis, and iron indices showing iron deficiency without anemia. Most patients will also have low erythropoietin levels, splenomegaly, and a hypercellular bone marrow. Because patients with PV can develop thrombosis in uncommon locations such as mesenteric, portal, splenic, and hepatic (Budd-Chiari) veins, JAK2 mutation testing is indicated in patients with otherwise unexplained clots in these locations.\(^13\)\(^15\)\(^16\)

**Treatment**

Treatment of PV helps control symptoms and reduces the rate of thrombotic and bleeding complications.\(^13\)\(^16\)\(^17\) Cardiovascular risk factors should be managed aggressively, and smoking cessation should be strongly encouraged. The standard treatment for patients at low risk for thrombosis is low-dose aspirin and phlebotomy, with a target hematocrit of 45% in men and 42% in women. Patients should be educated to avoid iron supplements because they may worsen erythrocytosis, although
an iron-poor diet is not recommended. In patients older than the age of 60 years and/or at high risk for thrombosis, the treatment of choice is the antimetabolite hydroxyurea with low-dose aspirin. Hydroxyurea is usually well tolerated, and its main side effects include macrocytosis and pancytopenias. Long-term use can cause oral and leg ulcers. Erythromelalgia improves promptly with aspirin.\textsuperscript{17}

### Surveillance

Stable patients with PV need to undergo a clinical evaluation and a physical exam every 3 to 6 months to assess for side effects of therapy, thromboembolic events, and transformation of their disease to myelofibrosis or acute leukemia. Patients should be reminded to avoid iron supplementation including multivitamins that contain iron. A complete blood count with a white blood cell differential and liver function tests should be checked at these visits to determine the need for phlebotomy and/or medication adjustments.

### Prognosis

Un-treated symptomatic patients with PV have a life expectancy of less than 2 years and succumb to vascular events including strokes, myocardial infarctions, and venous thromboembolism. Treatment improves survival significantly, but patients with PV still have a 1.6-fold higher mortality than the general population and 3.3-fold higher mortality if they are younger than the age of 50 years.\textsuperscript{18} Patients with PV may evolve to secondary myelofibrosis or acute leukemia.

### ESSENTIAL THROMBOCYTHEMIA

ET is an MPN that involves only the megakaryocytic lineage. Patients present between the ages of 50 and 60 years, with a second incidence peak in females in their 30s.\textsuperscript{19} The pathogenesis and risk factors for ET are unknown. The JAK2 mutation is found in approximately 50\% of patients, and approximately 6\% of cases are familial.\textsuperscript{14}

### Diagnosis

ET should be considered when there is a persistent thrombocytosis of above 450,000 per µL and secondary causes of thrombocytosis, especially bleeding, iron deficiency, and inflammation, have been ruled out (Table 65-4). The JAK2 V617F mutation is found in approximately 50\% of patients. In patients who lack the JAK2 V617F mutation, BCR–ABL testing should be performed to rule out CML, and a bone marrow biopsy and aspiration is recommended.\textsuperscript{16,19,20}

### TABLE 65-5 Risk Stratification and Treatment of Essential Thrombocythemia

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age &lt;60 y</td>
<td>• Neither low- nor high-risk disease</td>
<td>• Age of at least 60 y or history of thromboembolism</td>
</tr>
<tr>
<td>• No thromboembolism history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Platelet count &lt;1.5 million/µL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment is low-dose ASA</th>
<th>Treatment is low-dose ASA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment is low-dose ASA + hydroxyurea</th>
</tr>
</thead>
</table>
| For patients with platelets > 1 million/µL, clinically significant acquired von Willebrand disease should be excluded prior to ASA initiation. ASA, acetylsalicylic acid.

### PRIMARY MYELOFIBROSIS

PMF is characterized by an initial proliferation of granulocytes and megakaryocytes, progressive reactive deposition of fibrous connective tissue in the bone marrow, and extramedullary hematopoiesis. It usually occurs in the sixth to seventh decade of life.\textsuperscript{16,23} Risk factors include exposures to benzene and ionizing radiation. In 8\% of patients, the disease is familial.\textsuperscript{14}

### Diagnosis

The diagnosis of PMF is usually suspected after review of the blood counts and peripheral blood smear, which typically shows teardrop and nucleated red blood cells, a left shift in the myeloid series, and giant platelets. Approximately 50\% of patients have the JAK2 V617F mutation. The bone marrow biopsy demonstrates megakaryocytic proliferation and atypia and increased fibrosis. Secondary causes of bone marrow fibrosis (other hematologic disorders, cancer metastatic to the
bone marrow, renal osteodystrophy, autoimmune disorders, granulomatous disorders) must be ruled out in patients who do not have the JAK2 mutation.16,23

Treatment and Prognosis

Treatment is mainly supportive and may include hydroxyurea, high-dose erythroid-stimulating agents, red blood cell transfusions, splenectomy, and/or splenic irradiation.16,21,24 Ruxolitinib, an oral JAK2 inhibitor, can reduce spleen size and constitutional symptoms in patients with PMF.25,26 Allogeneic stem cell transplantation is the only curative option. Patients usually succumb to complications of bone marrow failure, thrombosis, splenomegaly, iron overload, and/or evolution to acute leukemia. Poor prognostic factors include age older than 65 years, constitutional symptoms, anemia, and high circulating leukocyte and blast counts, and the median survival ranges from 27 to 135 months.18,22,27

References

CHAPTER 66
Soft Tissue and Bone Sarcomas
Martin M. Malawer, MD, FACS • Kristen Kellar-Graney, MS

KEY POINTS
- Bone and soft tissue sarcomas are mesenchymal tumors affecting approximately 1% of patients with cancer; 6,000 to 10,000 new cases in the United States each year.
- Plain radiographs (bone) and magnetic resonance imaging (soft tissue) provide important diagnostic information prior to biopsy.
- A core needle biopsy should be performed by a skilled interventional radiologist or the oncology surgeon to ensure adequate specimen collection while minimizing risk of collateral tissue contamination.
- Neoadjuvant chemotherapy is usually used for high-grade sarcomas. Surgical resection with wide margins and reconstruction is performed for 95% of patients. Adjuvant therapy is typically warranted. The most common drug regimens contain Adriamycin, cisplatin, and/or ifosfamide.

INTRODUCTION
Primary tumors arising from mesenchymal tissues represent only 1% of all cancers diagnosed in the United States each year. However, a primary care physician will typically be the first medical professional to encounter a patient with a primary soft tissue or bone sarcoma. It is imperative that any suspected bone or soft tissue tumor be thoroughly evaluated and properly referred to afford the patient the quickest and most effective course of treatment.1

Risk Factors
There are only a few risk factors for the development of bone tumors, specifically, the inherited genetic disorders of Li-Fraumeni syndrome, Rothmund-Thomson syndrome, Werner disease, Mafucci syndrome, and retinoblastoma.2 Also, there is a correlation between some bone tumors and the diagnoses of Paget disease and multiple enchondromatosis and exostosis. Similar to bone tumors, soft tissue sarcomas do not frequently have clearly defined natural risk factors—Li-Fraumeni syndrome and neurofibromatosis being the most common prediagnostic conditions. Exposure to carcinogenic commercial chemicals such as vinyl chloride, phenoxycetic acids, arsenic, and chlorophenols as well as immunodeficiencies have also been identified as risk factors, as is previous exposure to radiation or radiation therapy.

Pathogenesis
All primary bone and soft tissue sarcomas arise from mesenchymal cells. Unlike carcinomas, these tumors tend to grow in a concentric “ball-like” manner, along the plane of least tissue resistance, typically displacing rather than invading adjacent structures. Tumors that arise in bone and soft tissues have characteristic patterns of biologic behavior because of their common mesenchymal origin and anatomic environment. It is only when primary tumors become extremely large do they invade surrounding anatomical structures. Most soft tissue sarcomas contain either acquired gene mutations (p53 is the most common), and a significant minority exhibit characteristic balanced translocations involving transcription or growth factors (examples include t[11;22] in Ewing sarcoma, t[x;18] in synovial sarcoma, and t[17;22] in dermatofibrosarcoma protuberans).3

Clinical Manifestations
The most common presenting symptoms for patients with bone sarcomas include dull, aching pain for several weeks to months duration. This pain frequently follows a circadian pattern with greatest intensity at night. The presenting symptoms and signs of soft tissue sarcomas are quite nonspecific. Most of these lesions commonly present as a painless, slow-growing mass, but about 20% of patients seek medical assistance for a very painful, rapidly growing mass. Physical examination may reveal swelling, localized pain or tenderness, changes to the overlying skin appearance, vascular changes, or paresthesias (Fig. 66-1).

Diagnosis
Patients with suspected primary bone or soft tissue tumors should immediately undergo radiographic and imaging evaluation. Biopsy is only performed following a thorough radiographic evaluation.
Evaluation of Suspected Bone Tumor

Is the lesion neoplastic?
- Nonneoplastic
  - No treatment
    - Observe
- Neoplastic
  - Is this benign or malignant?
    - Benign
      - No treatment
        - Observe
    - Malignant
      - Imaging studies
        - Surgery
          - Curettage vs. resection
          - Perform CT-guided needle biopsy

Low grade
- Resection or curettage
  - Possible bone graft
High grade
- Induction chemotherapy
  - Limb-sparing surgery
  - Postoperative chemotherapy

Evaluation of patient with soft tissue mass

Perform physical exam

Is the mass painful?
- Yes
  - Probably nonneoplastic
    - Consider inflammatory process
  - Probably neoplastic
    - Benign or malignant
- No
  - Is mass >5 cm in size?
    - No
      - Superficial or deep
        - Probably benign
        - Suspect benign
        - Imaging evaluation
          - CT/MRI scans
    - Yes
      - Deep location (below fascia)
        - Probably malignant
        - Suspect malignant
        - Needle biopsy
          - Obtain multiple cores
            - CT-guidance if lesion is deep

Benign
- Marginal wide excision
  - No radiation therapy
  - No chemotherapy
Malignant
- Low grade
  - Wide excision
    - Possible radiation therapy
    - Chemotherapy
- High grade
  - Wide excision
    - Radiation therapy
    - Chemotherapy

FIGURE 66-1. Flow charts for bone and soft tissue tumor evaluation. These series of questions are useful when determining if a tumor may require special studies or referral to an orthopedic oncologist. CT, computed tomography; MRI, magnetic resonance imaging. (Reprinted from Malawer MM, Kellar-Graney KL. Tumors of the musculoskeletal system. In: Wiesel SW, Delahay JN, eds. Essentials of Orthopedic Surgery. New York, NY: Springer Science+Business Media, LLC; 2010, with permission.)
Plain radiographs are often the first tool in the physician's armamentarium in the case of bone tumors and are often conclusively diagnostic. Most malignant bone tumors will feature evidence of bone destruction (either blastic, lytic, or both) and a wide area of bony transition with periosteal reaction is noted. Extension of the tumor beyond the periosteum and into the adjacent soft tissues, known as the reactive zone or pseudocapsule, is common. Lesions extending beyond the pseudocapsule are hallmark findings of sarcomas. Bone tumors with the aforementioned characteristics should raise a high level of suspicion for malignancy, and additional staging studies including bone scintigraphy, magnetic resonance imaging (MRI), computed tomography (CT), and angiography tests are performed to assist in delineating local tumor extent, any vascular displacement, and compartmental localization prior to biopsy.

MRI is the primary modality for evaluating soft tissue tumors. The signal intensity of a tumor is assessed by comparing it with that of the adjacent skeletal muscle and subcutaneous fat; characteristically, T2 and contrast-enhanced images are the most helpful. MRI also enables one to view a lesion in all three planes (axial, sagittal, and coronal). Contrast-enhanced MRI is useful in evaluating the relationship of a tumor to adjacent blood vessels or for characterizing cystic lesions (Figs. 66-2 and 66-3).

**Staging and Prognosis**

Staging studies include, most importantly, a chest CT to rule out pulmonary metastases. A CT and/or MRI of the entire involved extremity or local region is performed. Positron emission tomography (PET) and bone scans are useful to evaluate other skeletal structures, specifically metastatic lesions, as well as the pelvis and abdomen. Three-dimensional CT scans with contrast can be very helpful for surgical planning purposes. A biopsy is performed following completion of these studies.

The two most commonly used staging systems for bone and muscle sarcomas are those described by (1) Enneking and used by the Musculoskeletal Tumor Society and (2) the American Joint Committee on Cancer. Regardless of which system is used, the tumor grade is the most important variable in staging sarcomas. The Enneking staging system evaluates three factors: histologic grade (G), anatomical site (T), and the presence or absence of metastases (M). The anatomical site may be either intracompartamental (A) or extracompartamental (B).

A clear correlation between the extent of the tumor at presentation, its relation to the boundaries of the compartment in which it is located, and the extent of surgery as well as the correlation between surgical stage of bone sarcoma and patient survival has been well documented. Patient survival at 5-year follow-up is greater than 90% for patients with bone sarcoma with tumors staged IA, ~60% for IIB, and less than 5% for stage III. Overall survival of soft tissue sarcoma depends on the grade of the tumor (high vs. low grade), size of the tumor (if it is greater than or less than 5 cm in size), and depth of the tumor (above or below the fascia). In general, the 5-year overall survival of patients with high-grade soft tissue sarcoma is approximately 65%. Whereas adjuvant chemotherapy is extremely beneficial in treating bone sarcomas, the data regarding its efficacy with soft tissue sarcomas is conflicting—most meta-analysis data, including the Sarcoma Meta-analysis Collaboration (SMAC) and other large studies using ifosfamide-based protocols, show only a modest overall increased survival benefit for chemotherapy in the adjuvant setting for extremity sarcomas and not for truncal and abdominal (Table 66-1) sarcomas.

**Treatment**

**Biopsy**

To accurately treat a bone or soft tissue sarcoma, a properly placed biopsy in the proposed plane of surgical resection is performed. It is imperative that a skilled interventional radiologist, or ideally the oncology surgeon, obtains the diagnostic tissue to both histologically evaluate the tumor and prevent contamination of the collateral tissues. The biopsy site must be in line with the planned incision so as to be resected en bloc. A needle biopsy is usually diagnostic.
Treatment of malignant sarcomas is contingent on the stage of the tumor. Grade 1 (low-grade) tumors are surgically resected with a margin of tissues negative for microscopic malignant cell extension. Grade 2 (high-grade tumors) or 3 usually requires neoadjuvant or preoperative chemotherapy, en bloc resection of the tumor with reconstruction, and adjuvant chemotherapy or radiation therapy. Most bone and soft tissue sarcomas are treated by an en bloc limb-sparing resection. Today, only about 5% to 10% of all sarcomas require an amputation.1

Gastrointestinal Stromal Tumors

These spindle cell neoplasms are the most common sarcomas in adults and are usually located in the stomach or small intestine. They are characterized by the overexpression of the cluster of differentiation (CD) 117 antigen and the KIT receptor tyrosine kinase and sensitivity to tyrosine kinase inhibitors such as imatinib and sunitinib. They usually present with bleeding, an abdominal mass, and/or abdominal pain. Management is primarily surgical, with adjuvant imatinib offered to patients at high risk for recurrence. Patients with locally advanced and metastatic disease usually respond to imatinib for 2 to 3 years before developing resistance.2

Surveillance

The most common site for early and late metastases is the lung. To account for these potential complications, and barring the incidence of pain, swelling, or other obvious situations warranting immediate treatment, patients treated for primary bone or soft tissue sarcomas should have postoperative examinations and pertinent imaging studies, including CT scan of the chest every 3 months for the first 2 years, every 6 months for years 2 to 5, and yearly until 5 to 7 years posttreatment completion. Referral to a physical medicine or rehabilitation specialist is indicated in most patients, especially those who are at risk for decreased mobility because of their surgical procedure.5–11

TABLE 66-1
American Joint Committee on Cancer Staging System for Primary Malignant Tumors of Bone

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Metastasis in Lymph Node</th>
<th>Distant Metastases</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1a or T1b</td>
<td>N0</td>
<td>M0</td>
<td>G1 or G2</td>
</tr>
<tr>
<td>IB</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>G1 or G2</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>G1 or G2</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1a or T1b</td>
<td>N0</td>
<td>M0</td>
<td>G3 or G4</td>
</tr>
<tr>
<td>IIC</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>G3 or G4</td>
</tr>
<tr>
<td>III</td>
<td>Any T</td>
<td>N0 or N1</td>
<td>M1</td>
<td>Any G</td>
</tr>
</tbody>
</table>

I, tumor ≤5 cm in greatest dimension; T1a, superficial tumor; T1b, deep tumor; T2, tumor >5 cm in greatest dimension; T2a, superficial tumor; T2b, deep tumor.


References


Cancers of the nervous system include neoplasms that originate in the brain itself, which are referred to as primary brain tumors, or those that spread from elsewhere into the brain, and which are referred to as metastatic brain tumors.

Primary malignant brain tumors are rare, accounting for approximately 2% of all cancers in the United States. In 2010, approximately 22,020 new cases of primary brain and other nervous system neoplasms were diagnosed in the United States accounting for 13,140 deaths. Metastatic brain tumors are the most common types of brain tumors, with an estimated incidence approximately 10 times that of primary brain tumors. Between 20% and 40% of patients with systemic cancer will develop brain metastases.

RISK FACTORS

No definitive agent has been associated with central nervous system (CNS) tumors, and risk factors can be identified only in a minority of patients. There is no association with diet, exercise, alcohol, tobacco, and viruses that have been described for other malignancies. Exposure to ionizing radiation has been implicated, particularly with increased incidence of meningiomas, in those who received cranial/scalp irradiation. Radiation exposure also is a known risk factor for a small percentage of astrocytomas, sarcomas, and other tumors. A four-fold increase in incidence of primary brain tumors over what would be expected is seen in long-term survivors of prophylactic cranial irradiation given to children with acute leukemia. At this time, there is no definitive evidence that cell phones cause primary brain tumors. The International Commission on Non-Ionizing Radiation Protection Standing Committee evaluated a body of conflicting reports and concluded that there is not enough evidence to suggest a causal association between cellular phone use and high-grade glioma; however, the observation period was considered to be too short to make conclusive statements for slow-growing tumors.

The exception to this lack of causality for primary brain tumors is in the case of primary central nervous system lymphoma (PCNSL). The most notable risk factor for the development of PCNSL is immunodeficiency, including human immunodeficiency virus (HIV) infection, iatrogenic immune suppression, and congenital immune deficiency including ataxia-telangiectasia, Wiskott-Aldrich syndrome, and severe common and combined variable immunodeficiencies.

Optic gliomas, astrocytomas, and meningiomas occur at higher frequency in patients with neurofibromatosis type 1, and there is an increased frequency of vestibular and systemic schwannomas and meningiomas in neurofibromatosis type 2. Meningiomas and schwannomas occur more commonly in females; gliomas, medulloblastomas, and most other CNS tumors are more common in males. Meningiomas are more common in African Americans and gliomas and medulloblastomas in Caucasians.
(especially early morning), nausea, vomiting, gait and balance alterations, personality changes, and slowing of psychomotor function or somnolence. Headache is a common manifestation of brain tumors, and in about one-half of patients, it is the worst symptom. \(^\text{10}\) The headaches are usually dull and constant but occasionally throbbing. Severe headaches are infrequent, unless obstructive hydrocephalus or meningeal irritation is present. Although 5% to 10% of first-time seizures are a result of brain tumors, almost half of the patients with supratentorial brain tumors present with seizures. \(^\text{12}\) An adult with a first seizure that occurs without an obvious precipitating event should undergo contrast-enhanced cranial imaging, preferably magnetic resonance imaging (MRI).

Tumors can be associated with location-specific symptoms. For example, frontal lobe tumors can be associated with personality change, loss of initiative, and loss of ability to make independent decisions. Posterior frontal tumors can produce contralateral weakness by affecting the motor cortex and descending corticospinal tract, and lateral frontal tumors can produce dysarthria or expressive aphasia when involving the dominant hemisphere. Temporal tumors often produce seizures, impaired memory, auditory hallucinations, homonymous superior quadrantanopsia, and abnormal behavior. Dominant temporal lobe tumors can present fluent (Wernicke-like) aphasia. Parietal tumors can result in sensory disorders such as stereognosis, hemianesthesia, and/or homonymous inferior quadrantanopsia. Depending on the side, patients with parietal tumors can present with alexia and dysgraphia or contralateral neglect anosognosia and apraxia. Occipital tumors may produce contralateral homonymous hemianopsia or visual disturbances affecting perception of color, size, or location. Thalamic tumors can cause “thalamic” pain disorders and obstructive hydrocephalus. Pontine tumors can cause cranial nerve VI and VII palsies. Tumors in the medulla present with dysfunction of nerves IX, X, and XII; dysphagia; and dysarthria.

**DIAGNOSIS**

The imaging modality of choice for most CNS tumors is MRI, which can demonstrate anatomic and pathologic processes in detail. \(^\text{12}\) Computed tomography (CT) scan is generally reserved for those unable to undergo MRI because of an implanted pacemaker, retained metal fragment, or paramagnetic surgical clips (e.g., for treatment of an intracranial aneurysm). One must keep in mind the differential for an intracerebral mass lesion includes bacterial abscess, demyelination, and acute ischemic disease. In tumors such as medulloblastoma, ependymoma, and lymphoma, cerebrospinal fluid examination must be performed, if not contraindicated, to look for malignant cells. \(^\text{13}\) For most tumors, the diagnosis is made histopathologically after a surgical resection or biopsy.

**GENERAL CONSIDERATIONS**

Seizures are a common manifestation in patients with both primary and metastatic brain tumors. \(^\text{11}\) The diagnosis of a seizure disorder is usually made clinically. Electroencephalography (EEG) may be useful if the diagnosis is in doubt but is not needed for patients who give a clear history of seizures or for those without clinical evidence of a seizure. Some patients who are seizure free at diagnosis subsequently develop seizures, but routine prophylaxis with anticonvulsant medications is not routinely recommended. \(^\text{14}\) That said, prophylactic use of anticonvulsants is a frequent practice in patients who undergo surgery. \(^\text{15}\)

Vasogenic edema surrounding many brain tumors, particularly malignant ones, contributes significantly to morbidity. Glucocorticoid steroids are important in the management of patients with brain tumors, particularly in patients with bulky disease and those who have hydrocephalus. Most patients with brain tumors and peritumoral edema can be adequately managed with glucocorticoids. Reduction of ICP and improvement in neurologic symptoms usually begins within hours after starting glucocorticoids. In symptomatic patients, the usual dexamethasone regimen consists of a 10-mg loading dose, followed by 4 mg four times per day or 8 mg twice daily. Steroid therapy should be carefully monitored, and the lowest dose of steroids should be used for the shortest time possible. Once patients have responded, the steroid should be tapered about every 4 to 5 days because dexamethasone has a long half-life. For patients in good clinical condition, the dose may be reduced by steps of 50%. However, for those patients not tolerating the steroid taper, a slower withdrawal (25% dose reduction every week) may be required. Patients receiving radiation may have an exacerbation of vasogenic edema requiring increase of their steroid dosing.

Care should be taken to watch for development of side effects (including thrush, myopathy, cushingoid features, sleep disturbances, mood changes, osteoporosis, glaucoma, cata- racts, gastrointestinal ulcers, glucose intolerance, or diabetes), especially in patients on prolonged steroid therapy. Patients on steroid therapy should be provided with antacid therapy to reduce the risk of gastrointestinal ulceration. *Pneumocystis jirovecii* pneumonia (PCJ) is a life-threatening opportunistic infection that may occur in patients treated with prolonged steroid therapy. PCJ prophylaxis is generally recommended in patients who are on steroids for more than 4 to 6 weeks. Physicians caring for patients with brain tumors who are receiving glucocorticoids should maintain a high index of suspicion for PCJ. The treatment of PCJ in patients with brain tumors is the same as in other non–HIV-infected patients. \(^\text{16}\)

**TABLE 67-1** Signs and Symptoms of Cancers of the Nervous System

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset or change in pattern of headaches (gradually become more frequent and severe or occurring in the morning)</td>
</tr>
<tr>
<td>Unexplained nausea or vomiting</td>
</tr>
<tr>
<td>Seizures, especially if new onset</td>
</tr>
<tr>
<td>Neurocognitive dysfunction</td>
</tr>
<tr>
<td>Personality or behavior changes</td>
</tr>
<tr>
<td>Visual problems (blurred vision, double vision, or loss of vision)</td>
</tr>
<tr>
<td>Depressed level of consciousness</td>
</tr>
<tr>
<td>Speech difficulties</td>
</tr>
<tr>
<td>Loss of sensation or movement in an arm or a leg</td>
</tr>
<tr>
<td>Difficulty with balance</td>
</tr>
<tr>
<td>Cranial nerve palsies</td>
</tr>
<tr>
<td>Hearing problems</td>
</tr>
</tbody>
</table>
Presumably, injury to brain parenchyma can lead to release of tissue thromboplastins that increase the risk of clotting. Furthermore, immobility because of neurologic deficits increases the risk of thromboembolic disease in patients with brain tumors. Anticoagulation therapy of DVTs, particularly those above the knee, with low-molecular-weight heparin is usually effective and well tolerated. Patients with brain tumors receiving anticoagulation therapy (maintained within the therapeutic range) do not appear to have an increased risk of intracranial bleeding compared with those who are not on these drugs. In patients with contraindications to use of anticoagulation therapy (e.g., recent craniotomy, stroke), placement of an inferior vena cava (IVC) filter is preferred. Perioperative anticoagulation therapy may be associated with an elevated risk of intracranial hemorrhage, and other prophylactic measures (e.g., sequential intermittent compression devices) are often employed in patients undergoing brain tumor surgery.

Hospice care should be considered in patients who are not candidates for surgery, radiation therapy (RT), or chemotherapy because of poor performance status or those with deteriorating neurologic deficits despite therapy and because of tumor recurrence. Primary care clinicians can play an important role by working together with the medical oncologist, neurooncologist, radiation oncologist, and neurosurgeon to help patients and families make decisions about hospice care.

PROGNOSIS

The prognosis of patients with benign brain tumors, overall, is very favorable, and their tumors typically do not result in premature death. Very often, patients may incidentally be found to have a meningioma, and for a subset of these patients, no intervention is ever needed. For others, surgical treatment may be curative. Many patients with World Health Organization (WHO) grade I gliomas (e.g., pilocytic astrocytoma) can be cured with a complete resection of the tumor mass. In contrast, patients with primary malignant (WHO grade II to grade IV) or metastatic brain tumors frequently die as a result of their primary disease or from complications related to the disease or its treatment. The prognosis of patients with these malignant tumors can range from months to years to decades depending on the histology and location of the tumor. Patients with WHO grade II gliomas can live from 5 to 15 years, whereas patients with grade III gliomas survive between 2 and 5 years. Of note, a subset of patients with grade II or III gliomas may have tumors with a favorable genetic profile (e.g., loss of heterozygosity of chromosomes 1p and 19q), which is associated with prolonged survival, even beyond a decade. Patients with glioblastoma multiforme (GBM) have an average survival between 12 and 18 months. Several clinical variables have been evaluated for prognostic value. In general, these prognostic factors include WHO grade, age, and performance status. Some data sets suggest that a complete resection of the “gross” tumor also is associated with an improved prognosis. Average survival of patients who are immuno-competent with PCNSL is 5 to 6 years.

GLIOMAS

Gliomas account for more than 80% of primary CNS malignancies. Low-grade gliomas (WHO grades I and II) are tumors with increased cellularity and atypia but without mitoses, endothelial proliferation, or necrosis. Anaplastic gliomas (WHO grade III) exhibit mitoses but no endothelial proliferation or necrosis. Glioblastomas are WHO grade IV gliomas and they exhibit high cellularity and nuclear atypia, elevated mitotic activity, and either endothelial proliferation or necrosis. The treatment of choice for WHO grade I gliomas is surgical resection, which, if complete, is often curative. RT is reserved for the subsequent management of symptomatic patients who are not resectable or in whom progressive disease develops. Treatment options for WHO grade II gliomas include observation, surgical resection, RT or chemotherapy, or a combination of any of these modalities. Whereas at least a diagnostic surgical biopsy is performed prior to initiation of medical therapy, surgical resection may also be considered and is generally required for patients presenting with a large mass or mass effect–related neurologic symptoms. For patients with asymptomatic small tumors with no mass effect, surgical resection is a reasonable option. However, careful observation is an accepted alternative for these patients. Following surgery, RT is administered if there are persistent neurologic symptoms because of residual tumor present on post-operative MRI, in those with substantial residual disease (even if asymptomatic), in select patients with high (>3%) MIB-1 index (monoclonal antibody to detect the Ki-67 nuclear antigen), or age >40 years. However, there are data that suggest that delaying RT has no impact on overall survival. Cyotoxic chemotherapy is used for symptomatic patients with substantial residual tumor or progressive symptoms following radiation.

Nearly all patients with WHO grade III glioma undergo a maximal safe surgical resection followed by radiation and/or chemotherapy or, more recently, a combination of the two modalities. Ongoing studies are designed to more carefully define the optimal medical treatment for these tumors, and it is well accepted that the intensity of treatment is tailored to the presence or absence of 1p/19q codeletion. Standard upfront treatment for WHO grade IV glioma includes maximal safe surgical resection followed by combination of radiation and chemotherapy with temozolomide (an oral alkylating agent that causes DNA damage). As the disease progresses, repeat surgical resection with or without carmustine wafer placement (local chemotherapy), reirradiation, and treatment with bevaczimab, a monoclonal antibody that binds vascular endothelial growth factor (VEGF), are commonly used management options. We recommend that patients with grade II to grade IV gliomas be enrolled in clinical trials whenever available.

MENINGIOMAS

Meningiomas are usually benign (WHO grade I) and originate in the dura that covers the brain and spinal cord. Many meningiomas that are noted incidentally do not require treatment at the time of original diagnosis, and observation is appropriate because two-thirds of these patients will not have symptoms over time. If asymptomatic, the treatment of choice is usually complete resection. Surgery is often feasible if the meningioma is located over the cortical convexity, olfactory groove, anterior sagittal sinus, or posterior fossa. However, if complete resection is not performed, external beam radiotherapy or focal stereotactic radiosurgery may be used for tumor control. There is increasing interest in the use of radiosurgery as a primary treatment...
for these tumors. The initial treatment of meningioma with atypical (WHO grade II) or malignant (WHO grade III) histologic features also begins with surgical resection; however, RT is more commonly used as an adjuvant for these patients.\textsuperscript{29} No pharmaceutical intervention has shown any significant antitumor activity in meningiomas.

**PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA**

PCNSLs constitute approximately 2\% to 3\% of all brain tumors in patients who are immunocompetent.\textsuperscript{13} The role of surgery is restricted primarily to obtaining appropriate tissue for diagnosis, and this is usually accomplished via a stereotactically guided needle biopsy. The initial medical treatment of PCNSL has improved dramatically over the last few decades with the combination of methotrexate-based chemotherapy with or without whole-brain RT (WBRT).\textsuperscript{13}

**BRAIN METASTASES**

Brain metastases occur in 20\% to 40\% of adults with cancer and are most commonly associated with cancers of the lung, breast, and melanoma.\textsuperscript{2} Surgery and some form of radiation, radiosurgery with or without WBRT, are the treatments of choice in patients with a limited number of brain metastases.\textsuperscript{30–32} Patients with more extensive disease are more likely to receive WBRT alone, but even then, treatment sometimes may also include surgery or radiosurgery of larger lesions.\textsuperscript{33,34} Ultimately, proper patient selection is the most important variable affecting the outcome of treatment of patients with brain metastases; patients who have a poor performance status, widespread or uncontrolled systemic disease, or extensive intracranial metastases have a poor prognosis and are best managed palliatively. Chemotherapy is rarely used as primary therapy for brain metastases.

**SURVEILLANCE (TABLE 67-2)**

There is no single accepted or validated surveillance schedule for patients with brain tumors. However, patients with malignant tumors are generally followed with imaging on a more frequent basis than those with benign tumors. Patients with grade III or IV gliomas should be followed closely with serial MRI scans at 2 to 6 weeks post-RT, then every 2 to 4 months for at least 2 to 3 years, and then less frequently. A typical schedule for WHO grade II tumors is for an MRI to be done every 3 months in year 1, then every 6 to 12 months for another 5 years. Less frequent imaging is required beyond 5 to 10 years. For meningiomas, WHO grade III meningiomas or recurrent meningiomas of any grade are followed more closely than grades I and II tumors that are newly diagnosed and/or treated. Distinguishing RT-induced imaging changes from progressive disease is important to avoid premature and inappropriate discontinuation of a treatment regimen. This phenomenon has been termed pseudoprogression and is seen in one-third of patients with grade III to grade IV gliomas treated with a combination of RT and chemotherapy. It is typically seen in the first 6 months after completion of RT. Specialized imaging studies such as perfusion MRI is increasingly being employed to help distinguish between pseudoprogression and true disease progression, but there is no study that is absolutely reliable in making this distinction.

**CONCLUSION**

The prognosis of patients with brain tumors varies widely and depends on site of origin, tumor type (in some cases including molecular genetic subtype), WHO grade (for primary brain tumors), and accessibility to safe surgical treatment. Adjuvant medical treatment for many of these patients can be intense and associated with potentially serious but manageable risks. Coordination of care between neurosurgeons, neurologists, oncologists, and primary care clinicians is critical for optimal patient care.

**References**


KEY POINTS

- Well-differentiated thyroid cancers (papillary, follicular, and Hürthle cell) have very good long-term prognosis. Medullary and anaplastic thyroid cancers are more aggressive tumors with worse prognosis. The cornerstone of thyroid malignancy diagnosis is ultrasonography combined with fine needle aspiration of suspicious thyroid nodules. Cervical lymph nodes should also be evaluated in patients with thyroid cancer.
- Total thyroidectomy is the best treatment for thyroid cancers. Thyroid lobectomy may be a good alternative in few selected cases, with specific indications for more limited resection. Compartment-oriented cervical lymphadenectomies are recommended for lymph node metastases.
- Adrenocortical cancers are very aggressive adrenal tumors that can be functional or nonfunctional. Complete surgical resection is the main predictor of long-term survival.
- The diagnosis of malignant pheochromocytoma is made in the presence of metastatic disease or signs of tumor recurrence after previous adrenalectomy. Although complete cure is difficult, surgical tumor debulking, with or without radioactive iodine MIBG ablation, is indicated for control of symptoms and prevention of the complications of hypercatecholaminemia.

THYROID CANCER

The incidence of thyroid cancer is estimated to be as high as 16.3 per 100,000 patient years and has the fastest growing incidence of all malignancies in the past decade.

Well-differentiated thyroid cancers derived from follicular thyroid cells, comprise the majority of thyroid cancers and are generally associated with an excellent prognosis.

Papillary Thyroid Carcinoma

Papillary thyroid carcinoma (PTC) accounts for more than 80% of all thyroid cancers. Women are affected more commonly than men by a ratio of 3:1. Radiation exposure and family history of first-degree relatives with thyroid cancer are the most important risk factors. Several genetic alterations (e.g., mutations in Ret/PTC, BRAF, Ras) have been implicated in the pathogenesis of PTC. On microscopy, classic PTC is characterized by papillae of tumor cells surrounding a fibrovascular core.

Clinical Presentation

PTC is diagnosed during the workup of an asymptomatic, incidentally identified thyroid nodule (Table 68-1) or because of local symptoms such as dysphagia, dyspnea, or hoarseness. Most patients with PTC are euthyroid.

Evaluation of Thyroid Nodule and Papillary Thyroid Carcinoma

Ultrasonography is the cornerstone of any thyroid nodule evaluation. Sonographically suspicious nodules (size >1 cm, irregular margins, microcalcifications, central blood flow) or enlarging nodules should be biopsied by fine needle aspiration (FNA). Benign-appearing, small thyroid nodules or cysts can be observed through serial ultrasonographic evaluations. Radioactive iodine (RAI) thyroid scan should only be performed when hyperthyroidism is present (low thyroid-stimulating hormone [TSH]) to differentiate Graves disease (which can be medically managed) from toxic adenoma (which should be resected).

If thyroid cancer is diagnosed, ultrasonography of the neck is recommended to evaluate for lymphadenopathy. Suspicious lymphadenopathy will also need to be biopsied by FNA; if positive, the staging of the disease and the surgical plan may change. Even when cervical lymph node metastases or locally advanced tumors are present, distant hematogenous spread of PTC is uncommon, and, therefore, extensive, routine, staging, cross-sectional imaging is not recommended. Indirect or flexible laryngoscopy should be performed in the presence of hoarseness or a history of previous central neck operation for evaluation of possible recurrent laryngeal nerve palsy (either from cancerous infiltration or iatrogenic).

Treatment

Management of patients with PTC consists of surgery, possible adjuvant RAI ablation, TSH suppression, and surveillance. The overall prognosis of PTC is excellent, with an estimated 25-year mortality of only 5%. Patients are stratified as low, intermediate, or high risk for recurrence based on clinicopathologic features, which also determine the need for postoperative RAI ablation.
Surgery
Total thyroidectomy is recommended, given the high risk of multifocality of PTC and the overall low morbidity in experienced surgeons’ hands.1–3 Hemithyroidectomy may be considered for solitary tumors smaller than 1 cm (papillary microcarcinomas), when high-risk features are absent, and the patient prefers a more limited resection.3 Metastatic lymphadenopathy should be treated with compartment-oriented lymphadenectomy of the central or lateral neck. Prophylactic central neck dissection in the absence of macroscopically obvious lymphadenopathy remains controversial.5

Radioactive Iodine
The need for adjuvant RAI ablation is determined by the risk of recurrence. Temporary withdrawal from thyroid hormone replacement or administration of recombinant TSH prior to the RAI ablation increases the efficacy of treatment by increasing the avidity of the residual postthyroidectomy thyroid tissue to RAI.

Thyroid Hormone Suppression
After completion of surgical treatment, with or without RAI, thyroid hormone replacement is adjusted to keep TSH low (<0.1 mU per L for high-risk patients) to eliminate the trophic effect of TSH on any residual thyroid tissue or tumor cells.3

Surveillance
Surveillance is performed mainly through clinical and biochemical evaluation, supplemented by ultrasonography or other imaging modalities as needed (Table 68-2). Biochemical surveillance is based on the measurement of serum thyroglobulin (a precursor of thyroid hormone), which is expected to be undetectable after complete extirpation of the thyroid malignancy. Thyroglobulin levels remain undetectable in the absence of recurrence, even when the test is performed after iatrogenic stimulation with recombinant TSH. Rise of serum thyroglobulin should prompt further workup, such as ultrasound, for detection of the site of recurrence.3

 Follicular Thyroid Carcinoma and Hürthle Cell Carcinoma
Follicular thyroid carcinoma (FTC) accounts for 5% to 10% of all thyroid cancers in iodine-sufficient areas. Hürthle cell carcinomas (HCs) account for only 3% to 5% of all well-differentiated thyroid cancers. Both tumors are derived from the follicular thyroid cells. HC can metastasize to bone or lymph nodes in 30% of patients, whereas FTC metastasizes in 20% of patients to bone or lung. Overall, HC confers poorer prognosis compared to FTC (10-year survival 76% vs. 85%).1–3,8

Clinical Presentation and Evaluation
Both FTC and HC have clinical manifestations similar to PTC and are evaluated in a similar fashion. However, in contrast to PTC, follicular or Hürthle cell neoplasms cannot be easily diagnosed on FNA and are often interpreted as indeterminate or suspicious on cytologic evaluation.1,2

Surgery
Diagnostic hemithyroidectomy is usually recommended for an FNA suggestive of follicular or Hürthle cell neoplasm.1–3 However, if the patient has multiple nodules, is hypothyroid, or has a history of radiation exposure, total thyroidectomy is recommended.

Postoperative Management and Surveillance
Both postoperative management and surveillance are similar to PTC.3

Medullary Thyroid Cancer
Medullary thyroid cancer (MTC) accounts for 4% of thyroid cancers. It is a tumor of the parafollicular or C cells of the thyroid and presents as a sporadic tumor in 75% to 80% of the cases and as part of familial syndromes (multiple endocrine neoplasia [MEN] 2A, MEN 2B, familial MTC) in the remainder.1,2 Germline mutations of the RET proto-oncogene cause the inherited syndromes, whereas somatic RET mutations are present in almost 50% of patients with sporadic MTC.10,11

Clinical Presentation
Sporadic MTCs usually present as solitary thyroid nodules. In most patients, the disease has already metastasized at the time of diagnosis, and clinically detectable cervical lymph nodes are common. Up to 15% of patients have symptoms from compression or invasion of the airway, the esophagus, or the recurrent laryngeal nerve. About 5% of patients present with distant metastatic disease. Familial MTCs present at a younger age and are multifocal. Symptoms related to the coexistent syndromic features of MEN 2 (pheochromocytoma, hyperparathyroidism, neural gangliomas, skeletal abnormalities) may be present.1,2,10,11

Evaluation
The evaluation of patients with MTC is presented in Table 68-3. Serum calcitonin and carcinoembryonic antigen (CEA) are not recommended as screening tools for MTC in patients with thyroid nodules.10,11 However, they both play a significant role in postoperative surveillance as markers of recurrence. Cross-sectional imaging is important for accurate

<table>
<thead>
<tr>
<th>TABLE 68-1</th>
<th>Initial Evaluation of Thyroid Nodule</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
<td></td>
</tr>
<tr>
<td>Serum TSH</td>
<td></td>
</tr>
<tr>
<td>Ultrasound of thyroid</td>
<td></td>
</tr>
<tr>
<td>Fine needle aspiration of nodule</td>
<td></td>
</tr>
<tr>
<td>Thyroid iodine scan (only in hyperthyroidism from a toxic adenoma)</td>
<td></td>
</tr>
<tr>
<td>Ultrasound of neck (only for proven thyroid cancer to detect cervical lymphadenopathy)</td>
<td></td>
</tr>
</tbody>
</table>

TSH, thyroid-stimulating hormone.

<table>
<thead>
<tr>
<th>TABLE 68-2</th>
<th>Postthyroidectomy Surveillance for Papillary Thyroid Cancer Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
<td></td>
</tr>
<tr>
<td>Serum thyroglobulin every 6–12 mo initially</td>
<td></td>
</tr>
<tr>
<td>Stimulated serum thyroglobulin (if TSH-suppressed thyroglobulin is undetectable)</td>
<td></td>
</tr>
<tr>
<td>Ultrasound of neck every 6–12 mo initially</td>
<td></td>
</tr>
<tr>
<td>Thyroid iodine scan 6–12 mo after ablation</td>
<td></td>
</tr>
<tr>
<td>FDG-PET scan as needed</td>
<td></td>
</tr>
</tbody>
</table>

TSH, thyroid-stimulating hormone; FDG-PET, fluorodeoxyglucose positron emission tomography.
staging. Genetic testing for RET mutations should be offered to all MTC patients, including patients without a suspicious family history. The detection of germline RET mutations should prompt evaluation of family members because preventive surgery and close monitoring may be indicated for them. These patients should also be screened for the presence of a pheochromocytoma and hyperparathyroidism.

Surgery and Postoperative Management
Total thyroidectomy with central neck dissection is the recommended treatment. Lateral neck lymphadenectomy is indicated for metastatic disease to the lateral cervical lymph nodes. The completeness of surgical resection is of paramount importance, given the lack of role for RAI in the treatment of MTC (parafollicular cells are not iodine avid). Replacement rather than suppressive hormone therapy (target serum TSH of 0.5 to 2.5 mIU per L) is recommended postoperatively.10

Prognosis and Surveillance
Prognosis of MTC is worse than well-differentiated thyroid cancer, with an estimated 10-year survival of 75%. High preoperative levels of serum calcitonin and CEA and rapid doubling times postoperatively have been associated with a more dismal prognosis. Long-term biochemical monitoring with annual serum calcitonin and CEA levels is recommended for patients with complete postoperative biochemical cure (undetectable serum calcitonin). Patients with detectable calcitonin levels after surgery should be monitored closely, and signs of recurrence should prompt evaluation with ultrasound and cross-sectional imaging.10,11 In patients with metastatic disease, disease free survival can be prolonged with two novel oral kinase inhibitors, vandetanib and cabozantinib.

Anaplastic Thyroid Cancer
Anaplastic thyroid cancer or undifferentiated thyroid cancer is rare (2% to 5% of all thyroid cancers) but is the most aggressive of thyroid malignancies, with a mortality approaching 100%.1,2,12

Clinical Presentation
Almost all patients present with a rapidly enlarging neck mass. Most of them have signs of locally advanced disease (involving larynx, trachea, esophagus, cervical lymph nodes, vessels, muscle) or distant disease (lungs, bones, brain) at the time of diagnosis.1,2,12

Evaluation
FNA is used for diagnosis, but core needle or a surgical biopsy may be required for diagnosis.1,2 Computed tomography (CT) is used to assess the size of the primary tumor, invasion of surrounding structures, and lymphadenopathy.

Treatment
Treatment of anaplastic thyroid cancer is almost never curative. Surgery is often not possible because of the extent of the disease at the time of diagnosis. When the tumor is resectable, total thyroidectomy is recommended to help prevent devastating local invasion. Adjuvant external beam radiation combined with chemotherapy may confer some survival benefit to patients without distant metastases.12 Locally advanced disease is commonly inoperable, and planning should include consideration of end-of-life issues and comfort measures. Patients with advanced anaplastic thyroid cancer should also be considered for participation in clinical trials.

ADRENOCORTICAL CARCINOMA
Adrenocortical carcinomas (ACCs) are rare but very aggressive tumors. Their incidence is estimated at 1 to 2 per million people years. ACCs are usually sporadic, although association with some hereditary syndromes (Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, MEN 1) has been described.1,2,13

Clinical Presentation
More than 50% of ACCs are functional and present with symptoms of Cushing syndrome, virilization, or both (Table 68-4). Symptoms usually develop rapidly, underscoring the aggressive nature of the disease. Nonfunctional tumors will present with symptoms of local growth after reaching a large size (often >10 cm).2

Evaluation
Hormonal evaluation should be performed to assess the functionality of the ACC, which may influence clinical management (Table 68-5). CT is essential in the evaluation of adrenal tumors and can differentiate benign from malignant lesions. Magnetic resonance imaging (MRI) is a useful, complementary imaging tool when local or vascular invasion (e.g., inferior vena cava) is suspected.12 FNA of suspected ACC should not be performed because cytology cannot differentiate adrenal adenoma from carcinoma and a possible risk of tumor seeding along the needle tract is present.

### TABLE 68-4

<table>
<thead>
<tr>
<th>Clinical Manifestations of Adrenocortical Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Cushing syndrome (weight gain, muscle atrophy, weakness, hyperglycemia, insomnia)</td>
</tr>
<tr>
<td>Virilization syndrome (hirsutism, amenorrhea, clitoral enlargement)</td>
</tr>
<tr>
<td>Hyperaldosteronism (hypertension, hypokalemia, muscle weakness)</td>
</tr>
<tr>
<td>Feminization</td>
</tr>
<tr>
<td>Abdominal or flank pain, early satiety</td>
</tr>
<tr>
<td>Constitutional symptoms (anorexia, weight loss, fever)</td>
</tr>
</tbody>
</table>

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### TABLE 68-5  Evaluation of Adrenocortical Carcinoma

<table>
<thead>
<tr>
<th>Hormonal evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-free metanephrines and normetanephrines</td>
</tr>
<tr>
<td>Plasma aldosterone concentration: plasma renin activity ratio</td>
</tr>
<tr>
<td>Morning fasting serum cortisol after 1 mg oral dexamethasone at 11 p.m. (low-dose dexamethasone suppression test)</td>
</tr>
<tr>
<td>Adrenal androgens (DHES, androstenedione, testosterone, 17-OH-progesterone)</td>
</tr>
<tr>
<td>Serum estradiol</td>
</tr>
<tr>
<td>Imaging studies</td>
</tr>
<tr>
<td>CT, MRI of abdomen and distant sites (e.g., chest)</td>
</tr>
<tr>
<td>FDG-PET (as needed)</td>
</tr>
</tbody>
</table>

DHES, dehydroepiandrosterone sulfate; CT, computed tomography; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose positron emission tomography

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**Treatment**

Surgery is recommended for resectable ACC. The completeness of the initial surgical resection is a determining factor of long-term survival, and intraoperative spillage of the tumor should be avoided. Caution should be taken perioperatively to avoid adrenal insufficiency if a cortisol-producing ACC is resected. Mitotane is an adrenocorticolytic drug that is used either as an adjuvant therapy after surgery or as a primary therapy in patients with unresectable or metastatic ACC. Treatment of hypercortisolism may include the use of ketoconazole or metyrapone either preoperatively or in the setting of unresectable or recurrent disease.

**Prognosis and Surveillance**

Overall, 5-year survival has been estimated between 50% and 60%. Monitoring for reemergence of increased adrenal hormone levels, along with the use of cross-sectional imaging and fluorodeoxyglucose positron emission tomography (FDG-PET), constitute the most common methods of surveillance after ACC resection.

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**MALIGNANT PHEOCHROMOCYTOMA**

Phaeochromocytomas are rare, catecholamine-secreting tumors that arise from the adrenal medulla. Their incidence is estimated to be less than 1 per 100,000 person years. Between 3% and 13% of all pheochromocytomas are malignant. Pheochromocytomas are diagnosed as malignant when metastases (to bone, lungs, liver, kidney, or lymph nodes), local invasion, or recurrence are present. It is otherwise difficult to determine whether a pheochromocytoma is benign or malignant.

**Clinical Presentation and Diagnosis**

Headache, palpitations, hypertension (often episodic), diaphoresis, anxiety, weight loss, weakness, and flushing are some of the clinical manifestations of pheochromocytoma. Diagnosis requires the detection of elevated levels of plasma catecholamines (epinephrine, norepinephrine, metanephrines, normetanephrines) or urinary catecholamines and their metabolites (24-hour urine metanephrines, normetanephrines, vanillylmandelic acid [VMA]). No laboratory test is specific to malignancy. CT and MRI are usually used for localization and evaluation for evidence of multifocal or metastatic disease. Iodine-131-metaiodobenzylguanidine (I-131-MIBG) may also be used in the evaluation of a patient with pheochromocytoma to detect ectopic or metastatic disease.

**Therapy**

The diagnosis of malignant pheochromocytoma indicates, by definition, the presence of metastatic or recurrent disease. Surgical resection of the primary tumor or debulking is important to reduce the levels of circulating catecholamines and potentially increase the efficacy of postoperative I-131-MIBG ablation. Preoperative preparation with α- and β-blockade and fluid resuscitation, in conjunction with careful intraoperative blood pressure control, are necessary for safe surgery. Medical management with α-adrenergic blockers and calcium channel blockers are essential in inoperable cases for symptom control. Catecholamine synthesis inhibitor, α-methyl-paratyrosine, can also be used.

**Prognosis and Surveillance**

Prognosis for malignant pheochromocytoma is poor secondary to metastases or local recurrence. Five-year survival is estimated between 20% and 50%. Surveillance after resection of any pheochromocytoma is indicated because subsequent recurrence or distant metastases will indicate malignancy. Clear guidelines have not been established, but biochemical surveillance with plasma metanephrines every 6 to 12 months is suggested, supplemented by CT or I-131-MIBG as needed.

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**References**


CHAPTER 69 Cancer of Unknown Primary

F. Anthony Greco, MD • John D. Hainsworth, MD

KEY POINTS

- Carcinoma of unknown primary site is a common clinical syndrome, accounting for approximately 3% of all cancer diagnoses.
- Clinical evaluation should always include CT scans of the chest and abdomen, focused evaluation of symptomatic areas, and biopsy of the most accessible metastases.
- Optimum pathologic evaluation for most patients requires specialized studies (immunohistochemical stains, molecular profiling) in addition to histologic examination. Fine needle aspiration biopsies are often inadequate to complete such an evaluation.
- The prognosis of patients with carcinoma of unknown primary site is highly variable, ranging from totally treatment resistant to potentially curable.
- Favorable patient subsets, defined by clinical and/or pathologic features, should be recognized and given specific treatment. Most of the patients with highly favorable treatment outcomes are contained in these groups.

A patient is considered to have cancer of unknown primary site when metastatic cancer is detected at one or more locations and a routine evaluation (see the following text) does not reveal a primary site. This syndrome is relatively common, accounting for approximately 3% of all new cancer diagnoses. Patients with this syndrome are diverse in their clinical presentation, pathologic findings, response to treatment, and prognosis.1

Most patients with cancer of unknown primary site have carcinomas, although a few patients are found to have melanoma, sarcoma, or lymphoma after complete evaluation. Adenocarcinoma is the most common histology.

PATHOGENESIS

Cancers of unknown primary share the ability to metastasize at a time when the primary tumor remains relatively small. In autopsy series, primary sites (usually less than 2 cm) can be detected in approximately 75% of patients.2 The most common primary sites identified at autopsy are in various gastrointestinal sites (colorectum, pancreas, stomach, liver) and in the lung.

CLINICAL MANIFESTATIONS

The presenting signs and symptoms of patients in this heterogeneous group are variable. In most patients, the presence of advanced cancer is relatively easy to detect. Symptoms are usually related to the areas of metastatic tumor involvement. In addition, systemic symptoms frequently associated with advanced cancer are common, including anorexia, weight loss, weakness, and fatigue. The most common metastatic sites include the liver, lungs, lymph nodes, and skeletal system; however, many other sites can be involved.

DIAGNOSTIC EVALUATION

Once it becomes evident that the patient has advanced cancer, a focused evaluation should answer the following questions:

- Can a primary site be identified? Because the prognosis of several advanced cancer types is improved markedly with specific treatments, accurate identification of patients with these primary sites is an important prerequisite to administering optimal therapy.
- If a primary site cannot be identified, does the patient have clinical or pathologic features that predict a more favorable treatment outcome? Specific treatable subsets are discussed subsequently.
- What is the extent of metastatic involvement? Precise definition of the extent and location of disease can aid in treatment planning and in determining prognosis.

Initial Clinical Evaluation

A relatively limited clinical evaluation is usually sufficient to establish the presence of metastatic cancer. Recommended initial evaluation includes a complete medical history, physical examination, chemistry profile, complete blood counts, and computed tomography (CT) scans of the chest and abdomen. The physical examination should include a full skin exam, rectal exam, testicular exam (men), and breast and pelvic exams (women). Additional radiologic and/or endoscopic
evaluation of symptomatic areas should be pursued. Once a metastatic cancer is suspected, a biopsy should be performed without further delay.

Selection of a Biopsy Site
Diagnostic material should generally be obtained from the most easily approachable and accessible metastatic site identified during initial evaluation. Cytologic evaluation, as obtained from a fine needle aspiration biopsy, can accurately determine whether a malignancy is present; however, a larger biopsy (core needle or excisional) is usually necessary for an appropriate pathologic evaluation.

Additional Clinical Evaluation
Based on results of the initial clinical evaluation and biopsy, additional clinical testing is appropriate for specific patient subsets as summarized in Table 69-1.

Asymptomatic Areas
In general, extensive radiologic or endoscopic evaluation of asymptomatic areas is not productive and should be avoided. A possible exception is the positron emission tomography (PET) scan; in a number of small studies, unsuspected primary sites have been identified in approximately 40% of patients.

PATHOLOGIC EVALUATION
The pathologic evaluation is critical in the management of patients with cancer of unknown primary site. In most cases, specialized pathologic evaluation is required in addition to standard light microscopic histologic examination. Several important questions should be addressed by the pathologist.

Carcinoma versus Other Cancer Types
In patients with undifferentiated neoplasms, the pathologist cannot determine the lineage of the cancer by histologic examination. In this group, approximately two-thirds of patients have high-grade lymphomas; these patients are important to identify initially because more than 50% can be cured with first-line R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) therapy. Immunohistochemical (IHC) stains are almost always successful in differentiating carcinoma from other cancer types including lymphoma, melanoma, and sarcoma.

Determination of Carcinoma Subtypes
The identification of neuroendocrine carcinoma, either by histologic examination or IHC staining (chromogranin or synaptophysin), is important. Even when the primary site is not identified, specific treatments are available for neuroendocrine carcinoma (see the following text).

Identifying a Primary Site
The histologic appearance and IHC staining of most metastatic adenocarcinomas is not sufficiently distinctive to allow identification of the site of origin. An exception is the prostate-specific antigen (PSA) stain, which is sensitive and specific for prostate adenocarcinoma. Other IHC stains are useful when coupled with a typical clinical presentation.

Emerging molecular pathologic techniques are likely to further improve the diagnosis of patients with cancer of unknown primary site. Specific gene expression profiles based on the tissue of origin have been identified for many tumor types, and new assays are available to detect gene expression patterns in tumor tissue. Preliminary studies indicate that these molecular assays can predict a tissue of origin in most patients with unknown primary cancer.

TREATMENT
When clinical evaluation results in the identification of a primary site or specific tumor type (e.g., lymphoma), these patients should be treated according to guidelines established for the management of their specific tumor type.

Specific Treatable Subsets
Even if the initial evaluation is unsuccessful in identifying a primary site, several clinical presentations have been identified that require specific treatment and have a prognosis.

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Biopsy Result</th>
<th>Additional Diagnostic Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, axillary adenopathy</td>
<td>Adenocarcinoma</td>
<td>Mammogram, breast ultrasound, breast MRI</td>
</tr>
<tr>
<td>Men, bone metastases (particularly if blastic)</td>
<td>Adenocarcinoma</td>
<td>Serum PSA</td>
</tr>
<tr>
<td>Men &lt;45 y, mediastinal and/or retroperitoneal mass</td>
<td>Poorly differentiated carcinoma</td>
<td>Serum HCG, AFP, testicular ultrasound</td>
</tr>
<tr>
<td>Metastases limited to liver, peritoneum</td>
<td>Adenocarcinoma, suggestive of GI primary</td>
<td>Colonoscopy, upper GI endoscopy</td>
</tr>
<tr>
<td>Features of lung cancer (hilar, mediastinal adenopathy)</td>
<td>Carcinoma, TTF-1 positive</td>
<td>Bronchoscopy</td>
</tr>
<tr>
<td>Cervical adenopathy</td>
<td>Squamous carcinoma</td>
<td>ENT endoscopy with biopsy, PET scan, bronchoscopy (low cervical involvement)</td>
</tr>
<tr>
<td>Inguinal adenopathy</td>
<td>Squamous carcinoma</td>
<td>Pelvic exam, anoscopy</td>
</tr>
<tr>
<td>Single metastasis (any location)</td>
<td>Any carcinoma</td>
<td>PET scan</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; PSA, prostate-specific antigen; HCG, human chorionic gonadotropin; AFP, α-fetoprotein; GI, gastrointestinal; TTF-1, thyroid transcription factor 1; ENT, ear, nose, and throat; PET, positron emission tomography.
that is favorable compared to the remainder of patients with cancer of unknown primary site. Table 69-2 summarizes these favorable subsets and the outcomes achieved with specific therapy. It is critical to recognize these patients because curative therapy is available for some. These favorable subsets are discussed elsewhere in greater detail.1

**Empiric Chemotherapy**

Most patients with carcinoma of unknown primary site do not fit into any of these relatively favorable subgroups. Standard treatment for these patients includes the empiric use of “broad-spectrum” chemotherapy regimens, containing agents with some activity against various adenocarcinomas. The median survival with empiric chemotherapy is 8 to 11 months. However, some patients derive a more substantial benefit; approximately 25% are alive at 2 years, and occasional patients (approximately 5%) have prolonged survival.1 Because patients who have substantial benefit from empiric chemotherapy have been difficult to predict, a trial of empiric chemotherapy is recommended for all patients with a good performance status.

In the near future, it is likely that the number of patients who require empiric therapy will decrease, and many patients will have treatment directed against the tissue of origin predicted by molecular tumor profiling. However, substantial improvement in survival of patients with cancer of unknown primary site will depend on continued improvement in the efficacy of therapy for common solid tumor types, including lung, breast, and gastrointestinal malignancies.

**References**


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**Table 69-2** Summary of Clinicopathologic Features and Recommended Treatment of Favorable Patient Subsets

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Pathologic Features</th>
<th>Treatment</th>
<th>Treatment Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, peritoneal/carcinomatosis</td>
<td>Adenocarcinoma (some with serous papillary features)</td>
<td>Treat as stage III ovarian cancer</td>
<td>Median 28-mo survival; 20% 5-y survival</td>
</tr>
<tr>
<td>Women, isolated axillary adenopathy</td>
<td>Adenocarcinoma</td>
<td>Treat as stage II breast cancer</td>
<td>30%–50% cure rate</td>
</tr>
<tr>
<td>Women, clinical features of metastatic breast cancer (chest wall, pleural, or bone involvement)</td>
<td>Adenocarcinoma, ER/PR-positive</td>
<td>Treat as metastatic breast cancer</td>
<td>Median survival 24 mo</td>
</tr>
<tr>
<td>Men, bone metastases</td>
<td>Adenocarcinoma, PSA-positive</td>
<td>Treat as metastatic prostate cancer</td>
<td>Median survival 30–40 mo</td>
</tr>
<tr>
<td>Colon cancer profile (liver, peritoneal metastases)</td>
<td>Adenocarcinoma, CDX2-positive</td>
<td>Treat as metastatic colon cancer</td>
<td>Median survival 20–24 mo</td>
</tr>
<tr>
<td>Single metastasis</td>
<td>Any carcinoma</td>
<td>Resection and/or radiotherapy</td>
<td>Variable; 10%–15% long-term survival</td>
</tr>
<tr>
<td>Isolated cervical adenopathy</td>
<td>Squamous carcinoma</td>
<td>Treat as locally advanced head/neck carcinoma</td>
<td>40%–50% cure rate</td>
</tr>
<tr>
<td>Isolated inguinal adenopathy</td>
<td>Squamous carcinoma</td>
<td>Inguinal lymphadenectomy ± radiotherapy</td>
<td>20%–25% cure rate</td>
</tr>
<tr>
<td>Extragonadal germ cell cancer syndrome</td>
<td>Poorly differentiated carcinoma</td>
<td>Treat as poor prognosis germ cell tumor</td>
<td>30%–40% cure rate</td>
</tr>
<tr>
<td>Diverse clinical presentations</td>
<td>Neuroendocrine carcinoma, aggressive</td>
<td>Treat with platinum/etoposide</td>
<td>Median survival 12–15 mo; 5%–10% long-term survival</td>
</tr>
<tr>
<td>Diverse clinical presentations (usually liver metastases)</td>
<td>Neuroendocrine carcinoma, low grade</td>
<td>Treat as metastatic carcinoid</td>
<td>65%–70% 5-y survival</td>
</tr>
</tbody>
</table>

ER, estrogen receptor; PR, progesterone receptor; PSA, prostate-specific antigen.
HIV and Other Immunosuppression-Related Malignancies

Nitya Nathwani, MD • Amrita Y. Krishnan, MD, FACP

KEY POINTS

• Individuals who are infected with HIV as well as other patients who are chronically immunosuppressed have an elevated risk of developing malignancy.
• Three AIDS-defining malignancies: Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and invasive cervical cancer.
• In the HAART (highly active antiretroviral therapy) era, the incidence of KS and NHL has decreased, but cervical cancer incidence has remained stable.
• There are several non–AIDS-defining malignancies, their incidence has been increasing over time, and they now constitute most cancers in this population.
• HAART is an important component of therapy and generally enables administration of definitive treatment for the malignancy.
• Non-HIV immunodeficiency-related malignancies may occur post–solid organ transplantation, in patients with cell-mediated immune deficiencies, and with the use of antitumor necrosis factor inhibitors.

With the advent of highly active antiretroviral therapy (HAART), the survival of patients infected with HIV has improved dramatically because patients are no longer dying of opportunistic infections or other AIDS-related syndromes. Although the incidence of opportunistic infections in the post-HAART era has declined, malignancies continue to be a significant cause of mortality in these patients. The pathogenesis of these tumors is complex and multifactorial. There are three AIDS-defining malignancies, namely, Kaposi sarcoma (KS), invasive cervical cancer, and non-Hodgkin lymphoma (NHL). There are several non–AIDS-defining malignancies, which occur in patients infected with HIV as well as in patients without HIV who are chronically immunosuppressed such as patients post solid organ transplantation and patients with cell-mediated immune deficiencies. These will be discussed together.

EPIDEMIOLOGY AND PATHOGENESIS

Compared to the general population, patients infected with HIV have an elevated risk of developing several malignancies. Non–AIDS-defining cancers were a minority in the pre-HAART compared with the post-HAART eras. In the HAART era, the incidence of the AIDS-defining KS and NHL have decreased markedly, but the incidence of cervical cancer has remained stable. Overall, the incidence of non–AIDS-defining cancers has been increasing over time because of lowered mortality from infection, with patients therefore living longer and developing cancer. Now, non–AIDS-defining malignancies constitute the most cancers in this population.

AIDS-DEFINING MALIGNANCIES

There are three AIDS-defining malignancies, namely, KS, invasive cervical cancer, and NHL.

Kaposi Sarcoma

Classic KS was originally described in 1872 by a Hungarian dermatologist, Moritz Kaposi, at the University of Vienna. It is a low-grade sarcoma of vascular origin, associated with infection with human herpesvirus (HHV)-8. AIDS-associated KS was first reported in 1994. Besides classic KS, and AIDS-associated or epidemic KS, there are two other clinical types, namely, the endemic variety seen in Africa and the iatrogenic/immunosuppression-related type seen predominantly in solid organ transplant recipients. This review is limited to AIDS-related KS.
They range from indolent lymphomas, which are often just observed to aggressive lymphomas, which frequently require urgent, sometimes emergent, treatment. The incidence of high-grade NHL, central nervous system (CNS) lymphoma, and primary effusion lymphoma are increased in the population who are HIV positive. The incidence of NHL increases with worsening immunosuppression in individuals infected with HIV. The presence of “B” symptoms, which include fevers, drenching night sweats, and weight loss of more than 10% in the last 6 months, are common. Compared to systemic lymphomas in HIV-negative individuals, these patients generally have more frequent B symptoms, more advanced disease, and often extranodal presentations with GI, lung, liver, CNS, and bone marrow involvement.

An elevated lactate dehydrogenase (LDH) may signify a high tumor burden and, consequently, a poorer prognosis. A biopsy of the affected lymph node or organ is mandatory for appropriate diagnosis and classification of this large group of diseases. It is important for the primary care clinician to be aware that a fine needle aspiration alone is inadequate to diagnose these cases, and a core or ideally an excisional biopsy is required for accurate diagnosis and treatment. It is preferable to obtain a biopsy before any treatment, including corticosteroids, is initiated because this may interfere with interpretation of the biopsy. Unfortunately, this is not always possible because patients may present emergently such as in the case of spinal cord compression, acute airway obstruction, and superior vena cava obstruction.

In the HAART era, both tumor burden and systemic illness signify a worse prognosis.6 Patients with a low CD4 count and the presence of HHV-8 DNA may do worse. HAART is invariably used as first-line therapy and often leads to regression in KS lesions. Patients with advanced visceral disease are candidates for systemic chemotherapy.

Non-Hodgkin Lymphoma

The non–Hodgkin-type lymphomas are a large and heterogeneous group of malignant neoplasms of the lymphoid tissues.

As previously mentioned, it is an AIDS-defining illness and the most common tumor in individuals infected with HIV. It primarily affects homosexual or bisexual men and is of particular importance for primary care clinicians to recognize because it may lead to a diagnosis of a previously unrecognized HIV infection.

Clinical manifestations are protean, anywhere from asymptomatic skin involvement to disseminated disease. Skin involvement is common, typically with popular lesions of varying sizes and colors because of their vascularity but occasionally with plaque-like or fungating lesions (Fig. 70-1). Lesions are generally symmetrical, nonpruritic, seldom painful, and most commonly occur on the lower extremities, face, oral mucosa, and genital areas. Diagnosis of suspected lesions should be confirmed by a biopsy to differentiate from bacillary angiomatosis. In a patient with suspected KS, a detailed physical examination is mandatory to document the extent of involvement. Visceral involvement, especially in patients with low cluster of differentiation (CD) 4 counts, is not uncommon. Although any organ can be involved, gastrointestinal (GI) and pulmonary involvement predominate. GI involvement may be asymptomatic or manifested by nonspecific symptoms such as bleeding, nausea, vomiting, diarrhea, or abdominal pain. An endoscopy for symptomatic patients generally reveals hemorrhagic nodules. Similarly, pulmonary involvement may be asymptomatic and detected on chest radiograph. Bronchoscopy typically reveals cherry red, raised lesions.

In the HAART era, both tumor burden and systemic illness signify a worse prognosis.6 Patients with a low CD4 count and the presence of HHV-8 DNA may do worse. HAART is invariably used as first-line therapy and often leads to regression in KS lesions. Patients with advanced visceral disease are candidates for systemic chemotherapy.

FIGURE 70-1. Skin lesions in AIDS-related Kaposi sarcoma.
Randomized trials of standard doses of combination chemotherapy versus reduced doses showed inferior results for the standard dose arm because of increased hematologic toxicity and infections. In the post-HAART era, it became possible to treat patients with more aggressive therapy because of improved hematologic reserve in patients on HAART. Patients are now treated with regimens identical to patients with NHL without HIV. Consequently, the median survival of these patients has improved and the remission rates that are seen when aggressive multiagent combination chemotherapy is given together with HAART approach those of HIV-negative patients. As a result, more aggressive therapies such as high-dose chemotherapy and stem cell transplantation have been explored in the HAART era with encouraging results.

Choice of therapy is primarily determined by the subtype of NHL and the stage of the disease. HAART is an important component of all treatment and enables administration of chemotherapy or radiation, although it remains a point of controversy whether to give HAART concomitantly with chemotherapy or to temporarily suspend antiretroviral therapy during chemotherapy because of concerns of drug interactions. For diffuse large B-cell lymphoma (DLBCL), the most common subtype in this population, the principles of treatment are similar to those in the HIV-negative population. Limited stage disease is usually treated with chemotherapy and involved field radiation. As mentioned previously, most of this population have advanced-stage disease and are consequently treated with combination chemotherapy. The most widely used regimen employs a combination of rituximab (immunotherapy directed against CD20) with cyclophosphamide, the anthracycline Adriamycin, vincristine, and prednisone (R-CHOP). Rituximab, etoposide, vincristine (Oncovin), Adriamycin, cyclophosphamide, and prednisone (R-EPOCH) has shown high remission rates and durable remissions. Attention should be given to appropriate infection prophylaxis while patients are being treated with chemotherapy.

### Cervical Cancer

Women who are HIV positive have a higher incidence of cervical neoplasia than the HIV-negative population, and invasive cervical cancer is now considered an AIDS-defining malignancy. These are HPV-driven cancers caused by certain serotypes of HPV, in particular, HPV-16 and HPV-18. Women who are HIV positive are at higher risk for HPV infection compared to their HIV-negative counterparts, and this risk increases as the HIV viral load increases and CD4 count decreases. Therefore, cervical cancer screening with Pap smears for women who are HIV positive is extremely important. There is a fivefold increase in incidence of cervical precursor lesions in women who are HIV positive, and these are treated similar to HIV-negative women. When these women develop cervical cancer, it is clinically more aggressive and of advanced-stage disease; and although it is treated akin to HIV-negative individuals with surgery, radiation, and chemotherapy depending on the stage, the outcome is less favorable than in HIV-negative patients.

### NON–AIDS-DEFINING MALIGNANCIES

There are several non–AIDS-defining malignancies, which contribute to mortality in the HIV population. These are listed in Table 70-1. They generally occur at a younger age and are often more aggressive, both histologically and clinically. Various other factors complicate their management and are responsible for the poorer outcome in these patients. These include poor performance status and, particularly in patients with defined AIDS, difficulty in staging because of the challenges in interpreting imaging studies and drug interactions between chemotherapy and HAART. The various malignancies will be briefly discussed as follows.

### Lung Cancer

Lung cancer is the most common cancer worldwide and remains the leading cause of cancer death in the United States. Patients who are HIV positive are at higher risk for developing lung cancer as compared to the HIV-negative population in both the pre- and post-HAART era. This increased incidence of lung cancer is also found in recipients of solid organ transplants. In addition to a smoking history, which is common in individuals infected with HIV, HIV itself appears to be an independent risk factor. Individuals infected with HIV with lung cancer tend to present at a younger age and with more advanced disease (stage III or IV). The commonest histologic subtype is adenocarcinoma followed by squamous cell carcinoma (SCC). The treatment principles are similar to those in HIV-negative patients. Surgery is the preferred treatment for localized disease; however, unfortunately, many patients present with advanced disease and are therefore unresectable; others have a poor performance status with comorbidities precluding surgery. Treatment options include radiation alone, chemotherapy, or a combined approach, depending on the stage, performance status, and comorbidities. Because lung cancer is so common and treatment generally yields disappointing results, it is particularly important for primary care clinicians to counsel patients on smoking cessation and to aggressively work up pulmonary symptoms and/or radiographic abnormalities in this population.

<table>
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<tr>
<th>AIDS-defining malignancies</th>
<th>Kaposi sarcoma</th>
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<td>Non-Hodgkin lymphoma</td>
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<td>Cervical cancer</td>
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<td>Non–AIDS-defining malignancies</td>
<td>Lung cancer</td>
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<td>Hodgkin lymphoma</td>
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<td>Skin cancer</td>
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<td>Head and neck cancer</td>
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<td>Hepatocellular cancer</td>
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<td>Colorectal cancer</td>
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<td>Testicular seminomas</td>
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<td>Conjunctival cancer</td>
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<td>Esophageal cancer</td>
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<tr>
<td>Renal cell carcinoma</td>
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<tr>
<td>Sarcomas (especially leiomyosarcomas)</td>
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Hodgkin Lymphoma

This is more common in individuals infected with HIV compared to the general population, and the incidence is higher in individuals who are HIV positive in the HAART era. This interesting finding appears to be related to the proliferation and survival of the malignant Reed-Sternberg cells, which occur in a certain milieu, consisting of CD4 lymphocytes, which are higher in patients with HIV with better immune function because of HAART. The lymphomas are usually Epstein-Barr virus (EBV) positive. Patients infected with HIV commonly have more unfavorable histology, B symptoms, advanced stage, and extranodal disease with bone marrow involvement. The optimal therapy is not clearly established, but HAART in combination with one of the commonly used regimens such as Adriamycin/doxorubicin, bleomycin, vinblastine, and dacarbazin (ABVD) is often employed and the survival has improved.

Anal Cancer

HIV-related anal cancer is similar in several respects to cervical cancer, wherein oncogenic subtypes of HPV are invariably implicated, leading to a spectrum of precancerous changes called anal intraepithelial neoplasia (AIN), which may progress and lead to anal cancer. Anal cancer rates are significantly higher in individuals infected with HIV with respect to the general population and particularly in men infected with HIV who have sex with men. It is important for the primary care clinician to recognize that like cervical cancer, anal cancer can be prevented by appropriate recognition and treatment of high-grade intraepithelial lesions, and that cytologic screening, followed by anoscopy and biopsy as needed, particularly in high-risk groups, may decrease the incidence of anal cancer. Treatment of AIN depends on factors such as histologic grade and presence or absence of symptoms. Treatment options range from observation to local therapies such as trichloroacetic acid (TCA) or imiquimod application, infrared coagulation, electrocautery, laser ablation, and surgical excision. For invasive anal cancer, combined chemoradiotherapy is the preferred treatment because it has a high cure rate and allows preservation of the anal sphincter. The concurrent use of 5-fluorouracil and mitomycin with radiation is arguably the most common approach. Primary care clinicians should be aware of the recently approved HPV vaccine for prevention of anal cancer in addition to cervical cancer prevention.

Skin Cancer

Primary skin cancer is one of the most frequent non–AIDS-defining malignancies. The incidence of both melanomas and nonmelanomatous skin cancers are increased in the population who are HIV positive, and basal cell carcinoma (BCC) is the most common cutaneous malignancy. Individuals who are HIV positive with BCC and SCC are often younger and have tumors in multiple, synchronous, atypical, non–sun-exposed locations. Their recurrence rate is higher, treatment complications are more frequent, and outcome is generally worse. BCCs seem to appear mainly on the trunk and SCCs on the head and neck. The recommendation is to treat BCCs in this population similar to HIV-negative individuals. Primary care clinicians should counsel patients on primary prevention of SCC and BCC with the help of sunscreen and sun avoidance and secondary prevention with thorough periodic physical examination and early biopsy of any suspicious lesions.

Head and Neck Cancers

Head and neck cancers are more frequent in the population who are HIV positive. This is probably multifactorial and in part because of the higher tobacco and alcohol use in this population because these are both independent risk factors, coupled with association with oncogenic viruses, EBV in the nasopharynx, and HPV in the oropharynx. Almost half the cases of head and neck cancers in patients with HIV are related to HPV. Patients with HPV-related head and neck cancers have a better outcome than those related to tobacco. They are treated similarly to the HIV-negative population with surgery, radiation, chemotherapy, or a combination of these treatments; however, toxicity may be higher in these patients, particularly from radiation, and the outcome is generally worse.

Other Cancers

There are numerous other cancers associated with HIV. Hepatocellular cancer (HCC) is more frequent in patients with HIV, presumably resulting from coinfection with hepatitis B and C. Patients are generally treated similar to the HIV-negative population. Colorectal cancer appears to be commoner in the population with HIV, occurring at a relatively young age, with advanced stage. This is important for the primary care clinician to be aware of, and consideration should be made to screen these patients at a younger age. Sigmoidoscopy may miss right-sided colon cancers, which may be more frequent in this population.

Testicular seminomas are also more common in patients with HIV, but the clinical presentation, treatment, and outcomes are similar to the HIV-negative population. Other solid tumors described more in these individuals include conjunctival cancer, esophageal cancer, renal cancer, and sarcomas, in particular HIV-associated leiomyosarcoma.

Among the hematologic neoplasms, other than Hodgkin lymphoma and NHL, which have been discussed previously, plasma cell disorders and acute myeloid leukemia have also been found at a higher frequency in the population with HIV.

NON-HIV IMMUNOSUPPRESSION-RELATED MALIGNANCIES

Patients without HIV who are chronically immunosuppressed such as patients post–solid organ transplantation and patients with cell-mediated immune deficiencies are at elevated risk for developing cancer. Patients receiving tumor necrosis factor α inhibitors, particularly in combination with cyclophosphamide, may have a higher risk of developing malignancy in the form of solid tumors, lymphomas, and especially nonmelanoma skin cancers.

Following solid organ transplantation, this increased risk of developing various cancers is well described. It may be related to factors such as immunosuppression, viral infections, and sun exposure. In this population, periodic screening
is recommended, and this depends on type of cancer. Periodic, complete skin examination is important in transplant recipients. Pretransplant, both the donor and recipient, should be carefully screened to rule out a preexisting malignancy. In certain scenarios, reduction of immunosuppression may lead to tumor regression, and it is important to know that the initial treatment may be withdrawal of iatrogenic immunosuppression in many cases. A large, recently published study of more than 175,732 solid organ transplant recipients between 1987 and 2008 reveals that the overall cancer risk was elevated, and malignancy was identified in 10,656 cases. This corresponds to an incidence of 1,374.7 per 100,000 person years; the standardized incidence ratio (SIR) was 2.1 (95% confidence interval [CI], 2.06 to 2.14). Some of the most strikingly elevated cancer risks are presented in Table 70-2.

### References


KEY POINTS

- Childhood cancer is rare and may be difficult to diagnose. Symptoms and survival rates vary, but most children with cancer are cured with current treatments.
- Pediatric and adult malignancies differ greatly in incidence, risk factors, cytogenetics, and treatment. Leukemia and brain tumors each account for about one-third of cancer diagnoses in children.
- Prompt recognition of symptoms and early referral to a pediatric oncologist are essential for optimal management of pediatric malignancies. Adolescents and young adults with ALL are more likely to be cured when treated on pediatric-inspired ALL protocols.
- Continued monitoring for relapsed disease, side effects of therapy, and secondary malignancies are important aspects in the care of childhood cancer survivors. It is important for primary care clinicians to know the specific risks associated with the therapy administered to their patients.

Primary care clinicians face unique challenges regarding pediatric oncology patients. In contrast to cancer in adults, childhood cancer is rare. There are approximately 12,000 new pediatric cancer cases diagnosed per year in the United States. Of all cancers diagnosed from 2005 to 2009, only 1.1% were in patients younger than the age of 20 years. Nonetheless, cancer is the leading cause of disease-related mortality in children younger than the age of 15 years and is the fourth leading cause of death overall behind accidental injury, homicide, and suicide. Given its rarity, primary care clinicians often have limited experience in diagnosing pediatric cancers. Symptoms can often be vague, insidious in onset, and can mimic more common pediatric disorders. Delay in diagnosis of pediatric malignancies has been shown to be associated with a child’s age, parent education, type and site of cancer, presenting symptoms, cancer stage, and the first medical specialty consulted.

Despite these facts, most children diagnosed with cancer are cured. Survival varies by site, age at diagnosis, gender, and race, but overall 5-year survival rates now reach 80% when all children aged 0 to 19 years are considered. Early referral to a pediatric oncologist is important because prompt recognition and timely treatment may improve survival and reduce complications.

Primary care clinicians are charged with identifying children who warrant an evaluation for malignancy. They may also be called on to participate in the care of children and their families while cancer treatment is ongoing. Additionally, because most children diagnosed with cancer will survive their disease, primary care clinicians often manage the long-term effects of both the disease and treatment. A comprehensive review of current therapy and outcomes in pediatric cancer is beyond the scope of this chapter. Instead, this chapter will highlight presentations of the most common types of pediatric malignancies, address issues most frequently seen by primary care clinicians, explore how pediatric and adult malignancies differ, and emphasize important ongoing areas of care for pediatric oncology survivors.

DIFFERENCES FROM ADULT MALIGNANCES

The spectrum of pediatric cancer differs substantially from that seen in adults (Fig. 71-1). The distinction begins with differences in diagnostic types between pediatric and adult malignancies that ultimately underlie etiology, risk factors, presentation, incidence, response to therapy, and long-term outcomes. The most common types of cancer in adults, that is, carcinomas, are rarely seen in children. Furthermore, the distribution of pediatric cancers varies greatly by age group. In contrast to adult cancers, childhood cancers tend to have shorter latency times, grow more rapidly, and are more likely to be disseminated at the time of presentation. As such, few pediatric cancers are amenable to surgical excision as a primary modality. Despite this, childhood cancers are, by and large, more curable than adult malignancies. The increased ability to cure childhood malignancies is related to factors intrinsic to the cancers that children develop, their responsiveness to available treatments, and to the greater ability of children to tolerate therapy.

In comparison to adult survivors, childhood cancer survivors face a lifetime of potential consequences related to their disease and treatment. Permanent effects on growth,
neurocognitive development, and reproductive function affect children disproportionately. Survivors may live long enough to experience the late effects of chemotherapy and radiation that arise decades after treatment, including secondary malignancies and cardiovascular disease. Primary care clinicians need to be cognizant of the unique challenges that face childhood cancer survivors.

**EPIDEMIOLOGY**

The incidence of pediatric malignancies has a bimodal distribution with a peak in the first 5 years of life, a nadir in the school age years, and then a gradual rise after the age of 15 years. The peak incidence of specific childhood malignancies occurs at different ages, and thus consideration of the age of a child is a major factor in the differential diagnosis (Fig. 71-2).

Leukemia is the most common type of childhood malignancy, accounting for approximately one-third of all cancers diagnosed in children. Unlike in adults, acute lymphoblastic leukemia (ALL) is relatively more common than acute myeloid leukemia (AML) in children. The peak age of diagnosis of childhood ALL is 2 to 3 years, whereas the incidence of pediatric AML has a small peak in the first year of life, subsequently decreases until late childhood, and then gradually increases into adulthood. Chronic leukemias are extremely uncommon in childhood because chronic myeloid leukemia (CML) accounts for only 3% to 4% of childhood leukemia and chronic lymphoid leukemia is essentially nonexistent. Regarding lymphomas, Hodgkin lymphoma (HL) accounts for about 5% of all pediatric cancers and non-Hodgkin lymphomas (NHLs) for an additional 3%.

Among pediatric solid tumors, brain tumors are the most common. Although they represent a diverse group of malignant neoplasms, taken together, they comprise approximately 30% of childhood cancer. Neuroblastoma is the most common extracranial solid tumor, representing 8% of childhood cancers, followed closely by Wilms tumor, which accounts for 6% of childhood cancers. Both of these tumors primarily affect children younger than the age of 5 years. Bone sarcomas, including osteosarcoma and Ewing sarcoma, comprise about 5% of childhood cancer. They primarily affect older children, with the highest incidence in adolescence and young adulthood.

**ETIOLOGY AND RISK FACTORS**

In most children with cancer, no predisposing factors are identified. However, a few known factors are associated with an increased risk of certain types of childhood cancer. In utero exposure to ionizing radiation is thought to increase the risk of childhood malignancy, particularly leukemia, by 1.5-fold to twofold over baseline. Prior exposure to therapeutic chemotherapy and/or radiotherapy is associated with an increased risk of a second malignancy. External beam radiation is associated with an increased risk of osteosarcoma within the radiation field. Alkylating agents and topoisomerase inhibitors are linked to the subsequent development of myelodysplastic syndrome and leukemia. Treatment of ALL has been associated with the later development of myeloid malignancies, lymphoma, carcinomas, sarcomas, and brain tumors.

Several genetic syndromes are associated with the development of childhood malignancies. Children with Down syndrome are at a roughly 20-fold increased risk of developing leukemia, characteristically AML in infancy and ALL in childhood. Several other cancer predisposition syndromes carry an elevated risk of developing a childhood malignancy, including neurofibromatosis, Beckwith-Wiedemann syndrome, ataxiatalangiectasia, and Li-Fraumeni syndrome (Table 71-1).

**HEMATOLOGIC MALIGNANCIES**

**Leukemia**

Leukemias result from the malignant transformation of precursors of lymphoid (ALL) or myeloid (AML) cell lineages. Children with acute leukemia typically present with symptoms related to impaired production of normal blood cells because of infiltration of the marrow by leukemia cells. The symptoms of ALL and AML may be indistinguishable from one another and are similar to the presentation of these diseases in adults.
The diagnosis of a new case of leukemia in a child may be subtle or obvious. Often, the differential diagnosis will include benign conditions, including acute viral infection (such as Epstein-Barr virus), aplastic anemia, rheumatologic conditions, hemophagocytic syndrome, and other rare congenital disorders. Rarely, leukemia is diagnosed by an incidental finding of leukemic “blasts” on peripheral blood smear. Symptomatic patients may demonstrate pallor, fatigue, fever, bruising, and petechiae. Patients may complain of bone or joint pain and may develop limp or refusal to stand or walk. Leukemia cells may infiltrate the lymph nodes, liver, spleen, central nervous system (CNS), testes, gingivae, and eyes. Cutaneous involvement is characteristic of leukemias in neonates and infants. Malignant blasts may form solid masses, especially in the anterior mediastinum, leading to tracheal and/or vascular compression in ALL and orbital or epidural “chloromas” in AML. The primary care provider must be alert to the possibility of leukemia in a child presenting with cough, new onset “wheezing,” or joint and bone pain. Empiric use of corticosteroid for presumed asthma or arthritis in a child with undiagnosed lymphoblastic leukemia can lead to delay in diagnosis and adversely affect treatment outcome.

When leukemia is suspected in a baby or child, evaluation should begin with a complete blood count (CBC) and peripheral blood smear. Renal function and serum electrolytes including calcium, phosphate, uric acid, and lactate dehydrogenase (LDH) should be assessed because patients with a large burden of rapidly proliferating cells may present with features of acute tumor lysis syndrome even before initiation of chemotherapy. Coagulation studies should be obtained and abnormalities corrected before high-risk invasive procedures are performed. Blood culture should be obtained from patients presenting with fever, and empirical broad-spectrum antibiotics should be initiated, especially if the neutrophil count is low. A sample of blood should be sent to the blood bank in preparation for red blood cell and/or platelet transfusion. A screening chest radiograph is recommended to evaluate for mediastinal mass and effusions. Further diagnostic workup should proceed without delay in consultation with a pediatric hematologist/oncologist. Although evaluation of the peripheral blood smear is often helpful, examination of the bone marrow is usually required to establish a diagnosis of leukemia and to obtain all necessary studies. In addition to morphologic assessment, flow cytometry and cytogenetic studies should be performed on the bone marrow aspirate specimen. These studies have become increasingly important in risk stratification of patients with acute leukemia. Assessment of the cerebrospinal fluid (CSF) by lumbar puncture (LP) is performed to detect leukemic involvement of the CNS.

Progressive improvements in the outcome of childhood ALL has been one of the great cancer treatment successes of the past five decades. Five-year event-free survival (EFS) for pediatric ALL now exceeds 80%. Modern treatment of pediatric ALL starts with a 1-month induction period that results in complete remission in most children. Postremission therapy consists of a consolidation phase, the intensity of which varies in accordance with risk group, followed by a prolonged maintenance phase that typically lasts about 2 years. Chemophrophylaxis of the CNS is administered in all children with ALL, but cranial irradiation is now used in a minority. Determinants of risk group include age at presentation, presenting white blood cell count, immunophenotype, karyotype, molecular abnormalities, and treatment response. Sensitive measures of minimal residual disease are now being used to identify children at high risk for treatment failure for whom intensified therapy, investigational treatments, and/or hematopoietic cell transplant (HCT) are considered. In the past, HCT was universally recommended for children with Philadelphia chromosome-positive ALL, but more recently, the role of transplant has become controversial because relatively favorable outcomes have been observed in pediatric patients treated with tyrosine kinase inhibitors combined with chemotherapy.

In contrast to the excellent outcomes seen in childhood ALL, 5-year EFS in adult ALL only reaches about 40%. This is attributed to differences in biologic characteristics of the disease: Adult ALL generally displays a higher white blood cell count at presentation, increased prevalence of T phenotype, higher incidence of Ph positivity, and lower incidence of “favorable” karyotypic abnormalities—all of which confer a worse outcome. Importantly, several studies have linked superior outcome in similarly aged adolescent and young adults with ALL treated on pediatric protocols compared with adult protocols. This difference in outcome appears to be a consequence of significant differences in the composition and intensity of treatment between adult and pediatric protocols as well as disparities in treatment practices between adult and pediatric providers. Therefore, whenever possible, children, adolescents, and young adults with ALL should be referred to a center with experience in the delivery of pediatric-inspired ALL treatment.

In comparison to ALL, treatment of pediatric AML is more toxic and overall less successful. Even today, only approximately 50% of pediatric patients with AML are cured. Treatment of AML consists of one or two courses of intensely myelosuppressive induction chemotherapy, which yields remission in approximately 90% of children. Postremission therapy is determined by karyotypic and molecular features of the leukemia, response to therapy, and, in some cases, the availability of a suitable donor for allogeneic HCT. In comparison to adults, favorable karyotypic abnormalities are
relatively more frequent, comprising about 21% of cases of childhood AML. Postinduction therapy for favorable risk patients consists of two to three courses of consolidation chemotherapy. For children with high-risk AML, including those harboring the FLT-3 internal tandem duplication, allogeneic HCT using the best available donor in first remission is generally recommended. Optimal postremission treatment for children with standard risk AML, that is, neither favorable risk nor high risk, remains controversial. HCT is often considered the best option when a matched sibling donor is available. AML with recurrent genetic abnormalities, such as inv(16) or t(8;21), may also be treated with HCT.

**Lymphomas**

Lymphomas are a group of malignant neoplasms of the lymphoid lineage broadly classified as HL and NHL. HL is a relatively indolent malignancy that most commonly arises within lymphoid tissues of the neck. Involved nodes are usually nontender and may have a firm, rubbery, or matted texture on physical examination. Mediastinal involvement is common. Extranodal spread of tumor to liver, lung, cortical bone, and bone marrow occurs in advanced stages of the disease. Fevers, night sweats, and weight loss, collectively referred to as “B” symptoms, are associated with advanced disease. Inflammatory markers, including the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are often elevated at diagnosis and useful as markers of response to therapy and early indicators of recurrence.

The diagnosis of HL is typically made by excisional biopsy of an enlarged node. Many children come to biopsy after a course of oral antibiotics for presumed lymphadenitis is ineffective. Once the diagnosis of HL is established, staging evaluation is undertaken under the direction of the treating oncologist. Radiographic staging typically includes computed tomography (CT) of neck through pelvis and fluorodeoxyglucose positron emission tomography (FDG-PET) scan. Current therapy results in long-term disease-free survival in close to 100% of pediatric patients with localized disease and 70% to 90% with advanced stage disease. Minimizing the risks of late effects of therapy without decreasing efficacy has been a focus of clinical research in pediatric HL over the past decade. This is being achieved by reducing radiation exposure, field, and dose and limiting cumulative exposure to anthracyclines, bleomycin, and alkylating agents.

Four main pathologic subtypes of NHL occur in childhood. Lymphoblastic lymphoma (LL) comprises approximately 30%, Burkitt lymphoma 40%, diffuse large B-cell lymphoma (DLBCL) 20%, and anaplastic large cell lymphoma (ALCL) the remaining 10%. In contrast to adults, the indolent, low-grade forms of NHL are distinctly uncommon in children. LL is histologically identical to ALL except that the extent of bone marrow involvement is less than 25%, and it is treated similarly. Most cases of LL are of precursor T-cell origin and often present with an anterior mediastinal mass, which may compress the airway and/or vascular structures at the thoracic inlet. Burkitt lymphoma is a high-grade malignancy of mature B-cell origin, with most tumors presenting in the abdomen. The bone marrow and/or CNS are involved infrequently and confer an adverse prognosis. Because of the extremely rapid growth rate of this tumor, patients are at high risk for the development of hyperuricemia and acute tumor lysis syndrome at presentation and after initiation of treatment. Large cell lymphoma may be of B-, T-, or null cell origin. These tumors arise most commonly in the lymph nodes of the mediastinum and abdomen but may arise in or spread to skin, bone, and soft tissues.

**SOLID TUMORS**

**Neuroblastoma**

Neuroblastoma is the most common extracranial solid tumor in children and accounts for approximately 15% of pediatric oncology deaths. Ninety-six percent of cases occur in children younger than 10 years of age. Neuroblastoma is a variable disease, ranging from a localized tumor with benign behavior to disseminated disease with extremely aggressive features. Prognosis varies widely according to patient’s age, histology, and tumor extent.

Neuroblastoma arises from primitive neural crest elements that exist throughout the body. Most tumors arise in the abdomen, especially in the adrenal gland. Thoracic neuroblastomas also occur, especially in infants, and may present with an incidental finding on chest radiograph or with respiratory distress, wheezing, or facial swelling. Tumors of the retroperitoneum and chest may extend into the spinal canal and can cause spinal cord compression. To limit the risk of irreversible spinal cord injury in these cases, treatment must be expedited. Neuroblastoma may disseminate to cortical bone, bone marrow, liver, and skin (cutaneous involvement is characteristic of infants with metastatic disease). Depending on where lesions are located, patients with disseminated disease experience bone pain, irritability, fatigue, pallor, bruising, and/or fevers. Spread of neuroblastoma to the orbital bones may lead to proptosis and orbital discoloration, a characteristic sign referred to as “raccoon eyes.” A phenomenon called opsomyoclonus (dancing eyes, dancing feet) can occur in up to 5% of children with neuroblastoma. This results from the production by the tumor of autoantibodies to neural tissue.

Elevated levels of the catecholamines vanillylmandelic acid (VMA) and homovanillic acid (HVA) are found in the urine in most cases of neuroblastoma. Histopathologic examination of the primary tumor or a metastatic site is necessary to establish
the diagnosis. When neuroblastoma is suspected, sufficient biopsy tissue should be obtained for analysis of MYCN amplification status and ploidy because these are variables that influence prognosis. Staging evaluation includes CT/magnetic resonance imaging (MRI) imaging, bone scan, metaiodobenzylguanidine (MIBG) imaging, bone marrow aspirates and biopsies, and spinal MRI scan if there is suspicion of spinal cord involvement.

Neuroblastoma treatment depends on risk group, which is determined by age, stage, and biologic features of the tumor. Low- and intermediate-risk neuroblastomas are treated very successfully with surgery and relatively mild chemotherapy. On the other hand, despite the most aggressive combination of multiagent chemotherapy, radiation, surgery, immunotherapy, and differentiation therapy, high-risk neuroblastoma is cured in only approximately 50% of patients.

Renal Tumors
Most primary malignant renal tumors in children are Wilms tumor; however, several other histologic types occur. Abdominal distension, without other symptoms, is the most common presenting feature, although abdominal pain may result with stretching of the renal capsule. Gross or microscopic hematuria may be present at the time of presentation, and hypertension is commonly seen. Abdominal ultrasound is the initial study of choice because it can be useful in confirming the presence of a mass, probable site of origin in the kidney, and the presence of tumor thrombus in the inferior vena cava. CT imaging with contrast may demonstrate the characteristic “claw sign” of preserved renal parenchyma “gripping” the adjacent tumor. Bilateral Wilms tumors do occur, typically in association with a genetic predisposition, and, therefore, the contralateral kidney should be evaluated. Metastatic Wilms Tumor characteristically spreads via the renal vein into the inferior vena cava and to the lungs. In the United States, up-front nephrectomy is performed when feasible for unilateral tumors that do not extend into the renal vein. Surgical management of renal masses in children should be done by an experienced pediatric surgeon because tumor spillage may affect prognosis. In some circumstances, preoperative chemotherapy is administered to shrink the tumor to make the resection easier. Chemotherapy is risk stratified, and radiation is administered in high-stage tumors. Overall, more than 90% of children with Wilms tumor are cured.

Bone Tumors
Primary tumors of bone tend to affect older children and young adults more frequently than children younger than the age of 10 years. Osteosarcoma is the most common primary malignant bone tumor in children and adolescents, followed closely by Ewing sarcoma. Although both types of tumors can arise in any bone, Ewing sarcoma is more likely to arise in the axial skeleton and soft tissues, whereas more than 50% of osteosarcomas arise from the long bones around the knee. Because these tumors grow relatively slowly, pain is often chronic and progressive and may be attributed to a sports injury or trauma. A hallmark of bone malignancy is “deep” unrelenting pain that often occurs at night, wakes the patient from sleep, and is poorly controlled with analgesics. Pathologic fracture may precipitate diagnosis. Blood work is usually normal, but the alkaline phosphatase and/or LDH are elevated in some cases. Metastatic disease to the lungs and other bones may be present at diagnosis or may develop later and confer a significantly worse prognosis. Unlike osteosarcoma, Ewing sarcoma may metastasize to the bone marrow. In disseminated Ewing sarcoma, systemic symptoms such as fever, malaise, and weight loss may occur. If a primary bone tumor is suspected, referral to a multidisciplinary team experienced in the surgical and medical management of pediatric bone malignancies is strongly encouraged. Percutaneous biopsy is performed to establish the diagnosis in most cases. Surgical resection, or in some cases radiation therapy to the primary tumor, is necessary for cure but may be delayed until after neoadjuvant chemotherapy is administered. With a combination of chemotherapy and surgery, cure rates for localized osteosarcoma reach 70%, whereas survival for patients with metastatic disease is only about 25%. Similarly, nonmetastatic Ewing sarcoma is cured in approximately 70%, but patients with metastatic disease are much less likely to be cured.

OTHER PEDIATRIC SOLID TUMORS
Several other tumors that are relatively unique to childhood deserve mention including rhabdomyosarcoma, hepatoblastoma, retinoblastoma, and germ cell tumors. Patients with these cancers present with symptoms related to the location and extent of their tumor. Rhabdomyosarcoma is a soft tissue sarcoma with histologic features of primitive muscle development. The most common sites of disease are the head and neck, genitourinary tract, and extremities, although it can arise anywhere in the body. In advanced stages, rhabdomyosarcoma may spread to lung, bone, and bone marrow and has a poor prognosis. Hepatoblastoma is a primary tumor of the liver that occurs almost exclusively in children less than 2 years of age. Children with a history or prematurity and those with Beckwith-Wiedemann syndrome are at increased risk for the development of this tumor. Abdominal distension is the most common presenting symptom. In most cases, serum levels of α-fetoprotein (AFP) and/or β-human chorionic gonadotropin (hBHC) are elevated.

Retinoblastoma is a tumor of retinal origin that occurs in young children. It has the distinction of being the first tumor associated with a genetic defect, namely a mutation of the RB gene on chromosome 13. Children with constitutional mutations involving this genetic locus are at high risk for developing early, multiple, and bilateral tumors. Some of these lesions can be present at birth. Patients with a family history of retinoblastoma should begin screening by an experienced pediatric ophthalmologist shortly after birth. The sporadic (nongermline) form of the disease accounts for about 60% of cases. Patients with sporadic disease have unilateral tumors and they have a slightly older age at diagnosis. The most common presenting sign of retinoblastoma is leukocoria or loss of the normal red retinal reflex. If the tumor is large, it may manifest as a painful red eye. Germ cell tumors are a relatively rare, heterogeneous group of malignant tumors comprised of several different histologic types. Taken together, they account for only about 1% of cancers in children. These tumors may arise in gonadal or extragonadal (usually midline) sites, and, therefore, a mass in the abdomen or pelvis or in the male testis is the usual presenting complaint. Germ cell tumors may secrete tumor markers including AFP, hBHC, LDH, and placental alkaline phosphatase (PLAP). If elevated at diagnosis, tumor markers may be useful in following patients for response to therapy and disease recurrence.
Central Nervous System Tumors

Taken as a group, brain tumors, or CNS tumors, are the most common type of solid tumors in children. They comprise a histologically diverse group of tumors that occur in the brain, brain stem, spinal cord, or the ependymal lining of the ventricles. In contrast to adults in whom most intracranial tumors are the result of metastases, most brain tumors in children are primary CNS tumors.

Pediatric brain tumors can be broadly classified into tumors of glial origin and those of primitive neuroectodermal cell origin. Tumors of glial cell origin may arise anywhere within the craniospinal axis and are of variable grade. Specific tumors in this group range from low-grade astrocytomas to high-grade glioblastoma multiforme and ependymoma. Primitive undifferentiated cells in the CNS give rise to the neuroectodermal tumors. Tumors with this histology that arise in the cerebellum are called medulloblastoma, whereas in the supratentorium they are called primitive neuroectodermal tumors (PNETs).

Presentations of pediatric brain tumors are largely dependent on the location of the tumor. Often, children come to medical attention because of signs and symptoms of increased intracranial pressure or because of the development of focal neurologic signs. In young children whose fontanelle has not yet closed and sutures have not yet fused, the only presenting sign may be an abnormal increase in head circumference. Infratentorial tumors, which account for more than half of all pediatric brain tumors, obstruct the flow of CSF, leading to headache and vomiting (characteristically without nausea, especially in the morning). As symptoms of elevated intracranial pressure progress, patients may experience severe headache, intractable emesis, visual disturbance, abnormal eye movements, and eventually altered mental status. Infants may demonstrate bulging of the anterior fontanelle. Children with cerebellar tumors may demonstrate nystagmus and ataxia. Supratentorial tumors sometimes cause symptoms of increased intracranial pressure but more commonly come to medical attention because of focal seizures, hemiparesis, or visual changes. Vague complaints of personality change, ranging from lethargy to irritability may be noted. Imaging of the brain is usually the first step in the evaluation of a patient with a suspected brain tumor. CT scan may be needed emergently if there is suspicion of hydrocephalus, cerebral edema, or hemorrhage; however, in a nonemergent situation, MRI is the preferred study for diagnosis and follow-up of pediatric brain tumors because it is more sensitive than CT and does not expose the child to ionizing radiation. In the setting of increased intracranial pressure, LP should not be performed because it may precipitate fatal herniation of the cerebellar tonsils.

When a brain tumor is suspected, the patient should be referred to a pediatric neurosurgeon, preferably one who works collaboratively with an experienced neurooncologist and neurologist. Depending on the size, appearance, and location of the tumor, biopsy, subtotal resection, or complete resection may be undertaken. Sometimes biopsy is not recommended because the radiographic appearance of the tumor is characteristic or because the tumor is in a location that makes biopsy extremely risky. Patients with optic pathway gliomas, especially those known to have neurofibromatosis, and diffuse intrinsic pontine gliomas are usually not subjected to biopsy.

Follow-up Care of Childhood Malignancies

After completion of therapy, children with cancer require regular monitoring of their disease to detect relapse. In some cases, such as osteosarcoma, early detection of recurrence may permit complete surgical resection, which may be curative. In other cases, such as neuroblastoma, early detection and treatment of recurrence may preempt the development of symptoms, although it does not lead to cure. For patients with solid tumors, lymphomas, and brain tumors, imaging studies are performed at decreasing frequency for a period of up to 5 years. In certain tumors, such as hepatoblastoma or germ cell tumors, tumor markers can also be helpful in monitoring for relapse, whereas inflammatory markers can be useful in monitoring for lymphomas. For patients with leukemia, regular monitoring of CBC and physical examination is performed because bone marrow surveillance does not influence outcome. Although monitoring can be useful in detecting relapse, primary care clinicians need to maintain a high index of suspicion in patients with childhood malignancies for symptoms that may indicate a relapse.

Surveillance of patients with childhood malignancies must also include monitoring for side effects of treatment. Monitoring and mitigation of these side effects are important because children have a lifetime at risk for potential side effects ahead of them. Depending on the type of therapy received, childhood cancer survivors are at increased risk for poor growth, short stature, gonadal and neuroendocrine dysfunction that can affect pubertal development and impair fertility, obesity, osteoporosis, cardiovascular disease, pulmonary disease and fibrosis, thyroid dysfunction, renal dysfunction, early cataracts, neurocognitive issues, and of course, secondary malignancies. Primary care clinicians need to be well versed in current recommendations for ongoing screening of their patients who are survivors of childhood cancer. These risks are discussed in detail in another section of this book.

References


**Adenocarcinoma** Cancer derived from epithelial cells that demonstrates gland-like properties.

**Adjuvant therapy** Antineoplastic therapy that is given after the primary cancer treatment to reduce the risk of recurrence. Adjuvant therapy can be chemotherapy, hormonal therapy, and/or radiation therapy.

**Aneuploidy** Abnormal chromosome number (caused by either gain or loss of chromosomes).

**Apoptosis** The normal cellular process that leads to cell death.

**Blast cell** Undifferentiated or minimally differentiated hematopoietic cell that normally comprises less than 5% of bone marrow cells. An increase in percentage of blast cells in the bone marrow or peripheral blood usually indicates a hematopoietic malignancy.

**Brachytherapy** Type of radiation therapy in which radioactive seeds or catheters are implanted directly in or near a tumor site.

**Carcinoma** Cancer derived from epithelial cells.

**Chromosomal translocation** Change in chromosome structure that is caused by a break in at least two chromosomes with an exchange of material between them.

**Chromosome** Structure in the nucleus of a cell that contains DNA and the supporting proteins. Human cells contain 23 pairs of chromosomes.

**Cytogenetic analysis** Analysis of the structure of the chromosomes of a malignancy; used most frequently to characterize hematologic malignancies.

**Cytokine** A protein secreted by cells that affects intercellular communication and signaling.

**Epidermal growth factor receptor (EGFR)** A cell surface protein that regulates growth. It is found on multiple types of cancer cells and serves as a target for several anticancer agents. Examples include erlotinib (lung and pancreas cancer), cetuximab (colorectal and head and neck cancer), and panitumumab (colorectal cancer).

**Exon** DNA sequences that encode proteins.

**Flow cytometry** A laboratory technique in which cell suspensions are mixed with fluorescent-tagged antibodies against proteins. Populations of cells are then identified based on their patterns of fluorescence. Flow cytometry is used predominantly to classify hematologic malignancies, especially leukemias and lymphomas.

**Fluorescence in situ hybridization (FISH)** A laboratory method in which a DNA sequence is detected in a cell by using a complimentary piece of DNA attached to a fluorescent dye.

**Germline mutation** Alteration in DNA that occurs in the sperm and/or egg cell and are therefore passed on to children and present in all cells of the body.

**Growth factor** A protein that regulates growth, differentiation, and/or survival of cells.

**HER2/neu** Also called human epidermal growth factor receptor 2. A tyrosine kinase present on the surface of some malignancies including breast, gastric, and ovarian cancers. HER2/neu is a target for several anticancer agents including trastuzumab and lapatinib.

**Histone deacetylase (HDAC)** An enzyme that regulates DNA expression by removing acetyl group from histones, which are chromosomal proteins. Vorinostat is an HDAC inhibitor used to treat cutaneous T-cell lymphoma.

**Human leukocyte antigen (HLA)** Proteins found on the surface of leukocytes and other cells that are a major determinant of the immune response to transplanted organs. The most important HLA antigen groups for predicting hematopoietic stem cell transplant success are A, B, C, DRB1, and DQB1. Because each person has two copies of each gene, an optimal HLA match is often called a “10/10” match.

**Interleukin** A cytokine made by white blood cells that regulates the immune response.

**Intron** DNA sequences that undergo transcription into mRNA but do not encode a protein product and are deleted (spliced) prior to translation of the mRNA into protein.

**Kinase** An enzyme that catalyzes the transfer of a phosphate group between molecules.

**KRAS** An oncogene that may cause cancer when mutated. The protein product is involved in cell growth, signaling pathways, and apoptosis. Patients with colorectal cancers in which the KRAS gene carries specific mutations do not benefit from cetuximab and panitumumab, which are EGFR blockers.

**Leukemia** Malignancy of white blood cells that predominantly involves bone marrow and blood.

**Lymphoma** Malignancy of lymphocytes that usually involves only lymph nodes and spleen but can also be found in extranodal sites such as skin, gastrointestinal tract, and/or lungs.

**Metachronous cancers** Two or more primary cancers of the same organ, which are diagnosed more than 6 months from each other.

**Mammalian target of rapamycin (mTOR)** A kinase that is part of an intracellular signaling pathway that controls multiple cell functions including growth, proliferation, survival, and protein synthesis. The mTOR inhibitors (e.g., everolimus, temsirolimus) are used for the treatment of renal cell cancer and pancreatic neuroendocrine cancers.

**Mutation** Alterations in the DNA sequence of a cell or cells.

**Oncogene** A gene that regulates cell growth. If mutated, an oncogene can contribute to the development of cancer.

**Polymerase chain reaction (PCR)** A laboratory technique in which multiple copies of a short segment of DNA are produced.

**Sarcoma** Cancer derived from connective tissue.

**Sentinel lymph node** The first lymph node draining a primary cancer. The sentinel node is identified by injecting the cancer with a
marker (a radioactive tracer and/or a dye) and following the path of drainage of the marker. The node can then be excised to determine if it is involved with cancer.

**Somatic mutation** Alteration in DNA that occurs after conception (therefore is not present in the germ cells, is not passed on to children, and is not present in all cells of the body). Most cancers are caused by somatic mutations.

**Stem cells** Undifferentiated cells that have the ability to self-renew and to differentiate into different types of specialized cells.

**Synchronous cancers** Two or more separate primary cancers of the same organ, which are diagnosed within 6 months of each other.

**Transcription** The process of copying information contained in DNA to messenger RNA.

**Transcription factor** A protein that regulates transcription.

**Translation** The process of synthesizing proteins based on information contained in messenger RNA.

**Trisomy** The presence of three copies of the same chromosome in a cell.

**Tyrosine kinase** An enzyme that transfers a phosphate group from adenosine triphosphate (ATP) to tyrosine, an amino acid in a protein. Tyrosine kinases control key cellular processes and are mutated or overexpressed in multiple malignancies.

**Vascular endothelial growth factor (VEGF)** A group of proteins that stimulate the growth of blood vessels. VEGF is a target of several chemotherapeutic agents such as bevacizumab, sunitinib, sorafenib, and others.
Appendix

Useful Internet and Community Resources for Cancer Care

Bonnie Indeck, MSW, LCSW • Nora Rightmer, LCSW

GENERAL
American Cancer Society www.cancer.org
American Institute for Cancer Research www.aicr.org
Association of Cancer Online Resources www.acor.org
Cancer Care Inc www.cancercare.org
Cancer Hope Network www.cancerhopenetwork.org
Cancer Support Community www.cancersupportcommunity.org
ChemoCare www.chemocare.com
Gilda’s Club/The Wellness Community www.gildasclub.org
Imberman Angels www.imermanangels.org
Info Line www.211.org
Lance Armstrong Foundation www.livestrong.org
Cancer and Careers www.cancerandcareers.org
Lotsa Helping Hands www.lotsahelpinghands.com
National Cancer Institute www.cancer.gov
National LGBT Cancer Project www.lgbtcancer.com
National Lymphedema Network www.lymphnet.org
People Living with Cancer www.cancer.net
Social Security Disability Information www.ssa.gov

CATEGORIZED BY TOPIC

CAREGIVERS — addresses the needs of the well spouse/partner
Well Spouse Association www.wellspouse.org

CHILDREN WHOSE PARENTS HAVE CANCER — information and resources for children and for parents to assist children
The Children’s Treehouse Foundation www.childrenstreethousefdn.org
Jack & Jill Late Stage Cancer Foundation www.jajf.org
Kids Konnected www.kidskonnected.org
Parenting at a Challenging Time (PACT)—Massachusetts General Hospital www.mghpact.org/home.php

CLINICAL TRIALS — information about clinical trials and how to access them
Clinical Trials Information www.centerwatch.com
Coalition of Cancer Cooperative Groups www.cancertrialshelp.org

COMPLEMENTARY THERAPY — sites that provide information and education about complementary and alternative medicine
Memorial Sloan-Kettering Cancer Center: About Herbs, Botanicals, and Other Products www.mskcc.org/mskcc/html/11570.cfm?herbsaccept=yes
Society for Integrative Oncology www.integrativeonc.org

EMPLOYMENT— websites that provide information, resources, and guidance regarding the legal aspects of employment during cancer treatment
Cancer and Careers www.cancerandcareers.org
Job Accommodation Network www.askjan.org
U.S. Department of Labor www.dol.gov
Workplace Fairness www.workplacefairness.org

END-OF-LIFE/PALLIATIVE CARE — information and guidance regarding palliative care, pain issues, hospice resources, and general end-of-life concerns
American Pain Foundation www.painfoundation.org
American Pain Society www.ampainsoc.org
Center to Advance Palliative Care www.capc.org
Growth House www.growthhouse.org
Hospice Education Institute www.hospiciworld.org
Hospice Foundation of America www.hospicefoundation.org
Hospice Patients Alliance www.hospicepatients.org
National Association for Home Care & Hospice www.nahc.org
National Hospice and Palliative Care Organization www.nhpco.org
Promoting Excellence in End-of-Life Care www.promotingexcellence.org

FERTILITY — resources about pregnancy and fertility for women with cancer
American Society for Reproductive Medicine www.asrm.org
Cancer in Pregnancy www.motherisk.org/women/cancer.jsp

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TRANSPORTATION
Air Charity Network www.aircharitynetwork.org
Angel Flight America Central www.angelflightcentral.org
Northeast www.angelflightne.org
Southeast www.angelflightse.org
West www.angelflight.org
Corporate Angel Network www.corpangelnetwork.org
Miracle Flights for Kids www.miracleflights.org
National Patient Travel Center www.patienttravel.org
Operation Liftoff www.operationliftoff.com
Patient AirLift Services www.palservices.org

WISH FOUNDATIONS—agencies that provide “wishes” for people with cancer
Dream Foundation www.dreamfoundation.com
Make-A-Wish Foundation www.makeawish.org
Sunshine Foundation www.sunshinefoundation.org
A Wish with Wings www.awishwithwings.com

YOUNG ADULTS WITH CANCER—specific resources for young adults with cancer
I’m Too Young for This (i2y) www.imtooyoungforthis.org
Planet Cancer www.planetcancer.org
Surviving and Moving Forward: The SAMFund www.thesamfund.org
The Ulman Cancer Fund for Young Adults www.ulmanfund.org

CATEGORIZED BY DISEASE
BLADDER CANCER
American Urological Association www.urologyhealth.org/urology/index.cfm?article=100
Bladder Cancer Advocacy Network www.bcan.org
Bladder Cancer WebCafé http://blcwebcafe.org

BRAIN CANCER
American Brain Tumor Association www.abta.org
Brain Tumor Foundation www.brain tumorfoundation.org
Financial Assistance for the Treatment of Brain Cancer www.mission4maureen.org/
Musella Foundation for Brain Tumor Research and Information www.virtualtrials.com

BREAST CANCER
Breast Cancer Information and Awareness www.breastcancer.org
Breast Cancer Information/Jewish Backgrounds www.sharsheret.org
Breast Cancer Network of Strength www.networkofstrength.org
Facing Our Risk of Cancer Empowered (FORCE) www.facingourrisk.org
Inflammatory Breast Cancer Research Foundation www.ibcresearch.org
Living Beyond Breast Cancer www.lbservice.org
Men Against Breast Cancer (MABC) www.menagainstbreastcancer.org
Mothers Supporting Daughters with Breast Cancer (MSDBC) www.mothersdaughters.org

HOUSING—temporary housing resources near treatment centers
American Cancer Society (ACS): Hope Lodge www.cancer.org/Treatment/SupportProgramsServices/HopeLodge/index
Joe’s House www.joeshouse.org
National Association of Hospital Hospitality Houses www.nahhh.org
Ronald McDonald House Charities www.rmhc.com

LEGAL RESOURCES—resources detailing legal rights for people with cancer
American Bar Association www.findlegalhelp.org
Cancer Legal Resource Center www.cancerlegalresourcecenter.org
LawHelp www.lawhelp.org

PERSONAL COMMUNICATION WEBSITES—free private blogs that connect patients with family and friends during a health crisis
CarePages www.carepages.com
CaringBridge www.caringbridge.org
MyHopeSpace www.myhopespace.com
MyLifeLine www.my lifeline.org

SURVIVORSHIP
American Society of Clinical Oncology (ASCO): Survivorship www.cancer.net/patient/Survivorship
Beyond the Cure www.beyondthecure.org
Journey Forward www.journeyforward.org
Lance Armstrong Foundation www.livestrong.org
National Coalition for Cancer Survivorship www.canceradvocacy.org
### HEAD AND NECK CANCERS
- American Head & Neck Society [www.headandneckcancer.org](http://www.headandneckcancer.org)
- International Association of Laryngectomees [www.larynxlink.com](http://www.larynxlink.com)
- Oral Cancer Foundation [www.oralcancerfoundation.org](http://www.oralcancerfoundation.org)
- Support for People with Oral and Head and Neck Cancer [www.spohnc.org](http://www.spohnc.org)

### KIDNEY CANCER
- Kidney Cancer Association [www.curekidneycancer.org](http://www.curekidneycancer.org)

### LIVER CANCER
- American Liver Foundation [www.liverfoundation.org](http://www.liverfoundation.org)
- YES! Beat Liver Tumors [www.beatlivertumors.org](http://www.beatlivertumors.org)

### LUNG CANCER
- Alliance for Lung Cancer Advocacy, Support and Education [www.alcase.org](http://www.alcase.org)
- American Lung Association [www.lungusa.org](http://www.lungusa.org)
- Lung Cancer Alliance [www.lungcanceralliance.org](http://www.lungcanceralliance.org)
- Lung Cancer Online [www.lungcanceronline.org](http://www.lungcanceronline.org)

### LYMPHEDEMA
- Lymphedema Research Foundation [www.lymphaticresearch.org](http://www.lymphaticresearch.org)
- National Lymphedema Network [www.lymphnet.org](http://www.lymphnet.org)

### LYMPHEDEMA
- Lymphedema Research Foundation [www.lymphaticresearch.org](http://www.lymphaticresearch.org)
- National Lymphedema Network [www.lymphnet.org](http://www.lymphnet.org)

### MELANOMA
- Aim at Melanoma [www.aimatmelanoma.org](http://www.aimatmelanoma.org)
- Melanoma Foundation of New England [www.melanomafoundationne.org](http://www.melanomafoundationne.org)
- Melanoma International Foundation [www.melanomaintl.org](http://www.melanomaintl.org)
- Melanoma Research Foundation [www.melanomaresources.info](http://www.melanomaresources.info)
- Skin Cancer Foundation [www.skincancer.org](http://www.skincancer.org)

### MESOTHELIOMA
- Asbestos Disease Awareness Organization [www.asbestosdiseaseawareness.org](http://www.asbestosdiseaseawareness.org)
- Mesothelioma Applied Research Foundation [www.curemeso.org](http://www.curemeso.org)
- Mesothelioma: Overview of Malignant Mesothelioma Cancer [www.researchmesotheliomacancer.com](http://www.researchmesotheliomacancer.com)

### MULTIPLE MYELOMA
- International Myeloma Foundation [www.myeloma.org](http://www.myeloma.org)
- Institute for Myeloma & Bone Cancer Research [www.imbcr.org](http://www.imbcr.org)
- Leukemia & Lymphoma Society: Myeloma [www.lls.org/diseaseinformation/myeloma](http://www.lls.org/diseaseinformation/myeloma)
- Multiple Myeloma Research Foundation [www.themmrf.org](http://www.themmrf.org)

### PANCREATIC CANCER
- Lustgarten Foundation for Pancreatic Cancer Research [www.lustgarten.org](http://www.lustgarten.org)
- Pancreatica: Confronting Pancreatic Cancer [www.pancreatica.org](http://www.pancreatica.org)
- Pancreatic Cancer Action Network [www.pancan.org](http://www.pancan.org)
PROSTATE CANCER
Urology Care Foundation www.urologyhealth.org
Center for Prostate Disease Research www.cpdr.org
Malecare www.malecare.org
Patient Advocates for Advanced Cancer Treatments www.paactusa.org
Prostate Cancer Foundation www.prostatecancerfoundation.org
Prostate Cancer Research Institute www.pcri.org
Us TOO International Prostate Cancer Education & Support Network www.ustoo.com

SARCOMA
Sarcoma Alliance www.sarcomaalliance.org
Sarcoma Foundation of America www.curesarcoma.org

TESTICULAR CANCER
Lance Armstrong Foundation www.livestrong.org
Testicular Cancer Resource Center tcrc.acor.org

THYROID CANCER
American Thyroid Association www.thyroid.org
ThyCA: Thyroid Cancer Survivors’ Association, Inc. www.thyca.org
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