

66 APPROACH TO THE PATIENT WITH CANCER

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The application of current treatment techniques (surgery, radiation therapy, chemotherapy, and biological therapy) results in the cure of >50% of patients diagnosed with cancer. Nevertheless, patients experience the diagnosis of cancer as one of the most traumatic and revolutionary events that has ever happened to them. Independent of prognosis, the diagnosis brings with it a change in a person's self-image and in his or her role in the home and workplace. The prognosis of a person who has just been found to have pancreatic cancer is the same as the prognosis of the person with aortic stenosis who develops the first symptoms of congestive heart failure (median survival, about 8 months). However, the patient with heart disease may remain functional and maintain a self-image as a fully intact person with just a malfunctioning part, a diseased organ ("a bum ticker"). By contrast, the patient with pancreatic cancer has a completely altered self-image and is viewed differently by family and anyone who knows the diagnosis. He or she is being attacked and invaded by a disease that could be anywhere in the body. Every ache or pain takes on desperate significance. Cancer is an exception to the coordinated interaction among cells and organs. In general, the cells of a multicellular organism are programmed for collaboration. Many diseases occur because the specialized cells fail to perform their assigned task. Cancer takes this malfunction one step further. Not only is there a failure of the cancer cell to maintain its specialized function, but it also strikes out on its own; the cancer cell competes to survive using natural mutability and natural selection to seek advantage over normal cells in a recapitulation of evolution. One consequence of the traitorous behavior of cancer cells is that the patient feels betrayed by his or her body. The cancer patient feels that he or she, and not just a body part, is diseased.

THE MAGNITUDE OF THE PROBLEM

No nationwide cancer registry exists; therefore, the incidence of cancer is estimated on the basis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which tabulates cancer incidence and death figures from nine sites, accounting for about 10% of the U.S. population, and from population data from the Bureau of the Census. In 2004, 1.36 million new cases of invasive cancer (699,560 men, 668,470 women) were diagnosed and 563,700 persons (290,890 men, 272,810 women) died from cancer. The percent distribution of new cancer cases and cancer deaths by site for men and women are shown in Table 66-1. Cancer incidence has been declining by about 2% each year since 1992.

The most significant risk factor for cancer overall is age; two-thirds of all cases were in those over age 65. Cancer incidence increases as the third, fourth, or fifth power of age in different sites. For the interval between birth and age 39, 1 in 72 men and 1 in 51 women will develop cancer; for the interval between ages 40 and 59, 1 in 12 men and 1 in 11 women will develop cancer; and for the interval between ages 60 and 79, 1 in 3 men and 1 in 5 women will develop cancer.

Cancer is the second leading cause of death behind heart disease. Deaths from heart disease have declined 45% in the United States since 1950 and continue to decline. After a 70-year period of increases, cancer deaths began to decline in 1997 (Fig. 66-1). The five leading causes of cancer deaths are shown for various populations in Table 66-2. Along with the decrease in incidence has come an increase in survival for cancer patients. The 5-year survival for white patients was 39% in 1960–1963 and 64% in 1992–1998. Cancers are more often deadly in blacks; the 5-year survival was 53% for the 1992–1998

TABLE 66-1 Distribution of Cancer Incidence and Deaths for 2004^a

Sites	Male		Female		
	%	Number	Sites	%	Number
CANCER INCIDENCE					
Prostate	33	230,110	Breast	32	215,990
Lung and bronchus	13	93,110	Lung and bronchus	12	80,660
Colon and rectum	11	73,620	Colon and rectum	11	73,380
Bladder	6	44,640	Endometrium	6	40,320
Melanoma	4	29,900	Ovary	4	25,580
Lymphoma	4	28,850	Lymphoma	4	25,520
Kidney	3	22,080	Melanoma	4	25,200
Leukemia	3	19,020	Thyroid	3	17,640
Oral cavity	3	18,550	Pancreas	2	16,120
Pancreas	2	15,740	Bladder	2	15,600
All other	18	123,940	All other	20	132,460
CANCER DEATHS					
Lung and bronchus	32	91,930	Lung and bronchus	25	68,510
Prostate	10	29,900	Breast	15	40,110
Colon and rectum	10	28,320	Colon and rectum	10	28,410
Pancreas	5	15,440	Ovary	6	16,090
Leukemia	5	12,990	Pancreas	6	15,830
Lymphoma	4	11,090	Leukemia	6	10,310
Esophagus	4	10,250	Lymphoma	4	9,020
Liver and bile duct	3	9,450	Endometrium	3	7,090
Bladder	3	8,780	Myeloma	2	5,640
Kidney	3	7,870	Brain	2	5,490
All other	21	64,870	All other	24	66,310

^a Data exclude basal and squamous cell skin cancers and carcinoma in situ except the bladder.

Source: From Jemal et al, with permission.

interval. Incidence and mortality vary among racial and ethnic groups (Table 66-3). The basis for these differences is unclear.

PATIENT MANAGEMENT

Important information is obtained from every portion of the routine history and physical examination. The duration of symptoms may reveal the chronicity of disease. The past medical history may alert the physician to the presence of underlying diseases that may affect the choice of therapy or the side effects of treatment. The social history may reveal occupational exposure to carcinogens or habits, such as smoking or alcohol consumption, that may influence the course of disease and its treatment. The family history may suggest an underlying familial cancer predisposition and point out the need to begin surveillance or other preventive therapy for unaffected siblings of the patient. The review of systems may suggest early symptoms of metastatic disease or a paraneoplastic syndrome.

DIAGNOSIS The diagnosis of cancer relies most heavily on invasive tissue biopsy and should never be made without obtaining tissue; no noninvasive diagnostic test is sufficient to define a disease process as cancer. Although in rare clinical settings (e.g., thyroid nodules) fine-needle aspiration is an acceptable diagnostic procedure, the diagnosis generally depends on obtaining adequate tissue to permit careful eval-

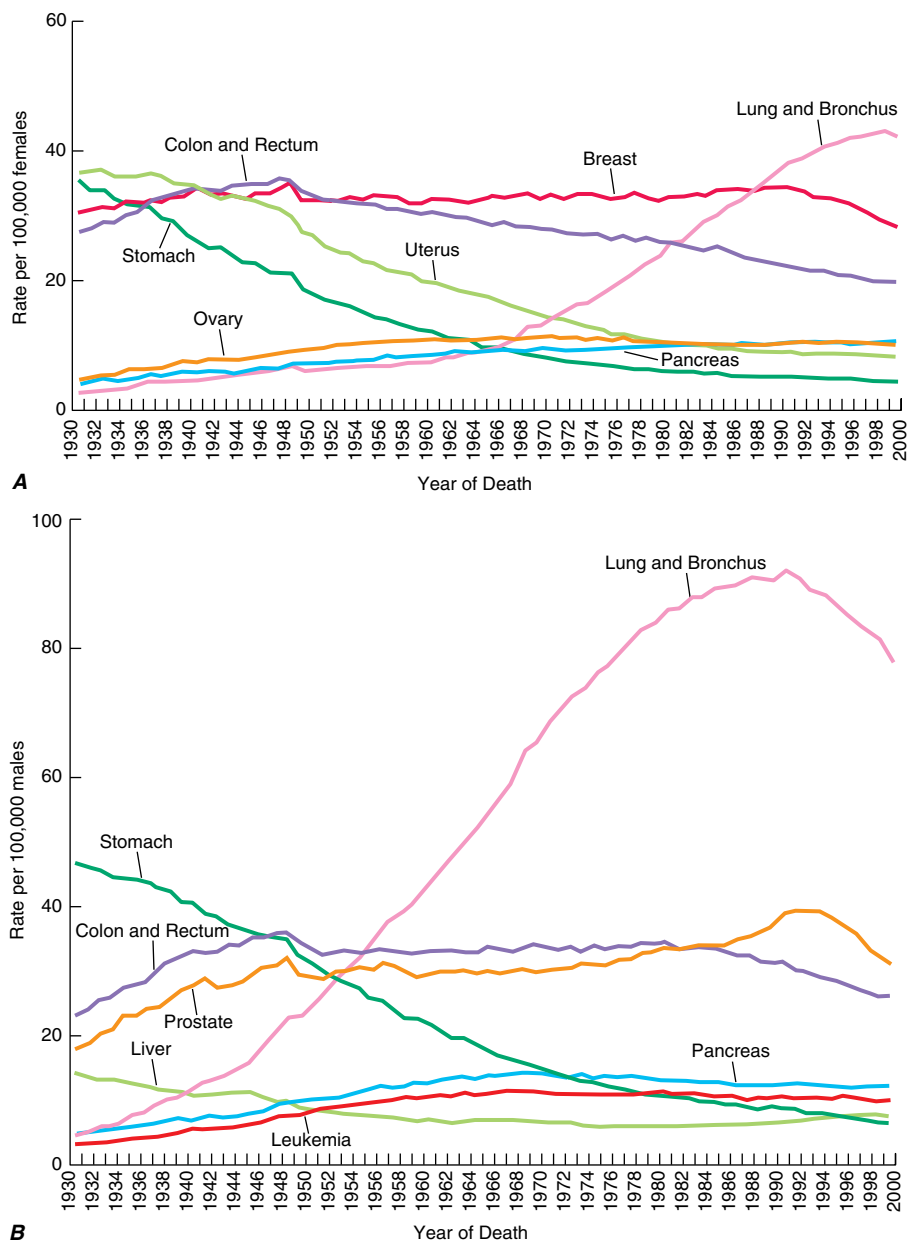


FIGURE 66-1 Sixty-year trend in cancer death rates for (A) women and (B) men, by site in the United States, 1930-1999. Rates are per 100,000 age-adjusted to the 2000 U.S. standard population. (From Jemal et al.)

uation of the histology of the tumor, its grade, and its invasiveness and to yield further molecular diagnostic information, such as the expression of cell-surface markers or intracellular proteins that typify a particular cancer, or the presence of a molecular marker, such as the

which might include intraoperative palpation, resection of regional lymph nodes and/or tissue adjacent to the tumor, and inspection and biopsy of organs commonly involved in disease spread. Pathologic staging includes histologic examination of all tissues removed during

t(8;14) translocation of Burkitt's lymphoma. Increasing evidence links the expression of certain genes with the prognosis and response to therapy (Chaps. 68, 69).

Occasionally a patient will present with a metastatic disease process that is defined as cancer on biopsy but has no apparent primary site of disease. Efforts should be made to define the primary site based on age, sex, sites of involvement, histology and tumor markers, and personal and family history. Particular attention should be focused on ruling out the most treatable causes (Chap. 85).

Once the diagnosis of cancer is made, the management of the patient is best undertaken as a multidisciplinary collaboration among the primary care physician, medical oncologists, surgical oncologists, radiation oncologists, oncology nurse specialists, pharmacists, social workers, rehabilitation medicine specialists, and a number of other consulting professionals working closely with each other and with the patient and family.

DEFINING THE EXTENT OF DISEASE AND THE PROGNOSIS

The first priority in patient management after the diagnosis of cancer is established and shared with the patient is to determine the extent of disease. The curability of a tumor usually is inversely proportional to the tumor burden. Ideally, the tumor will be diagnosed before symptoms develop or as a consequence of screening efforts (Chap. 67). A very high proportion of such patients can be cured. However, most patients with cancer present with symptoms related to the cancer, caused either by mass effects of the tumor or by alterations associated with the production of cytokines or hormones by the tumor.

For most cancers, the extent of disease is evaluated by a variety of noninvasive and invasive diagnostic tests and procedures. This process is called *staging*. There are two types. *Clinical staging* is based on physical examination, radiographs, isotopic scans, computed tomography, and other imaging procedures; *pathologic staging* takes into account information obtained during a surgical procedure, which might include intraoperative palpation, resection of regional lymph nodes and/or tissue adjacent to the tumor, and inspection and biopsy of organs commonly involved in disease spread. Pathologic staging includes histologic examination of all tissues removed during the surgical procedure. Surgical procedures performed may include a simple lymph node biopsy or more extensive procedures such as thoracotomy, mediastinoscopy, or laparotomy. Surgical staging may occur in a separate procedure or may be done at the time of definitive surgical resection of the primary tumor.

Knowledge of the predilection of particular tumors for spread to adjacent or distant organs helps direct the staging evaluation.

Information obtained from staging is used to define the extent of disease either as localized, as exhibiting spread

TABLE 66-2 The Five Leading Primary Tumor Sites for Patients Dying of Cancer Based on Age and Sex in 2001

Rank	Age					
	All Ages	Under 20	20-39	40-59	60-79	>80
1	M,F: lung	M,F: leukemia	M: leukemia F: breast	M: lung F: breast	M,F: lung	M,F: lung
2	M: prostate F: breast	M,F: brain	M: brain F: cervix	M: colorectal F: lung	M: colorectal F: breast	M: prostate F: colorectal
3	M,F: colorectal	M: bone sarcoma F: endocrine	M: colorectal F: leukemia	M: pancreas F: colorectal	M: prostate F: colorectal	M: colorectal F: breast
4	M,F: pancreas	M: endocrine F: bone sarcoma	M: lymphoma F: lung	M: liver F: ovary	M,F: pancreas	M: bladder F: pancreas
5	M: leukemia F: ovary	M: F: soft tissue sarcoma	M: lung F: brain	M: esophagus F: pancreas	M: leukemia F: ovary	M: leukemia F: lymphoma

Note: M, male; F, female.

outside of the organ of origin to regional but not distant sites, or as metastatic to distant sites. The most widely used system of staging is the TNM (tumor, node, metastasis) system codified by the International Union Against Cancer and the American Joint Committee on Cancer (AJCC).¹ The TNM classification is an anatomically based system that categorizes the tumor on the basis of the size of the primary tumor lesion (T1–4, where a higher number indicates a tumor of larger size), the presence of nodal involvement (usually N0 and N1 for the absence and presence, respectively, of involved nodes, although some tumors have more elaborate systems of nodal grading), and the presence of metastatic disease (M0 and M1 for the absence and presence, respectively, of metastases). The various permutations of T, N, and M scores (sometimes including tumor histologic grade G) are then broken into stages, usually designated by the roman numerals I through IV. Tumor burden increases and curability decreases with increasing stage. Other anatomic staging systems are used for some tumors, e.g., the Dukes classification for colorectal cancers, the International Federation of Gynecologists and Obstetricians (FIGO) classification for gynecologic cancers, and the Ann Arbor classification for Hodgkin's disease.

Certain tumors cannot be grouped on the basis of anatomic considerations. For example, hematopoietic tumors such as leukemia, myeloma, and lymphoma are often disseminated at presentation and do not spread like solid tumors. For these tumors, other prognostic factors have been identified (Chaps. 96, 97, 98).

In addition to tumor burden, a second major determinant of treatment outcome is the physiologic reserve of the patient. Patients who are bedridden before developing cancer are likely to fare worse, stage for stage, than fully active patients. Physiologic reserve is a determinant of how a patient is likely to cope with the physiologic stresses imposed by the cancer and its treatment. This factor is difficult to assess directly. Instead, surrogate markers for physiologic reserve are used, such as the patient's age or Karnofsky performance status (Table 66-4). Older patients and those with a Karnofsky performance status <70 have a poor prognosis unless the poor performance is a reversible consequence of the tumor.

Increasingly, biologic features of the tumor are being related to prognosis. The expression of particular oncogenes, drug-resistance genes, apoptosis-related genes, and genes involved in metastasis are being found to influence response to therapy and prognosis. The presence of selected cytogenetic abnormalities may influence survival. Tumors with higher growth fractions, as assessed by expression of proliferation-related markers such as proliferating cell nuclear antigen (PCNA), behave more aggressively than tumors with lower growth fractions. Information obtained from studying the tumor itself will increasingly be used to influence treatment decisions.

MAKING A TREATMENT PLAN From information on the extent of disease and the prognosis and in conjunction with the patient's wishes, it is determined whether the treatment approach should be curative or palliative in intent. Cooperation among the various professionals involved in cancer treatment is of the utmost importance in treatment planning. For some cancers, chemotherapy or chemotherapy plus radiation therapy delivered before the use of definitive surgical treatment (so-called neoadjuvant therapy) may improve the outcome, as seems to be the

TABLE 66-3 Cancer Incidence and Mortality in Racial and Ethnic Groups 1992–1999

Site	White	Black	Asian/Pacific Islander	American Indian	Hispanic
INCIDENCE PER 100,000 POPULATION					
All	M: 568.2 F: 424.4	M: 703.6 F: 404.8	M: 408.9 F: 306.5	M: 277.7 F: 224.2	M: 393.1 F: 290.5
Breast (F)	137	120.7	93.4	59.4	82.6
Colon/rectum	M: 64.4 F: 46.1	M: 70.7 F: 55.8	M: 58.7 F: 39.5	M: 40.7 F: 30.8	M: 43.9 F: 29.7
Lung	M: 82.9 F: 51.1	M: 124.1 F: 53.2	M: 63.8 F: 28.5	M: 51.4 F: 23.3	M: 44.1 F: 22.8
Prostate (M)	172.9	275.3	107.2	60.7	127.6
MORTALITY PER 100,000 POPULATION					
All	M: 258.1 F: 171.2	M: 369 F: 204.5	M: 160.6 F: 104.4	M: 154.5 F: 110.4	M: 163.7 F: 105.7
Breast (F)	29.3	37.3	13.1	14.8	17.5
Colon	M: 26.1 F: 18.4	M: 34.8 F: 25.4	M: 16.5 F: 11.6	M: 14.6 F: 11.3	M: 16.6 F: 10.6
Lung	M: 81.7 F: 41.1	M: 113 F: 39.6	M: 42.3 F: 19.3	M: 49.3 F: 24.9	M: 38.2 F: 13.8
Prostate (M)	32.9	75.1	15.1	18.8	22.6

Note: M, male; F, female.

case for locally advanced breast cancer and head and neck cancers. In certain settings in which combined modality therapy is intended, coordination among the medical oncologist, radiation oncologist, and surgeon is crucial to achieving optimal results. Sometimes the chemotherapy and radiation therapy need to be delivered sequentially, and other times concurrently. Surgical procedures may precede or follow other treatment approaches. It is best for the treatment plan either to follow a standard protocol precisely or else to be part of an ongoing clinical research protocol evaluating new treatments. Ad hoc modifications of standard protocols are likely to compromise treatment results.

The choice of treatment approaches was formerly dominated by the local culture in both the university and the practice settings. However, it is now possible to gain access electronically to standard treatment protocols and to every approved clinical research study in North America through a personal computer interface with the Internet.²

The skilled physician also has much to offer the patient for whom curative therapy is no longer an option. Often a combination of guilt and frustration over the inability to cure the patient and the pressure of a busy schedule greatly limit the time a physician spends with a patient who is receiving only palliative care. Resist these forces. In addition to the medicines administered to alleviate symptoms (see below), it is important to remember the comfort that is provided by holding the patient's hand, continuing regular examinations, and taking time to talk.

MANAGEMENT OF DISEASE AND TREATMENT COMPLICATIONS Because cancer therapies are toxic (Chaps. 70, 71), patient management involves addressing complications of both the disease and its treatment as well as the complex psychosocial problems associated with cancer. In the short term during a course of curative therapy, the patient's functional status may decline. Treatment-induced toxicity is less acceptable if the goal of therapy is palliation. The most common side effects of treatment are nausea and vomiting (see below), febrile neutropenia (Chap. 72), and myelosuppression (Chap. 70). Therapeutic tools are now available to minimize the acute toxicity of cancer treatment.

New symptoms developing in the course of cancer treatment should

¹The AJCC *Manual for Staging Cancer*, 5th edition, can be obtained from the AJCC at 55 East Erie Street, Chicago, IL, 60611.

²The National Cancer Institute maintains a database called PDQ (Physician Data Query) that is accessible on the Internet under the name CancerNet at www.wicic.nci.nih.gov/health.htm. Information can be obtained through a facsimile machine using CancerFax by dialing 301-402-5874. Patient information is also provided by the National Cancer Institute in at least three formats: on the Internet via CancerNet at www.wicic.nci.nih.gov/patient.htm, through the CancerFax number listed above, or by calling 1-800-4-CANCER. The quality control for the information provided through these services is rigorous.

TABLE 66-4 Karnofsky Performance Index

Performance Status	Functional Capability of the Patient
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death is not imminent
20	Very sick; hospitalization necessary; active supportive treatment is necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

always be assumed to be reversible until proven otherwise. The fatalistic attribution of anorexia, weight loss, and jaundice to recurrent or progressive tumor could result in a patient dying from a reversible intercurrent cholecystitis. Intestinal obstruction may be due to reversible adhesions rather than progressive tumor. Systemic infections, sometimes with unusual pathogens, may be a consequence of the immunosuppression associated with cancer therapy. Some drugs used to treat cancer or its complications (e.g., nausea) may produce central nervous system symptoms that look like metastatic disease or may mimic paraneoplastic syndromes such as the syndrome of inappropriate antidiuretic hormone. A definitive diagnosis should be pursued and may even require a repeat biopsy.

A critical component of cancer management is assessing the response to treatment. In addition to a careful physical examination in which all sites of disease are physically measured and recorded in a flow chart by date, response assessment usually requires periodic repeating of imaging tests that were abnormal at the time of staging. If imaging tests have become normal, repeat biopsy of previously involved tissue is performed to document complete response by pathologic criteria. Biopsies are not usually required if there is macroscopic residual disease. A *complete response* is defined as disappearance of all evidence of disease, and a *partial response* as >50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions. *Progressive disease* is defined as the appearance of any new lesion or an increase of >25% in the sum of the products of the perpendicular diameters of all measurable lesions. Tumor shrinkage or growth that does not meet any of these criteria is considered *stable disease*. Some sites of involvement (e.g., bone) or patterns of involvement (e.g., lymphangitic lung or diffuse pulmonary infiltrates) are considered unmeasurable. No response is complete without biopsy documentation of their resolution, but partial responses may exclude their assessment unless clear objective (though unmeasurable) progression has occurred.

Tumor markers may be useful in patient management in certain tumors. Response to therapy may be difficult to gauge with certainty. However, some tumors produce or elicit the production of markers that can be measured in the serum or urine and, in a particular patient, rising and falling levels of the marker are usually associated with increasing or decreasing tumor burden, respectively. Some clinically useful tumor markers are shown in Table 66-5. Tumor markers are not in themselves specific enough to permit a diagnosis of malignancy to be made, but once a malignancy has been diagnosed and shown to be associated with elevated levels of a tumor marker, the marker can be used to assess response to treatment.

The recognition and treatment of depression are important com-

ponents of management. The incidence of depression in cancer patients is ~25% overall and may be greater in patients with greater debility. This diagnosis is likely in a patient with a depressed mood (dysphoria) and/or a loss of interest in pleasure (anhedonia) for at least 2 weeks. In addition, three or more of the following symptoms are usually present: appetite change, sleep problems, psychomotor retardation or agitation, fatigue, feelings of guilt or worthlessness, inability to concentrate, and suicidal ideation. Patients with these symptoms should receive therapy. Medical therapy with a serotonin reuptake inhibitor such as fluoxetine (10 to 20 mg/d), sertraline (50 to 150 mg/d), or paroxetine (10 to 20 mg/d) or a tricyclic antidepressant such as amitriptyline (50 to 100 mg/d) or desipramine (75 to 150 mg/d) should be tried, allowing 4 to 6 weeks for response. Effective therapy should be continued at least 6 months after resolution of symptoms. If therapy is unsuccessful, other classes of antidepressants may be used. In addition to medication, psychosocial interventions such as support groups, psychotherapy, and guided imagery may be of benefit.

Many patients opt for unproven or unsound approaches to treatment when it appears that conventional medicine is unlikely to be curative. Those seeking such alternatives are often well educated and may be early in the course of their disease. Unsound approaches are usually hawked on the basis of unsubstantiated anecdotes and not only cannot help the patient but may be harmful. Physicians should strive to keep communications open and nonjudgmental, so that patients are more likely to discuss with the physician what they are actually doing. The appearance of unexpected toxicity may be an indication that a supplemental therapy is being taken.³

LONG-TERM FOLLOW-UP/LATE COMPLICATIONS At the completion of treatment, sites originally involved with tumor are reassessed, usually by radiography or imaging techniques, and any persistent abnormality is biopsied. If disease persists, the multidisciplinary team discusses a new salvage treatment plan. If the patient has been rendered disease-free by the original treatment, the patient is followed regularly for disease recurrence. The optimal guidelines for follow-up care are not known. For many years, a routine practice has been to follow the patient monthly for 6 to 12 months, then every other month for a year, every 3 months for a year, every 4 months for a year, every 6 months for a year, and then annually. At each visit, a battery of laboratory and radiographic and imaging tests were obtained on the assumption that it is best to detect recurrent disease before it becomes symptomatic. However, where follow-up procedures have been examined, this assumption has been found to be untrue. Studies of breast cancer, melanoma, lung cancer, colon cancer, and lymphoma have all failed to support the notion that asymptomatic relapses are more readily cured by salvage therapy than symptomatic relapses. In view of the enormous cost of a full battery of diagnostic tests and their manifest lack of impact on survival, new guidelines are emerging for less frequent follow-up visits, during which the history and physical examination are the major investigations performed.

As time passes, the likelihood of recurrence of the primary cancer diminishes. For many types of cancer, survival for 5 years without recurrence is tantamount to cure. However, important medical problems can occur in patients treated for cancer and must be examined (Chap. 89). Some problems emerge as a consequence of the disease and some as a consequence of the treatment. An understanding of these disease- and treatment-related problems may help in their detection and management.

Despite these concerns, most patients who are cured of cancer return to normal lives.

SUPPORTIVE CARE In many ways, the success of cancer therapy depends on the success of the supportive care. Failure to control the symptoms

³Information about unsound methods may be obtained from the National Council Against Health Fraud, Box 1276, Loma Linda, CA 92354, or from the Center for Medical Consumers and Health Care Information, 237 Thompson Street, New York, NY 10012.

of cancer and its treatment may lead patients to abandon curative therapy. Of equal importance, supportive care is a major determinant of quality of life. Even when life cannot be prolonged, the physician must strive to preserve its quality. Quality-of-life measurements have become common end-points of clinical research studies. Furthermore, palliative care has been shown to be cost-effective when approached in an organized fashion. A credo for oncology could be to cure sometimes, to extend life often, and to comfort always.

Pain Pain occurs with variable frequency in the cancer patient: 25 to 50% of patients present with pain at diagnosis, 33% have pain associated with treatment, and 75% have pain with progressive disease. The pain may have several causes. In about 70% of cases, pain is caused by the tumor itself—by invasion of bone, nerves, blood vessels, or mucous membranes or obstruction of a hollow viscus or duct. In about 20% of cases, pain is related to a surgical or invasive medical procedure, to radiation injury (mucositis, enteritis, or plexus or spinal cord injury), or to chemotherapy injury (mucositis, peripheral neuropathy, phlebitis, steroid-induced aseptic necrosis of the femoral head). In 10% of cases, pain is unrelated to cancer or its treatment.

Assessment of pain requires the methodical investigation of the history of the pain, its location, character, temporal features, provocative and palliative factors, and intensity (Chap. 11); a review of the oncologic history and past medical history as well as personal and social history; and a thorough physical examination. The patient should be given a 10-division visual analogue scale on which to indicate the severity of the pain. The clinical condition is often dynamic, making it necessary to reassess the patient frequently. Pain therapy should not be withheld while the cause of pain is being sought.

A variety of tools are available with which to address cancer pain. About 85% of patients will have pain relief from pharmacologic intervention. However, other modalities, including antitumor therapy (such as surgical relief of obstruction, radiation therapy, and strontium-89 or samarium-153 treatment for bone pain), neurostimulatory techniques, regional analgesia, or neuroablative procedures are effective in an additional 12% or so. Thus, very few patients will have inadequate pain relief if appropriate measures are taken. → *A specific approach to pain relief is detailed in Chap. 9.*

Nausea Emesis in the cancer patient is usually caused by chemotherapy (Chap. 70). Its severity can be predicted from the drugs used to treat the cancer. Three forms of emesis are recognized on the basis of their timing with regard to the noxious insult. *Acute emesis*, the most common variety, occurs within 24 h of treatment. *Delayed emesis* occurs 1 to 7 days after treatment; it is rare, but, when present, usually follows cisplatin administration. *Anticipatory emesis* occurs before administration of chemotherapy and represents a conditioned response to visual and olfactory stimuli previously associated with chemotherapy delivery.

Acute emesis is the best understood form. Stimuli that activate signals in the chemoreceptor trigger zone in the medulla, the cerebral cortex, and peripherally in the intestinal tract lead to stimulation of the vomiting center in the medulla, the motor center responsible for coordinating the secretory and muscle contraction activity that leads to emesis. Diverse receptor types participate in the process, including

TABLE 66-5 Tumor Markers

Tumor Markers	Cancer	Non-Neoplastic Conditions
HORMONES		
Human chorionic gonadotropin Calcitonin Catecholamines	Gestational trophoblastic disease, gonadal germ cell tumor Medullary cancer of the thyroid Pheochromocytoma	Pregnancy
ONCOFETAL ANTIGENS		
Alphafetoprotein	Hepatocellular carcinoma, gonadal germ cell tumor	Cirrhosis, hepatitis
Carcinoembryonic antigen	Adenocarcinomas of the colon, pancreas, lung, breast, ovary	Pancreatitis, hepatitis, inflammatory bowel disease, smoking
ENZYMES		
Prostatic acid phosphatase Neuron-specific enolase	Prostate cancer Small cell cancer of the lung, neuroblastoma	Prostatitis, prostatic hypertrophy
Lactate dehydrogenase	Lymphoma, Ewing's sarcoma	Hepatitis, hemolytic anemia, many others
TUMOR-ASSOCIATED PROTEINS		
Prostate-specific antigen Monoclonal immunoglobulin	Prostate cancer Myeloma	Prostatitis, prostatic hypertrophy Infection, MGUS ^a
CA-125 CA 19-9 CD30	Ovarian cancer, some lymphomas Colon, pancreatic, breast cancer Hodgkin's disease, anaplastic large cell lymphoma	Menstruation, peritonitis, pregnancy Pancreatitis, ulcerative colitis —
CD25	Hairy cell leukemia, adult T cell leukemia/lymphoma	—

^a MGUS, monoclonal gammopathy of uncertain significance.

dopamine, serotonin, histamine, opioid, and acetylcholine receptors. The serotonin receptor antagonists ondansetron and granisetron are the most effective drugs against highly emetogenic agents, but they are expensive.

As with the analgesia ladder, emesis therapy should be tailored to the situation. For mildly and moderately emetogenic agents, prochlorperazine, 5 to 10 mg orally or 25 mg rectally, is effective. Its efficacy may be enhanced by administering the drug before the chemotherapy is delivered. Dexamethasone, 10 to 20 mg intravenously, is also effective and may enhance the efficacy of prochlorperazine. For highly emetogenic agents such as cisplatin, mechlorethamine, dacarbazine, and streptozocin, combinations of agents work best and administration should begin 6 to 24 h before treatment. Ondansetron, 8 mg orally every 6 h the day before therapy and intravenously on the day of therapy, plus dexamethasone, 20 mg intravenously before treatment, is an effective regimen. Addition of oral aprepitant (a substance P/neurokinin 1 receptor antagonist) to this regimen (125 mg on day 1, 80 mg on days 2 and 3) further decreases the risk of both acute and delayed vomiting. Like pain, emesis is easier to prevent than to alleviate.

Delayed emesis may be related to bowel inflammation from the therapy and can be controlled with oral dexamethasone and oral metoclopramide, a dopamine receptor antagonist that also blocks serotonin receptors at high dosages. The best strategy for preventing anticipatory emesis is to control emesis in the early cycles of therapy to prevent the conditioning from taking place. If this is unsuccessful, prophylactic antiemetics the day before treatment may help. Experimental studies are evaluating behavior modification.

Effusions Fluid may accumulate abnormally in the pleural cavity, pericardium, or peritoneum. Asymptomatic malignant effusions may not require treatment. Symptomatic effusions occurring in tumors responsive to systemic therapy usually do not require local treatment but respond to the treatment for the underlying tumor. Symptomatic effusions occurring in tumors unresponsive to systemic therapy may require local treatment in patients with a life expectancy of at least 6 months.

Pleural effusions due to tumors may or may not contain malignant cells. Lung cancer, breast cancer, and lymphomas account for about 75% of malignant pleural effusions. Their exudative nature is usually gauged by an effusion/serum protein ratio of ≥ 0.5 or an effusion/serum lactate dehydrogenase ratio of ≥ 0.6 . When the condition is symptomatic, thoracentesis is usually performed first. In most cases, symptomatic improvement occurs for < 1 month. Chest tube drainage is required if symptoms recur within 2 weeks. Fluid is aspirated until the flow rate is < 100 mL in 24 h. Then either 60 units of bleomycin or 1 g of doxycycline is infused into the chest tube in 50 mL of 5% dextrose in water; the tube is clamped; the patient is rotated on four sides, spending 15 min in each position; and, after 1 to 2 h, the tube is again attached to suction for another 24 h. The tube is then disconnected from suction and allowed to drain by gravity. If < 100 mL drains over the next 24 h, the chest tube is pulled, and a radiograph taken 24 h later. If the chest tube continues to drain fluid at an unacceptably high rate, sclerosis can be repeated. Bleomycin may be somewhat more effective than doxycycline but is very expensive. Doxycycline is usually the drug of first choice. If neither doxycycline nor bleomycin is effective, talc can be used.

Symptomatic pericardial effusions are usually treated by creating a pericardial window or by stripping the pericardium. If the patient's condition does not permit a surgical procedure, sclerosis can be attempted with doxycycline and/or bleomycin.

Malignant ascites is usually treated with repeated paracentesis of small volumes of fluid. If the underlying malignancy is unresponsive to systemic therapy, peritoneovenous shunts may be inserted. Despite the fear of disseminating tumor cells into the circulation, widespread metastases are an unusual complication. The major complications are occlusion, leakage, and fluid overload. Patients with severe liver disease may develop disseminated intravascular coagulation.

Nutrition Cancer and its treatment may lead to a decrease in nutrient intake of sufficient magnitude to cause weight loss and alteration of intermediary metabolism. The prevalence of this problem is difficult to estimate because of variations in the definition of cancer cachexia, but most patients with advanced cancer experience weight loss and decreased appetite. A variety of both tumor-derived factors (e.g., bombesin, adrenocorticotropic hormone) and host-derived factors (e.g., tumor necrosis factor, interleukins 1 and 6, growth hormone) contribute to the altered metabolism, and a vicious cycle is established in which protein catabolism, glucose intolerance, and lipolysis cannot be reversed by the provision of calories.

It remains controversial how to assess nutritional status and when and how to intervene. Efforts to make the assessment objective have included the use of a prognostic nutritional index based on albumin levels, triceps skin fold thickness, transferrin levels, and delayed-type hypersensitivity skin testing. However, a simpler approach has been to define the threshold for nutritional intervention as $> 10\%$ unexplained body weight loss, serum transferrin level < 1500 mg/L (150 mg/dL), and serum albumin < 34 g/L (3.4 g/dL).

The decision is important, because it appears that cancer therapy is substantially more toxic and less effective in the face of malnutrition. Nevertheless, it remains unclear whether nutritional intervention can alter the natural history. Unless some pathology is affecting the absorptive function of the gastrointestinal tract, enteral nutrition provided orally or by tube feeding is preferred over parenteral supplementation. However, the risks associated with the tube may outweigh the benefits. Megestrol acetate, a progestational agent, has been advocated as a pharmacologic intervention to improve nutritional status. Research in this area may provide more tools in the future as cytokine-mediated mechanisms are further elucidated.

Psychosocial Support The psychosocial needs of patients vary with their situation. Patients undergoing treatment experience fear, anxiety, and depression. Self-image is often seriously compromised by deforming surgery and loss of hair. Women who receive cosmetic advice that

enables them to look better also feel better. Loss of control over how one spends time can contribute to the sense of vulnerability. Juggling the demands of work and family with the demands of treatment may create enormous stresses. Sexual dysfunction is highly prevalent and needs to be discussed openly with the patient. An empathetic health care team is sensitive to the individual patient's needs and permits negotiation where such flexibility will not adversely affect the course of treatment.

Cancer survivors have other sets of difficulties. Patients may have fears associated with the termination of a treatment they associate with their continued survival. Adjustments are required to physical losses and handicaps, real and perceived. Patients may be preoccupied with minor physical problems. They perceive a decline in their job mobility and view themselves as less desirable workers. They may be victims of job and/or insurance discrimination. Patients may experience difficulty reentering their normal past life. They may feel guilty for having survived and may carry a sense of vulnerability to colds and other illnesses. Perhaps the most pervasive and threatening concern is the ever-present fear of relapse (the Damocles syndrome).

Patients in whom therapy has been unsuccessful have other problems related to the end of life.

Death and Dying The most common causes of death in patients with cancer are infection (leading to circulatory failure), respiratory failure, hepatic failure, and renal failure. Intestinal blockage may lead to inanition and starvation. Central nervous system disease may lead to seizures, coma, and central hypoventilation. About 70% of patients develop dyspnea preterminally. However, many months usually pass between the diagnosis of cancer and the occurrence of these complications, and during this period the patient is severely affected by the possibility of death. The path of unsuccessful cancer treatment usually occurs in three phases. First, there is optimism at the hope of cure; when the tumor recurs, there is the acknowledgment of an incurable disease, and the goal of palliative therapy is embraced in the hope of being able to live with disease; finally, at the disclosure of imminent death, another adjustment in outlook takes place. The patient imagines the worst in preparation for the end of life and may go through stages of adjustment to the diagnosis. These stages include denial, isolation, anger, bargaining, depression, acceptance, and hope. Of course, patients do not all progress through all the stages or proceed through them in the same order or at the same rate. Nevertheless, developing an understanding of how the patient has been affected by the diagnosis and is coping with it is an important goal of patient management.

It is best to speak frankly with the patient and the family regarding the likely course of disease. These discussions can be difficult for the physician as well as for the patient and family. The critical features of the interaction are to reassure the patient and family that everything that can be done to provide comfort will be done. They will not be abandoned. Many patients prefer to be cared for in their homes or in a hospice setting rather than a hospital. The American College of Physicians has published a book called *Home Care Guide for Cancer: How to Care for Family and Friends at Home* that teaches an approach to successful problem-solving in home care. With appropriate planning, it should be possible to provide the patient with the necessary medical care as well as the psychological and spiritual support that will prevent the isolation and depersonalization that can attend in-hospital death.

The care of dying patients may take a toll on the physician. A "burnout" syndrome has been described that is characterized by fatigue, disengagement from patients and colleagues, and a loss of self-fulfillment. Efforts at stress reduction, maintenance of a balanced life, and setting realistic goals may combat this disorder.

End-of-Life Decisions Unfortunately, a smooth transition in treatment goals from curative to palliative may not be possible in all cases because of the occurrence of serious treatment-related complications or rapid disease progression. Vigorous and invasive medical support for a reversible disease or treatment complication is assumed to be justified. However, if the reversibility of the condition is in doubt, the

patient's wishes determine the level of medical care. These wishes should be elicited before the terminal phase of illness and reviewed periodically. Information about advance directives can be obtained from the American Association of Retired Persons, 601 E Street, NW, Washington, DC 20049, 202-434-2277 or Choice in Dying, 250 West 57th Street, New York, NY 10107, 212-366-5540. → *A full discussion of end-of-life management is in Chap. 9.*

FURTHER READING

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PREVENTION AND EARLY DETECTION OF CANCER

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Cancer prevention and control is a burgeoning field because of advances in understanding the biology of carcinogenesis. The field has expanded beyond the identification and avoidance of carcinogens to include studies of specific interventions to lower cancer risk, as well as screening for early detection of cancer.

Central to cancer prevention and control is the concept that carcinogenesis is not an event but a process, a series of discrete cellular changes that result in progressively more autonomous cellular processes. *Primary prevention* concerns the identification and manipulation of the genetic, biologic, and environmental factors in the causal pathway. Smoking cessation, diet modification, and chemoprevention are primary prevention activities. *Secondary prevention* concerns the identification of asymptomatic neoplastic lesions combined with effective therapy. Screening is a form of secondary prevention.

EDUCATION AND HEALTHFUL HABITS Public education on the avoidance of identified risk factors for cancer and encouraging healthy habits were among early efforts in cancer prevention and control. Many educational messages have come to the public through commercials in the print and electronic media and through school health courses. The physician is a potentially powerful messenger in this education campaign about the hazards of smoking, the benefits of a healthful diet and exercise, use of proven screening methods, and sun avoidance.

Smoking Cessation Tobacco use through cigarettes and other means is the most avoidable risk factor for cardiovascular disease and cancer. The degree of smoke exposure, meaning the number of cigarettes smoked per day as well as the level of inhalation of cigarette smoke, is correlated with risk of lung cancer mortality. Light and low-tar cigarettes are not safer because smokers tend to inhale them more frequently and deeply. Those who stop smoking have a lower lung cancer mortality rate than those who continue smoking, despite the fact that some carcinogen-induced genetic mutations persist for years. In addition to lung cancer, cigarette smoking is a causative agent in cancers of the larynx, oropharynx, esophagus, bladder, and pancreas.

Smoking cessation and avoidance have the potential to save and extend more lives than any other public health activity. A smoker has a one in three lifetime risk of dying prematurely of a smoking-related cancer or cardiovascular or pulmonary disease. Indeed, more human lives are lost due to cardiovascular disease caused by smoking than from smoking-related cancer. The risk of tobacco smoke is not necessarily limited to the smoker. Epidemiologic studies suggest that environmental tobacco smoke may cause lung cancer and other pulmonary diseases in nonsmokers.

Nonsmoking persons should be encouraged not to start smoking, and persons who smoke should be encouraged to stop. Tobacco prevention is a pediatric issue. Over 80% of American smokers begin smoking before the age of 18. Nearly 20% of Americans aged 12 to 18 have smoked a cigarette in the past month. Counseling of adolescents and young adults is critical to prevent smoking. A physician's

simple advice to not start smoking or to quit smoking can be of benefit. Physicians should query patients on tobacco use on every office visit, record the answer with the vital signs, and ask smokers if they would like assistance in quitting.

Current approaches to smoking cessation recognize that smoking is an addiction (Chap. 375). The smoker who is quitting goes through a process with identifiable stages that include contemplation of quitting, an action phase in which the smoker quits, and a maintenance phase. Smokers who quit completely are more likely to be successful than those who gradually reduce the number of cigarettes smoked or change to lower tar or nicotine cigarettes. More than 90% of the Americans who have successfully quit smoking did so on their own without participation in an organized cessation program, but cessation programs are helpful for some smokers. The Community Intervention Trial for Smoking Cessation (COMMIT) was a community-based 4-year program. COMMIT demonstrated that light smokers (<25 cigarettes per day) can benefit from simple cessation messages and cessation programs. The quit rate (fraction of the subjects followed who achieved and maintained cessation at the end of the trial) was 30.6% in the intervention communities and 27.5% in the control communities. This finding is statistically significant, but modest. The control communities enjoyed a substantial decrease in smoking through study participation. The COMMIT interventions were not successful for heavy smokers (>25 cigarettes per day). Heavy smokers need an intensive, broad-based cessation program that includes counseling, behavioral strategies, and pharmacologic adjuncts such as nicotine replacement and bupropion.

Cigar smoking has increased in the past 10 years, especially in younger adults. The health risks of cigars are similar to those of cigarettes. Smoking two cigars per day doubles the risk for oral and esophageal cancer; three to four cigars per day increases the risk of oral cancer eight-fold and esophageal cancer four-fold. The risks of occasional cigar smoking are unknown.

Smokeless tobacco is the fastest growing part of the tobacco industry and represents a significant health risk. Chewing tobacco is a carcinogen linked to dental caries, gingivitis, oral leukoplakia, and oral cancer. The systemic effects of smokeless tobacco may increase risks for other cancers.

Diet Modification Dietary modification may have significant potential for lowering cancer risk in western culture. Studies of international dietary patterns and animal studies suggest that diets high in fat increase the risk for cancers of the breast, colon, prostate, and endometrium. These cancers have their highest incidence and mortalities in western countries, where fat comprises an average of 40 to 45% of the total calories consumed. In populations at low risk for these cancers, fat accounts for <20% of calories.

Despite correlations, dietary fat has not been proven to cause cancer. Case-control and cohort epidemiologic studies give conflicting