6 Late Effects of Cancer Treatments

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Background and Significance

With continued advances in strategies to detect cancer early and treat it effectively, along with the aging of the population, the number of individuals living years beyond a cancer diagnosis can be expected to continue to increase. Statistical trends show that, in the absence of other competing causes of death, 64% of adults diagnosed with cancer today can expect to be alive in 5 years.[1–4] Relative 5-year survival rates for those diagnosed as children (age less than 19 years) are even higher, with almost 79% of childhood cancer survivors estimated to be alive at 5 years and 75% at 10 years.[5]

Survival from cancer has seen dramatic improvements over the past three decades, mainly as a result of advances in early detection, therapeutic strategies, and the widespread use of combined modality therapy (surgery, chemotherapy, and radiotherapy).[6–10] Medical and sociocultural factors such as psychosocial and behavioral interventions, active screening behaviors, and healthier lifestyles may also play an integral role in the length and quality of that survival.[11]

Although beneficial and often lifesaving against the diagnosed malignancy, most therapeutic modalities for cancer are associated with a spectrum of late complications ranging from minor and treatable to serious or, occasionally, potentially lethal.[2,6,12–15] While living for extended periods of time beyond their initial diagnosis, many cancer survivors often face various chronic and late physical and psychosocial sequelae of their disease or its treatment. Additionally, as the number of survivors and their length of survival expand, long-term health issues specific to cancer survival are also fast emerging as a public health concern. Questions of particular importance to cancer survivors include surveillance for the adverse sequelae, or late and long-term effects, of treatment; the development of new (second) cancers; and recurrence of their original cancer. One-fourth of *late deaths* occurring among survivors of childhood cancer during the extended survivorship period, when the chances of primary disease recurrence are negligible, can be attributed to a treatment-related effect such as a second cancer or cardiac dysfunction.[16] The most *frequently observed* medical sequelae among pediatric cancer survivors include endocrine complications, growth hormone deficiency, primary hypothyroidism, and primary ovarian failure. Also included within the rubric of late effects are second cancers arising as a result of genetic predisposition (e.g., familial cancer syndromes) or the mutagenic effects of therapy. These factors may act independently or synergistically. Synergistic effects of mutagenic agents such as cigarette smoke or toxins such as alcohol are largely unknown.[2,6,12]

Thus, there is today a greater recognition of symptoms that persist after the completion of treatment and which arise years after primary therapy. Both acute organ toxicities such as radiation pneumonitis and chronic toxicities such as congestive cardiac failure, neurocognitive deficits, infertility, and second malignancies are being described as the price of cure or prolonged survival.[2,6,12] The study of late effects, originally within the realm of pediatric cancer, is now germane to cancer survivors at all ages because concerns may continue to surface throughout the life cycle.[2,6] These concerns underscore the need to follow up and screen survivors of cancer for toxicities such as those mentioned and also to develop and provide effective interventions that carry the potential to prevent or ameliorate adverse outcomes.

The goal of survivorship research is to focus on the *health and life* of a person with a history of cancer *beyond* the acute diagnosis and treatment phase. Survivorship research seeks to examine the causes of, and to prevent and control the adverse effects associated with, cancer and its treatment and to optimize the physiologic, psychosocial, and functional outcomes for cancer survivors and their families. A hallmark of survivorship research is its emphasis on understanding the integration/interaction of multidisciplinary domains.

This chapter presents definitional issues relevant to cancer survivorship; examines late effects of cancer treatment among survivors of pediatric and adult cancer; and articulates gaps in knowledge and emerging research priorities in cancer survivorship research relevant to late effects of cancer treatment. It draws heavily from pediatric cancer survivorship research because a paucity of data continue to exist for medical late effects of treatment for survivors of cancer diagnosed as adults. Research on late effects of cancer treatment began in the realm of pediatric cancer and continues to yield important insights for the impact of cancer therapies among those diagnosed as adults.

Definitional Issues

Fitzhugh Mullan, a physician diagnosed with and treated for cancer himself, first described cancer survivorship as a concept.[17] Definitional issues for cancer survivorship encompass three related aspects:[2,6] (1) *Who is a cancer survivor?* Philosophically, anyone who has been diagnosed with cancer

is a survivor, from the time of diagnosis to the end of life.[1] Caregivers and family members are also included within this definition as secondary survivors. (2) *What is cancer survivorship?* Mullan described the survivorship experience as similar to the seasons of the year. Mullan recognized three seasons or phases of survival: acute (extending from diagnosis to the completion of initial treatment, encompassing issues dominated by treatment and its side effects); extended (beginning with the completion of initial treatment for the primary disease, remission of disease, or both, dominated by watchful waiting, regular follow-up examinations, and, perhaps, intermittent therapy); and permanent survival (not a single moment; evolves from extended disease-free survival when the likelihood of recurrence is sufficiently low). An understanding of these phases of survival is important for facilitating an optimal transition into and management of survivorship. (3) *What is cancer survivorship research?* Cancer survivorship research seeks to identify, examine, prevent, and control adverse cancer diagnosis and treatment-related outcomes (such as late effects of treatment, second cancers, and quality of life); to provide a knowledge base regarding optimal follow-up care and surveillance of cancer survivors; and to optimize health after cancer treatment.[2,6]

Other important definitions include those for long-term cancer survivorship and late versus long-term effects of cancer treatment. Generally, *long-term cancer survivors* are defined as those individuals who are 5 or more years beyond the diagnosis of their primary disease and embody the concept of permanent survival described by Mullan. *Late effects* refer specifically to unrecognized toxicities that are absent or subclinical at the end of therapy and become manifest later with the unmasking of hitherto unseen injury caused by any of the following factors: developmental processes; the failure of compensatory mechanisms with the passage of time; or organ senescence. *Long-term effects* refer to any side effects or complications of treatment for which a cancer patient must compensate; also known as persistent effects, they begin during treatment and continue beyond the end of treatment. Late effects, in contrast, appear months to years after the completion of treatment. Some researchers classify cognitive problems, fatigue, lymphedema, and peripheral neuropathy as long-term effects while others classify them as late effects.[18–21]

This chapter focuses largely on the *physiologic* or *medical* long-term and late effects of cancer treatment. Physiologic sequelae of cancer treatment can also be further classified as follows:

a. System-specific (e.g., organ damage, failure, or premature aging, immunosuppression or issues related to compromised immune systems, and endocrine damage);
b. Second malignant neoplasms (such as an increased risk of recurrent malignancy, increased risk of a certain cancer associated with the primary malignancy, and/or increased risk of secondary malignancies associated with cytotoxic or radiologic cancer therapies (this topic is not covered in detail in this chapter as it is reviewed comprehensively elsewhere in this book); and
c. Functional changes such as lymphedema, incontinence, pain syndromes, neuropathies, fatigue; cosmetic changes such as amputations, ostomies, and skin/hair alterations; and comorbidities such as osteoporosis, arthritis, and hypertension.

[1]From the National Coalition for Cancer Survivorship.

Late and Long-Term Effects of Cancer and Its Treatment: Overview and Generalizations

Consequent to the phenomenal success in treating cancer effectively and detecting it early, we are faced today with an increasing population of individuals who, although cancer free for many years, have issues and concerns regarding the persistent (chronic) and the late (delayed) effects of cancer therapies on their health, longevity, and quality of life. The long-term impact of cancer and its treatment can include premature mortality and long-term morbidity. The two most frequent causes of premature mortality in disease-free cancer survivors are (1) cardiac disease and (2) second malignant neoplasms.[22,23] The subject of late effects among children treated for cancer has been the topic of numerous reviews.[21,24–28] To varying degrees, it has been shown that disease- or treatment-specific subgroups of long-term survivors are at risk of developing adverse outcomes. These adverse consequences of cancer treatment include early death, second neoplasms, organ dysfunction (e.g., cardiac, pulmonary, gonadal), reduced growth and development, decreased fertility, impaired intellectual function, difficulties obtaining employment and insurance, and a decreased quality of life. This chapter summarizes selected aspects of the spectrum of outcomes relating to the late effects of therapy among individuals (adults, children, and adolescents) treated for cancer.

Generalizations About Late Effects

Several generalizations can be made.[2,6,29] It is now possible to anticipate certain types of late effects on the basis of specific therapies to which the survivor was exposed, the age of the survivor at the time of treatment, combinations of treatment modalities used, and the dosage administered. There are differences in susceptibility between pediatric and adult patients. Generally, chemotherapy results in acute toxicities that can persist whereas radiation leads to sequelae that are not apparent immediately and surface after a latent period. Combinations of chemotherapy and radiation therapy are more often associated with late effects in the survivorship period.[2,6,29]

Toxicities related to chemotherapy, especially those of an acute but possibly persistent nature, may be related to proliferation kinetics of individual cell populations as these drugs are usually cell cycle dependent. Thus, organs or tissues most susceptible are those with high cell proliferation (turnover) rates such as the skin (epidermis), bone marrow, gastrointestinal mucosa, liver, and testes. Theoretically, the least susceptible organs and tissues are those that replicate very slowly or not at all and include muscle cells, neurons, and the connective tissue.[2,6,29]

Issues Unique to Certain Cancer Sites

Late effects have been studied in greater depth for certain cancer sites. The examination of late effects for childhood cancers such as acute lymphoblastic leukemia, Hodgkin's

disease, and brain tumors have provided the foundation for this area of research. A body of knowledge on late effects of radiation and/or chemotherapy is subsequently being developed for adult sites such as breast cancer. For example, recent studies have evaluated and reported on the development of neurocognitive deficits after chemotherapy for breast cancer, a late effect that was initially observed among survivors of childhood cancer receiving cranial irradiation and/or chemotherapy. Late effects of bone marrow transplant have been studied for both adult and childhood cancer survivors, as have sequelae associated with particular chemotherapeutic regimens such as those for Hodgkin's disease or breast cancer.

Chemotherapeutic drugs for which late effects have been reported most frequently include adriamycin, bleomycin, vincristine, methotrexate, cytoxan, and many others (Table 6.1).

The side effects of radiotherapy, both alone and in conjunction with chemotherapy, have been reported fairly comprehensively for most childhood cancer sites associated with good survival rates. It is important to bear in mind that most cancer treatment regimens consist of chemotherapy in conjunction with surgery and/or radiation, and multidrug chemotherapeutic regimens are the rule rather the exception. As such, the risk of late effects must always be considered in light of all other treatment modalities to which the patient has been exposed.

Special Considerations of Primary Diagnosis and Treatment in Childhood

Cancer therapy may interfere with development in terms of physical and musculoskeletal growth, neurocognitive/intellectual growth, and pubertal development. These effects may be most *notable* during the adolescent growth spurt, even though they occur during the childhood period. These specific sequelae are covered in greater detail in the chapter by Bhatia et al. (see Chapter 7) and are not discussed here. A brief classification follows:

a. Alterations in physical growth
   i. Linear growth effects[30–32]
   ii. Impact of early puberty on growth[33,34]
   iii. Hypoplasia[35]
b. Alterations in intellectual development[36–39]
c. Altered pubertal development[40]
d. Obesity[41–43]

Special Considerations of Primary Diagnosis and Treatment During Adulthood

Some late effects of chemotherapy may assume special importance depending on the adult patient's age at the time of diagnosis and treatment. Diagnosis and treatment during the *young adult or reproductive years* may call for a special cognizance of the importance of maintaining reproductive

TABLE 6.1. Possible late effects of radiotherapy and chemotherapy.

Organ system	*Late effects/sequelae of radiotherapy*	*Late effects/sequelae of chemotherapy*	*Chemotherapeutic drugs responsible*
Bone and soft tissues	Short stature; atrophy, fibrosis, osteonecrosis	Avascular necrosis	Steroids
Cardiovascular	Pericardial effusion; pericarditis; CAD	Cardiomyopathy; CHF	Anthracylines Cyclophosphamide
Pulmonary	Pulmonary fibrosis; decreased lung volumes	Pulmonary fibrosis; interstitial pneumonitis	Bleomycin, BCNU Methotrexate, adriamycin
Central nervous system (CNS)	Neuropsychologic deficits, structural changes, hemorrhage	Neuropsychologic deficits, structural changes Hemiplegia; seizure	Methotrexate
Peripheral nervous system		Peripheral neuropathy; hearing loss	Cisplatin, vinca alkaloids
Hematologic	Cytopenia, myelodysplasia	Myelodyplastic syndromes	Alkylating agents
Renal	Decreased creatinine clearance	Decreased creatinine clearance	Cisplatin Methotrexate
	Hypertension	Increased creatinine Renal filtration Delayed renal filtration	Nitrosoureas
Genitourinary	Bladder fibrosis, contractures	Bladder fibrosis; hemorrhagic cystitis	Cyclophosphamide
Gastrointestinal	Malabsorption; stricture; abnormal LFT	Abnormal LFT; hepatic fibrosis; cirrhosis	Methotrexate, BCNU
Pituitary	Growth hormone deficiency; pituitary deficiency		
Thyroid	Hypothyroidism; nodules		
Gonadal	Men: risk of sterility, Leydig cell dysfunction.	Men: sterility	Alkylating agents
	Women: ovarian failure, early menopause	Women: sterility, premature menopause	Procarbazine
Dental/oral health	Poor enamel and root formation; dry mouth		
Opthalmologic	Cataracts; retinopathy	Cataracts	Steroids

CAD, coronary artery disease; CCF, congestive cardiac failure; LFT, liver function tests; BCNU, carmustine.

Source: Data from Ganz (1998, 2001)[12,13] and Aziz (2002, 2003).[2,6]

function and the prevention of second cancers. These are also key issues for children whose cancers are diagnosed during childhood.

Cancer patients diagnosed and treated during *middle age* may need specific attention to sequelae such as premature menopause, issues relating to sexuality and intimacy, pros and cons of using estrogen replacement therapy (ERT), prevention of neurocognitive, cardiac, and other sequelae of chemotherapy, and the prevention of coronary artery disease and osteoporosis. It has been reported that sexual dysfunction persists after breast cancer treatment, despite recovery in other domains, and includes vaginal discomfort, hot flashes, and alterations in bioavailable testosterone, luteinizing hormone, and sex hormone-binding globulin.[44] Menopausal symptoms such as hot flashes, vaginal dryness, and stress urinary incontinence are very common in breast cancer survivors and cannot be managed with standard estrogen replacement therapy.[45] The normal life expectancy of survivors of early-stage cancers during these years of life underscores the need to address their long-term health and quality of life issues.

Although *older patients* (65 years and over) bear a disproportionate burden of cancer, advancing age is associated with increased vulnerability to other age-related health problems and concurrent ailments such as diabetes, chronic obstructive pulmonary disease, heart disease, arthritis, and/or hypertension. Any of these could potentially affect treatment choice, prognosis, and survival. Hence, cancer treatment decisions may need to be made in the context of the older individual's preexisting health problems (comorbidities). Measures that can help evaluate the existence, nature, and severity of comorbidities among older cancer patients in a reliable manner are needed. Currently, there is little information on how comorbid age-related conditions influence treatment decisions, the subsequent course of the disease, the way that already-compromised older cancer patients tolerate the stress of cancer and its treatment, and how concomitant comorbid conditions are managed.[46]

Review of Late and Long-Term Effects by Organ System or Tissues Affected[2]

System-Specific Physiologic Sequelae[3]

Cardiac Sequelae

The heart may be damaged by both therapeutic irradiation and chemotherapeutic agents commonly used in the treatment for cancer. Several types of damage have been reported, including pericardial, myocardial, and vascular. Cardiac damage is most pronounced after treatment with the anthracycline drugs doxorubicin and daunorubicin, used widely in the treatment of most childhood cancers and adjuvant chemotherapy for breast and many other adult cancers. An additive effect has also been reported when anthracyclines are used in conjunction with cyclophosphamide and radiation therapy. Anthracyclines cause myocardial cell death, leading to a diminished number of myocytes and compensatory hypertrophy of residual myocytes.[47] Major clinical manifestations include reduced cardiac function, arrhythmia, and heart failure. Chronic cardiotoxicity usually manifests itself as cardiomyopathy, pericarditis, and congestive heart failure.

Cardiac injury that becomes clinically manifest during or shortly after completion of chemotherapy may progress, stabilize, or improve after the first year of treatment. This improvement may either be of a transient nature or last for a considerable length of time. There is also evidence of a continuum of injury that will manifest itself throughout the lives of these patients.[48] From a risk factor perspective, patients who exhibit reduced cardiac function within 6 months of completing chemotherapy are at increased risk for the development of late cardiac failure.[49] However, a significant incidence of late cardiac decompensation manifested by cardiac failure or lethal arrhythmia occurring 10 to 20 years after the administration of these drugs has also been reported.[50]

In a recent study of Hodgkin's disease (HD) survivors, investigators reported finding cardiac abnormalities in the majority of the participants.[51] This is an important finding especially because the sample consisted of individuals who did not manifest symptomatic heart disease at screening and described their health as "good." Manifestations of cardiac abnormalities included (a) restrictive cardiomyopathy (suggested by reduced average left ventricular dimension and mass without increased left ventricular wall thickness); (b) significant valvular defects; (c) conduction defects; (d) complete heart block; (e) autonomic dysfunction (suggested by a monotonous heart rate in 57%); (f) persistent tachycardia; and (g) blunted hemodynamic responses to exercise. The peak oxygen uptake (VO_{2max}) during exercise, a predictor of mortality in heart failure, was significantly reduced (less than 20 mL/kg/m^2) in 30% of survivors and was correlated with increasing fatigue, increasing shortness of breath, and a decreasing physical component score on the SF-36. Given the presence of these clinically significant cardiovascular abnormalities, investigators recommend serial, comprehensive cardiac screening of HD survivors who fit the profile of having received mediastinial irradiation at a young age.

Congestive cardiomyopathy is directly related to the total dose of the agent administered; the higher the dose, the greater the chance of cardiotoxicity. Subclinical abnormalities have also been noted at lower doses. The anthracyclines doxorubicin and daunorubicin are well-known causes of cardiomyopathy that can occur many years after completion of therapy. The incidence of anthracycline-induced cardiomyopathy, which is dose dependent, may exceed 30% among patients receiving cumulative doses in excess of 600 mg/m^2. A cumulative dose of anthracyclines greater than 300 mg/m^2 has been associated with an 11-fold-increased risk of clinical heart failure, compared with a cumulative dose of less than 300 mg/m^2, the estimated risk of clinical heart failure increasing with time from exposure and approaching 5% after 15 years.

A reduced incidence and severity of cardiac abnormalities was reported in a study of 120 long-term survivors of acute lymphoblastic leukemia (ALL) who had been treated with lower anthracycline doses (90–270 mg/m^2), compared with previous reports in which subjects had received moderate

[2]Common to both children and adults depending on cancer site and treatment(s) received.

[3]These include organ damage, failure, or premature aging resulting from chemotherapy, hormone therapy, radiation, surgery, or any combination thereof.

anthracycline doses (300–550 mg/m^2).[52,53] Twenty-three percent of the patients were found to have cardiac abnormalities, 21% had increased end-systolic stress, and only 2% had reduced contractility. The cumulative anthracycline dose within the 90 to 270 mg/m^2 range did not relate to cardiac abnormalities. The authors concluded that there may be no safe anthracycline dose to completely avoid late cardiotoxicity. A recent review of 30 published studies in childhood cancer survivors found that the frequency of clinically detected anthracycline cardiac heart failure ranged from 0% to 16%.[54] In an analysis of reported studies, the type of anthracycline (e.g., doxorubicin) and the maximum dose given in a 1-week period (e.g., more than 45 mg/m^2) was found to explain a large portion of the variation in the reported frequency of anthracycline-induced cardiac heart failure.

Cyclophosphamide has been associated with the development of congestive cardiomyopathy, especially when administered at the high doses used in transplant regimens. Cardiac toxicity may occur at lower doses when mediastinal radiation is combined with the chemotherapeutic drugs mentioned above. Late onset of congestive heart failure has been reported during pregnancy, rapid growth, or after the initiation of vigorous exercise programs in adults previously treated for cancer during childhood or young adulthood as a result of increased afterload and the impact of the additional stress of such events on marginal cardiac reserves. Initial improvement in cardiac function after completion of therapy appears to result, at least in part, from compensatory changes. Compensation may diminish in the presence of stressors such as those mentioned earlier and myocardial depressants such as alcohol.

The incidence of subclinical anthracycline myocardial damage has been the subject of considerable interest. Steinherz et al. found 23% of 201 patients who had received a median cumulative dose of doxorubicin of 450 mg/m^2 had echocardiographic abnormalities at a median of 7 years after therapy.[55] In a group of survivors of childhood cancer who received a median doxorubicin dose of 334 mg/m^2, it was found that progressive elevation of afterload or depression of left ventricular contractility was present in approximately 75% of patients.[47] A recent review of the literature on subclinical cardiotoxicity among children treated with an anthracycline found that the reported frequency of subclinical cardiotoxicity varied considerably across the 25 studies reviewed (frequency ranging from 0% to 57%).[56] Because of marked differences in the definition of outcomes for subclinical cardiotoxicity and the heterogeneity of the patient populations investigated, it is difficult to accurately evaluate the potential long-term outcomes within anthracycline-exposed patient populations or the potential impact of the subclinical findings.

Effects of radiation on the heart may be profound, and include valvular damage, pericardial thickening, and ischemic heart disease. Patients with radiation-related cardiac damage have a markedly increased relative risk of both angina and myocardial infarction [relative risk (RR), 2.56] years after mediastinal radiation for Hodgkin's disease in adult patients, whereas the risk of cardiac death is 3.1.[57] This risk was greatest among patients receiving more than 30 Gy of mantle irradiation and those treated before 20 to 21 years of age. Blocking the heart reduced the risk of cardiac death due to causes other than myocardial infarction.[58]

In general, among anthracycline-exposed patients, the risk of cardiotoxicity can be increased by mediastinal radiation,[59] uncontrolled hypertension,[60,61] underlying cardiac abnormalities,[62] exposure to nonanthracycline chemotherapeutic agents (especially cyclophosphamide, dactinomycin, mitomycin C, dacarbazine, vincristine, bleomycin, and methotrexate),[63,64] female gender,[65] younger age,[66] and electrolyte imbalances such as hypokalaemia and hypomagnesaemia.[67] Previous reports have suggested that doxorubicin-induced cardiotoxicity can be prevented by continuous infusion of the drug.[68] However, Lipshultz et al. compared cardiac outcomes in children receiving either bolus or continuous infusion of doxorubicin, and reported that continuous doxorubicin infusion over 48 hours for childhood leukemia did not offer a cardioprotective advantage over bolus infusion.[69] Both regimens were associated with progressive subclinical cardiotoxicity, thus suggesting that there is no benefit from continuous infusion of anthracyclines.

Chronic cardiotoxicity associated with radiation alone most commonly involves pericardial effusions or constrictive pericarditis, sometimes in association with pancarditis. Although a dose of 40 Gy of total heart irradiation appears to be the usual threshold, pericarditis has been reported after as little as 15 Gy, even in the absence of radiomimetic chemotherapy.[70,71] Symptomatic pericarditis, which usually develops 10 to 30 years after irradiation, is found in 2% to 10% of patients.[72] Subclinical pericardial and myocardial damage, as well as valvular thickening, may be common in this population.[73,74] Coronary artery disease has been reported after radiation to the mediastinum, although mortality rates have not been significantly higher in patients who receive mediastinal radiation than in the general population.[58]

Given the known acute and long-term cardiac complications of therapy, prevention of cardiotoxicity is a focus of active investigation. Several attempts have been made to minimize the cardiotoxicity of anthracyclines, such as the use of liposomal-formulated anthracyclines, less-cardiotoxic analogues, and the additional administration of cardioprotective agents. The advantages of these approaches are still controversial, but there are ongoing clinical trials to evaluate the long-term effects. Certain analogues of doxorubicin and daunorubicin, with decreased cardiotoxicity but equivalent antitumour activity, are being explored. Agents such as dexrazoxane, which are able to remove iron from anthracyclines, have been investigated as cardioprotectants. Clinical trials of dexrazoxane have been conducted in children, with encouraging evidence of short-term cardioprotection[75]; however, the long-term avoidance of cardiotoxicity with the use of this agent has yet to be sufficiently determined. The most recent study by Lipshultz et al. reported that dexrazoxane prevents or reduces cardiac injury, as reflected by elevations in troponin T, that is associated with the use of doxorubicin for childhood ALL without compromising the antileukemic efficacy of doxorubicin. Longer follow-up will be necessary to determine the influence of dexrazoxane on echocardiographic findings at four years and on event-free survival.[76]

Another key emerging issue is the interaction of taxanes with doxorubicin. Epirubicin–taxane combinations are active in treating metastatic breast cancer, and ongoing research is focusing on combining anthracyclines with taxanes in an effort to continue to improve outcomes following adjuvant therapy.[77] Clinically significant drug interactions have been

reported to occur when paclitaxel is administered with doxorubicin, cisplatin, or anticonvulsants (phenytoin, carbamazepine, and phenobarbital), and pharmacodynamic interactions have been reported to occur with these agents that are sequence- or schedule dependent.[78] Because the taxanes undergo hepatic oxidation via the cytochrome P-450 system, pharmacokinetic interactions from enzyme induction or inhibition can also occur. A higher than expected myelotoxicity has been reported. However, there is no enhanced doxorubicinol formation in human myocardium, a finding consistent with the cardiac safety of the regimen.[79] Investigators have suggested that doxorubicin and epirubicin should be administered 24 hours before paclitaxel and the cumulative anthracycline dose be limited to 360 mg/m^2, thereby preventing the enhanced toxicities caused by sequence- and schedule-dependent interactions between anthracyclines and paclitaxel.[78] Conversely, they also suggest that paclitaxel should be administered at least 24 hours before cisplatin to avoid a decrease in clearance and increase in myelosuppression. With concurrent anticonvulsant therapy, cytochrome P-450 enzyme induction results in decreased paclitaxel plasma steady-state concentrations, possibly requiring an increased dose of paclitaxel. A number of other drug interactions have been reported in preliminary studies for which clinical significance has yet to be established.[78]

The human epidermal growth factor receptor (HER) 2 is overexpressed in approximately 20% to 25% of human breast cancers and is an independent adverse prognostic factor. Targeted therapy directed against this receptor has been developed in the form of a humanized monoclonal antibody, trastuzumab. Unexpectedly, cardiac toxicity has developed in some patients treated with trastuzumab, and this has a higher incidence in those treated in combination with an anthracycline.[80,81] Both clinical and in vitro data suggest that cardiomyocyte HER2/erbB2 is uniquely susceptible to trastuzumab.[82] Tratuzumab has shown activity as a single agent in metastatic breast cancer both before chemotherapy and in heavily pretreated patients, and its use in combination with an anthracycline or paclitaxel results in a significant improvement in survival, time to progression, and response.[80] The HER2 status of a tumor is a critical determinant of response to trastuzumab-based treatment; those expressing HER2 at the highest level on immunohistochemistry, 3+, derive more benefit from treatment with trastuzumab than those with overexpression at the 2+ level. Interactions between the estrogen receptor and HER2 pathway has stimulated interest in using trastuzumab in combination with endocrine therapy. Current clinical trials are investigating the role of this agent in the adjuvant setting.

Neurocognitive Sequelae

Long-term survivors of cancer may be at risk of neurocognitive and neuropsychologic sequelae. Among survivors of childhood leukemia, neurocognitive late effects represent one of the more intensively studied topics. Adverse outcomes are generally associated with whole-brain radiation and/or therapy with high-dose systemic or intrathecal methotrexate or cytarabine.[83–85] High-risk characteristics, including higher dose of central nervous system (CNS) radiation, younger age at treatment, and female sex, have been well documented. Results from studies of neurocognitive outcomes are directly responsible for the marked reduction (particularly in younger children) in the use of cranial radiation, which is currently reserved for treatment of very high risk subgroups or patients with CNS involvement.[86]

A spectrum of clinical syndromes may occur, including radionecrosis, necrotizing leukoencephalopathy, mineralizing microangiopathy and dystropic calcification, cerebellar sclerosis, and spinal cord dysfunction.[87] Leukoencephalopathy has been primarily associated with methotrexate-induced injury of white matter. However, cranial radiation may play an additive role through the disruption of the blood–brain barrier, thus allowing greater exposure of the brain to systemic therapy.

Although abnormalities have been detected by diagnostic imaging studies, the abnormalities observed have not been well demonstrated to correlate with clinical findings and neurocognitive status.[88,89] Chemotherapy- or radiation-induced destruction in normal white matter partially explains intellectual and academic achievement deficits.[90] Evidence suggests that direct effects of chemotherapy and radiation on intracranial endothelial cells and brain white matter as well as immunologic mechanisms could be involved in the pathogenesis of central nervous system damage.

Neurocognitive deficits, as a general rule, usually become evident within several years following CNS radiation and tend to be progressive in nature. Leukemia survivors treated at a younger age (i.e., less than 6 years of age) may experience significant declines in intelligence quotient (IQ) scores.[91] However, reductions in IQ scores are typically not global, but rather reflect specific areas of impairment, such as attention and other nonverbal cognitive processing skills.[92] Affected children may experience information-processing deficits, resulting in academic difficulties. These children are particularly prone to problems with receptive and expressive language, attention span, and visual and perceptual motor skills, most often manifested in academic difficulties in the areas of reading, language, and mathematics. Accordingly, children treated with CNS radiation or systemic or intrathecal therapy with the potential to cause neurocognitive deficits should receive close monitoring of academic performance. Referral for neuropsychologic evaluation with appropriate intervention strategies, such as modifications in curriculum, speech and language therapy, or social skills training, implemented in a program tailored for the individual needs and deficits of the survivor should be taken into consideration.[93] Assessment of educational needs and subsequent educational attainment have found that survivors of childhood leukemia are significantly more likely to require special educational assistance, but have a high likelihood of successfully completing high school.[37,94] However, when compared with siblings, survivors of leukemia and non-Hodgkin's lymphoma (NHL) are at greater risk of not completing high school. As would be anticipated from the results of neurocognitive studies, it has been shown that survivors, particularly those under 6 years of age at treatment, who received cranial radiation and/or intrathecal chemotherapy were significantly more likely to require special education services and least likely to complete a formal education.[86,95,96]

Progressive dementia and dysfunction have been reported in some long-term cancer survivors as a result of whole-brain radiation with or without chemotherapy, and occur most often in brain tumor patients and patients with small cell

lung cancer who have received prophylactic therapy. Neuropsychologic abnormalities have also been reported after CNS prophylaxis utilizing whole-brain radiation for leukemia in childhood survivors. In fact, cognitive changes in children began to be recognized as treatments for childhood cancer, especially ALL, became increasingly effective. These observations have resulted in changes in treatment protocols for childhood ALL.[97,98]

Several recent studies have reported cognitive dysfunction in women treated with adjuvant therapy for breast cancer.[99,100] In one study,[101] investigators compared the neuropsychologic performance of long-term survivors of breast cancer and lymphoma treated with standard-dose chemotherapy who carried the epsilon 4 allele of the apolipoprotein E (APOE) gene to those who carry other APOE alleles. Survivors with at least one epsilon 4 allele scored significantly lower in the visual memory (*P* less than 0.03) and the spatial ability (*P* less than 0.05) domains and tended to score lower in the psychomotor functioning (*P* less than 0.08) domain as compared to survivors who did not carry an epsilon 4 allele. No group differences were found on depression, anxiety, or fatigue. The results of this study provide preliminary support for the hypothesis that the epsilon 4 allele of APOE may be a potential genetic marker for increased vulnerability to chemotherapy-induced cognitive decline.

Although cranial irradiation is the most frequently identified causal factor in both adults and children, current work in adults indicates that cognitive problems may also occur with surgery, chemotherapy, and biologic response modifiers.[102–104] These findings need to be validated in prospective studies along with the interaction between treatment with chemotherapeutic agents, menopausal status, and hormonal treatments. Emotional distress also has been related to cognitive issues in studies of patients beginning cancer treatment.

Patients have attributed problems in cognition to fatigue, and others have reported problems with concentration, short-term memory, problem-solving, and concerns about "chemobrain" or "mental pause."[105] Comparisons across studies are difficult because of different batteries of neuropsychologic tests used, and differences among patient samples by diagnosis, age, gender, or type of treatment received, and, finally, inconsistency in the timing of measures in relation to treatment landmarks. Despite these methodologic issues, studies have shown impairments in verbal information processing, complex information processing, concentration, and visual memory.[106–109]

Current studies indicate that cognitive deficits are often subtle but are observed consistently in a proportion of patients, may be durable, and can be disabling.[110] Deficits have been observed in a range of cognitive functions. Although underlying mechanisms are unknown, preliminary studies suggest a genetic predisposition. Cognitive impairment may be accompanied by changes in the brain detectable by neuroimaging. Priorities for future research include (1) large-scale clinical studies that use both a longitudinal design and concurrent evaluation of patients with cancer who do not receive chemotherapy—such studies should address the probability and magnitude of cognitive deficits, factors that predict them, and underlying mechanisms; (2) exploration of discrepancies between subjective reports of cognitive dysfunction and the objective results of cognitive testing; (3) studies of cognitive function in patients receiving treatment for diseases other than breast cancer, and in both men and women, to address the hypothesis that underlying mechanisms relate to changes in serum levels of sex hormones and/or to chemotherapy-induced menopause; (4) development of interventions to alleviate these problems; and (5) development of animal models and the use of imaging techniques to address mechanisms that might cause cognitive impairment.

Endocrinologic Sequelae

Thyroid

Radiation exposure to the head and neck is a known risk factor for subsequent abnormalities of the thyroid. Among survivors of Hodgkin's disease and, to a lesser extent, leukemia survivors, abnormalities of the thyroid gland, including hypothyroidism, hyperthyroidism, and thyroid neoplasms, have been reported to occur at rates significantly higher than found in the general population.[111–114] Hypothyroidism is the most common nonmalignant late effect involving the thyroid gland. Following radiation doses above 15 Gy, laboratory evidence of primary hypothyroidism is evident in 40% to 90% of patients with Hodgkin's disease, NHL, or head and neck malignancies.[113,115,116] In a recent analysis of 1,791 5-year survivors of pediatric Hodgkin's disease (median age at follow-up, 30 years), Sklar et al. reported the occurrence of at least one thyroid abnormality in 34% of subjects.[114] The risk of hypothyroidism was increased 17 fold compared with sibling control subjects, with increasing dose of radiation, older age at diagnosis of Hodgkin's disease, and female sex as significant independent predictors of an increased risk. The actuarial risk of hypothyroidism for subjects treated with 45 Gy or more was 50% at 20 years following diagnosis of their Hodgkin's disease. Hyperthyroidism was reported to occur in only 5%.

Hormones Affecting Growth

Poor linear growth and short adult stature are common complications after successful treatment of childhood cancers.[117] The adverse effect of CNS radiation on adult final height among childhood leukemia patients has been well documented, with final heights below the fifth percentile occurring in 10% to 15% of survivors.[43,118,119] The effects of cranial radiation appear to be related to age and gender, with children younger than 5 years at the time of therapy and female patients being more susceptible. The precise mechanisms by which cranial radiation induces short stature are not clear. Disturbances in growth hormone production have not been found to correlate well with observed growth patterns in these patients.[31,120] The phenomenon of early onset of puberty in girls receiving cranial radiation may also play some role in the reduction of final height.[33,121] In childhood leukemia survivors not treated with cranial radiation, there are conflicting results regarding the impact of chemotherapy on final height.[122]

Hormonal Rationale for Obesity

An increased prevalence of obesity has been reported among survivors of childhood ALL.[123–125] Craig et al. investigated the relationship between cranial irradiation received during treatment for childhood leukemia and obesity.[126] Two hundred thirteen (86 boys and 127 girls) irradiated patients and 85 (37

boys and 48 girls) nonirradiated patients were enrolled. For cranially irradiated patients, an increase in the body mass index (BMI) *Z* score at the final height was associated with female sex and lower radiation dose but not with age at diagnosis. Severe obesity, defined as a BMI *Z* score greater than 3 at final height, was only present in girls who received 18 to 20 Gy irradiation at a prevalence of 8%. Both male and female nonirradiated patients had raised BMI *Z* scores at latest follow-up, and there was no association with age at diagnosis. The authors concluded that these data demonstrated a sexually dimorphic and dose-dependent effect of cranial irradiation on BMI. In a recent analysis from the Childhood Cancer Survivor Study, Oeffinger et al. compared the distribution of BMI of 1,765 adult survivors of childhood ALL with that of 2,565 adult siblings of childhood cancer survivors.[127] Survivors were significantly more likely to be overweight (BMI, 25–30) or obese (BMI, 30 or more). Risk factors for obesity were cranial radiation, female gender, and age from 0 to 4 years at diagnosis of leukemia. Girls diagnosed under the age of 4 years who received a cranial radiation dose greater than 20 Gy were found to have a 3·8-fold-increased risk of obesity.

Gonadal Dysfunction

Treatment-related gonadal dysfunction has been well documented in both men and women following childhood malignancies.[128] However, survivors of leukemia and T-cell non-Hodgkin's lymphoma treated with modern conventional therapy are at a relatively low risk of infertility and delayed or impaired puberty. Treatment-related gonadal failure or dysfunction, expressed as amenorrhea or azoospermia, can lead to infertility in both male and female cancer survivors, and may have its onset during therapy.[129] Infertility can be transient, especially in men, and may recover over time after therapy. Reversibility is dependent on the dose of gonadal radiation or alkylating agents. Ovarian function is unlikely to recover long after the immediate treatment period because long-term amenorrhea commonly results from loss of ova. Cryopreservation of sperm before treatment is an option for men,[130] but limited means are available to preserve ova or protect against treatment-related ovarian failure for women.[131–133] A successful live birth after orthotopic autotransplantation of cryopreserved ovarian tissue has been recently reported.[134–137] A reasonable body of research on topics relating to the long-term gonadal effects of radiation and chemotherapy exists[138–161] and provides a basis for counseling patients and parents of the anticipated outcomes on pubertal development and fertility. For greater detail on this topic, please see Chapter 19.

Among survivors of adult cancer, the risk of premature onset of menopause in women treated with chemotherapeutic agents such as alkylating agents and procarbazine or with abdominal radiation therapy is age related, with women older than age 30 at the time of treatment having the greatest risk of treatment-induced amenorrhea and menopause, and sharply increased rates with chemotherapy around the age of 40 years. Tamoxifen has not been associated with the development of amenorrhea so far.[162] Cyclophosphamide at doses of 5 g/m^2 is likely to cause amenorrhea in women over 40, whereas many adolescents will continue to menstruate even after more than 20 g/m^2.[163] Although young women may not become amenorrheic after cytotoxic therapy, the risk of early menopause is significant. Female disease-free survivors of cancer diagnosed at ages 13 to 19 who were menstruating at age 21 were at fourfold-higher risk of menopause compared to controls.[140]

Fertility and Pregnancy Outcomes

Fertility The fertility of survivors of childhood cancer, evaluated in the aggregate, is impaired. In one study, the adjusted relative fertility of survivors compared with that of their siblings was 0.85 [95% confidence interval (CI), 0.78, 0.92]. The adjusted relative fertility of male survivors (0.76; 95% CI, 0.68, 0.86) was slightly lower than that of female survivors (0.93; 95% CI, 0.83, 1.04). The most significant differences in the relative fertility rates were demonstrated in male survivors who had been treated with alkylating agents with or without infradiaphragmatic irradiation.[164]

Fertility can be impaired by factors other than the absence of sperm and ova. Conception requires delivery of sperm to the uterine cervix and patency of the fallopian tubes for fertilization to occur and appropriate conditions in the uterus for implantation. Retrograde ejaculation occurs with a significant frequency in men who undergo bilateral retroperitoneal lymph node dissection. Uterine structure may be affected by abdominal irradiation. Uterine length was significantly reduced in 10 women with ovarian failure who had been treated with whole-abdomen irradiation. Endometrial thickness did not increase in response to hormone replacement therapy in 3 women who underwent weekly ultrasound examination. No flow was detectable with Doppler ultrasound through either uterine artery of 5 women and through one uterine artery in 3 additional women.[165,166] Similarly, 4 of 8 women who received 1,440 cGy total-body irradiation had reduced uterine volume and undetectable uterine artery blood flow.[167] These data are pertinent when considering the feasibility of assisted reproduction for these survivors.

Pregnancy Most chemotherapeutic agents are mutagenic, with the potential to cause germ cell chromosomal injury. Possible results of such injury include an increase in the frequency of genetic diseases and congenital anomalies in the offspring of successfully treated childhood and adolescent cancer patients. Several early studies of the offspring of patients treated for diverse types of childhood cancer identified no effect of previous treatment on pregnancy outcome and no increase in the frequency of congenital anomalies in the offspring.[168–170] However, a study of offspring of patients treated for Wilm's tumor demonstrated that the birth weight of children born to women who had received abdominal irradiation was significantly lower than that of children born to women who had not received such irradiation,[171] a finding that was confirmed in several subsequent studies.[172–174] The abnormalities of uterine structure and blood flow reported after abdominal irradiation might explain this clinical finding.

Prior studies of offspring of childhood cancer survivors were limited by the size of the population of offspring and the number of former patients who had been exposed to mutagenic therapy. Several recent studies that attempted to address some of these limitations did not identify an increased frequency of major congenital malformations,[175–180] genetic disease, or childhood cancer[181,182] in the offspring of former pediatric cancer patients, including those conceived

after bone marrow transplantation.[183] However, there are data suggesting a deficit of males in the offspring of the partners of male survivors in the Childhood Cancer Survivor Study cohort,[184] as well as an effect of prior treatment with doxorubicin or daunorubicin on the percentage of offspring with a birth weight less than 2,500 g born to female survivors in the Childhood Cancer Survivor Study who were treated with pelvic irradiation.[185]

Pulmonary Sequelae

The *acute* effects of chemotherapy on the lungs may be lethal, may subside over time, may progress insidiously to a level of clinical pulmonary dysfunction, or may be manifested by abnormal pulmonary function tests. Classically, high doses of bleomycin have been associated with pulmonary toxicity. However, drugs such as alkylating agents, methotrexate, and nitrosoureas may also lead to pulmonary fibrosis, especially when combined with radiation therapy. Radiation is thus an important contributor to pulmonary sequelae of chemotherapy.[186] Alkylating agents can injure the lung parenchyma, cause restrictive lung disease by inhibiting chest wall growth, and lead to thin anteroposterior chest diameters even 7 years after completion of therapy. Bleomycin may cause pulmonary insufficiency and interstitial pneumonitis.[187]

Pulmonary fibrosis can cause late death in the survivorship period. Among children treated for brain tumors with high doses of nitrosurea and radiotherapy, 35% died of pulmonary fibrosis, 12% within 3 years and 24% after a symptom-free period of 7 to 12 years.[188] The risk for overt decompensation continues for at least 1 year after cessation of therapy and can be precipitated by infection or exposure to intraoperative oxygen. In terms of long-term outcomes, a recent study noted that 22% of Hodgkin's disease patients with normal pulmonary function tests at the end of therapy (three cycles each of mechlorethamine (nitrogen mustard), vincristine, procarbazine, prednisone (MOPP) and adriamycin (doxovubicin), bleomycin, vinblastic, dacarbazine (ABVD) or two cycles of each plus 2,550 cGy of involved-field radiotherapy) developed abnormalities with follow-up of 1 to 7 years.

The long-term outcome of pulmonary toxicity is determined by factors such as the severity of the acute injury, the degree of tissue repair, and the level of compensation possible. Pulmonary dysfunction is usually subclinical and may be manifested by subconscious avoidance of exercise owing to symptoms. Premature respiratory insufficiency, especially with exertion, may also become evident with aging. Recent aggressive lung cancer treatment regimens consisting of surgery, radiation, and chemotherapy may well put patients at high risk for decreased pulmonary function and respiratory symptoms.

Genitourinary Tract

Several drugs such as cisplatin, methotrexate, and nitrosoureas have been associated with both acute and chronic toxicities such as glomerular and tubular injury.[189] Glomerular injury may recover over time whereas tubular injury generally persists. Hemodialysis to counteract the effects of chronic renal toxicity may be warranted for some patients. Ifosfamide may cause Fanconi's syndrome with glycosuria, phosphaturia, and aminoaciduria, and may affect glomerular filtration. Hypophosphatemia may result in slow growth with possible bone deformity if untreated.

Radiation therapy may cause tubular damage and hypertension as a result of renal artery stenosis, especially in doses greater than 20 Gy, especially among children.[190] Radiation and chemotherapy may act synergistically, the dysfunction occurring with only 10 to 15 Gy.

The bladder is particularly susceptible to certain cytotoxic agents. Acrolein, a metabolic by-product of cyclophosphamide and ifosfamide, may cause hemorrhagic cystitis, fibrosis, and occasionally diminished bladder volume. An increased risk of developing bladder cancer also exists. Radiation may lead to bladder fibrosis, diminished capacity, and decreased contractility, the severity proportional to dose and area irradiated. The resultant scarring may diminish urethral and ureteric function.

Gastrointestinal/Hepatic

There are few studies describing long-term effects to this system, either due to underdetection or to a longer latency period than for other organs. Hepatic effects may result from the deleterious effects of many chemotherapeutic agents and radiotherapy. Transfusions may increase the risk of viral hepatitis. Hepatitis C has also been identified in increasing numbers of survivors, 119 of 2,620 tested. Of these patients, 24 of 56 who agreed to participate in a longitudinal study underwent liver biopsy. Chronic hepatitis was noted in 83%, fibrosis in 67%, and cirrhosis in 13%. Fibrosis and adhesions are known to occur after radiotherapy to the bowel.

Compromised Immune System

Hematologic and immunologic impairments can occur after either chemotherapy or radiation and are usually acute in nature. They are temporally related to the cancer treatment. Occasionally, persistent cytopenias may persist after pelvic radiation or in patients who have received extensive therapy with alkylating agents. Alkylating agents may cause myelodysplastic syndrome or leukemia as a late sequela. Immunologic impairment is seen as a long-term problem in Hodgkin's disease, relating to both the underlying disease and the treatments used. Hodgkin's disease patients are also at risk for serious bacterial infections if they have undergone splenectomy.

Peripheral Neuropathies

These effects are particularly common after taxol, vincristine, and cisplatin. However, despite the frequent use of such chemotherapeutic agents, few studies have characterized the nature and course of neuropathies associated with these drug regimens or dose levels.[191,192] Peripheral neuropathy may or may not resolve over time, and potential residual deficits are possible. Clinical manifestations include numbness and tingling in the hands and feet years after completion of cancer treatment.

Second Malignant Neoplasms and Recurrence

Second malignant neoplasms occur as result of an increased risk of second primary cancers associated with (a) the primary

malignancy or (b) the iatrogenic effect of certain cancer therapies.[193–196] Examples include the development of breast cancer after Hodgkin's disease, ovarian cancer after primary breast cancer, and cancers associated with the HNPCC gene. Survivors of childhood cancer have an 8% to 10% risk of developing a second malignant neoplasm within 20 years of the primary diagnosis[197,198]; this is attributable to the mutagenic risk of both radiotherapy and chemotherapy.[199–213] This increased risk may be further potentiated in patients with genetic predispositions to malignancy.[214–220] The risk of secondary malignancy induced by cytotoxic agents is related to the cumulative dose of drug or radiotherapy (dose dependence). The risk of malignancy with normal aging results from the risk of cumulative cellular mutations. Compounding the normal aging process by exposure to mutagenic cytotoxic therapies results in an increased risk of secondary malignancy, particularly after radiotherapy, alkylating agents, and podophyllotoxins. Commonly cited secondary malignancies include (a) leukemia after alkylating agents and podophyllotoxins[221]; (b) solid tumors such as breast, bone, and thyroid cancer in the radiation fields in patients treated with radiotherapy[222]; (c) bladder cancer after cyclophosphamide; (d) a higher risk of contralateral breast cancer after primary breast cancer; and (e) ovarian cancer after breast cancer. Please refer to Chapter 17 for a detailed discussion of this significant issue.

Ancillary Sequelae

Lymphedema

Lymphedema can occur as a persistent or late effect of surgery and/or radiation treatment, and has been reported most commonly after breast cancer treatment, incidence rates ranging between 6% and 30%.[223] Lymphedema can occur in anyone with lymph node damage or obstruction to lymphatic drainage. Women undergoing axillary lymph node dissection and high-dose radiotherapy to the axilla for breast cancer are regarded as the highest risk group. Clinically, lymphedema symptoms may range from a feeling of fullness or heaviness in the affected limb to massive swelling and major functional impairment. Recommendations from the American Cancer Society conference on lymphedema in 1998 emphasize the need for additional research on prevention, monitoring, early intervention, and long-term treatment. Treatments suggested encompass multiple treatment modalities including skin care, massage, bandaging for compression, and exercise. Intermittent compression pumps were recommended only when used as an adjunct to manual approaches within a multidisciplinary treatment program, and routine use of medications such as diuretics, prophylactic antibiotics, bioflavinoids, and benzopyrones was discouraged in the absence of additional research. The impact of sentinel node biopsy in lieu of extensive axillary node dissection procedures for breast cancer on the incidence of lymphedema is not known at this time. A recent review by Erickson et al. found that arm edema was a common complication of breast cancer therapy, particularly when axillary dissection and axillary radiation therapy were used, and could result in substantial functional impairment and psychologic morbidity.[224] The authors note that although recommendations for "preventive" measures (e.g., avoidance of trauma) are anecdotally available, these measures have not been well studied. They found that nonpharmacologic treatments, such as massage and exercise, have been shown to be effective therapies for lymphedema, but the effect of pharmacologic interventions remains uncertain.

Fatigue

Fatigue has been reported as persistent side effect of treatment in many studies.[225–228] This is especially true among patients who have undergone bone marrow transplant.[229] Treatment-related fatigue may be associated with various factors such as anemia, infection, changes in hormonal levels, lack of physical activity, cytokine release, and sleep disorders.[230] The impact of exercise interventions on fatigue is a promising area of research. Fatigue is an important influence on quality of life for both the patient and the family and needs to be managed effectively.

Sexuality and Intimacy

Sexuality encompasses a spectrum of issues ranging from how one feels about one's body to the actual ability to function as a sexual being and has been reported as a persistent effect of treatment. In a recent study on breast, colon, lung, and prostate cancer survivors, issues related to sexual functioning were among the most persistent and severe problems reported. Preexisting sexual dysfunction may also be exacerbated by cancer and its treatment.[231] Please refer to Chapter 19 for further details.

Surgical and Radiation-Induced Toxicities

Surgical effects include increased risk of infections and physiologic comprise associated with nephrectomy (lifestyle changes to prevent trauma to remaining kidney), splenectomy (increased risk for sepsis resulting from encapsulated bacteria), and limb amputation.

Radiation therapy may especially exert effects on the musculoskeletal system and soft tissues among children and young adults, causing injury to the growth plates of long bones and muscle atrophy, osteonecrosis, and fractures.[2,5] Short stature can occur as a result of direct bone injury or pituitary radiation and resultant growth hormone deficiency. Chronic pain, the result of scarring and fibrosis in soft tissues surrounding the joints and large peripheral nerves, is a particularly distressing problem among patients who have received moderately high doses of radiation. Soft tissue sarcomas, skin cancers at previously irradiated sites, and pregnancy loss due to decreased uterine capacity in young girls after abdominal radiation are also possible.

Cancer Survivors, Healthcare Utilization, and Comorbid Conditions

Cancer survivors are high healthcare utilizers affecting distinct healthcare domains.[232,233] Data clearly show that cancer survivors are at greater risk for developing secondary cancers, late effects of cancer treatment, and chronic comorbid conditions. Exposures leading to these risks include cancer treatment, genetic predisposition and/or common lifestyle factors.[234–236] Although the threat of progressive or recurrent disease is at the forefront of health concerns for a cancer

survivor, increased morbidity and decreased functional status and disability that result from cancer, its treatment, or health-related sequelae also are significant concerns. The impact of chronic comorbid conditions on cancer and its treatment is heightened more so among those diagnosed as adults and those who are elderly at the time of diagnosis.

Presented next is a brief overview of some factors potentiating the risk for chronic comorbid conditions among cancer survivors. A brief discussion of the major comorbid illnesses observed among survivors is also presented.

Metabolic Syndrome-Associated Diseases: Obesity, Diabetes, and Cardiovascular Disease

Obesity is a well-established risk factor for cancers of the breast (postmenopausal), colon, kidney (renal cell), esophagus (adenocarcinoma), and endometrium; thus, a large proportion of cancer patients are overweight or obese at the time of diagnosis.[237,238] Additional weight gain also can occur during or after active cancer treatment, an occurrence that has been frequently documented among individuals with breast cancer, but recently has been reported among testicular and gastrointestinal cancer patients as well.[239,240] Given data that obesity is associated with cancer recurrence in both breast and prostate cancer, and reduced quality of life among survivors, there is compelling evidence to support weight control efforts in this population.[14,15,241] Also, gradual weight loss has proven benefits in controlling hypertension, hyperinsulinemia, pain, and dyslipidemia and in improving levels of physical functioning, conditions that reportedly are significant problems in the survivor population.[14,15,21,242] Accordingly, the ACS Recommendations for Cancer Survivors list the "achievement of a healthy weight" as a primary goal.[14]

Obesity represents one of several metabolic disorders that are frequently manifest among cancer survivors, disorders that are grouped under the umbrella of "the metabolic syndrome" and include diabetes and cardiovascular disease (CVD). Insulin resistance is the underlying event associated with the metabolic syndrome, and either insulin resistance, co-occurring hyperinsulinemia, or diabetes have been reported as health concerns among cancer survivors.[243–245] As Brown and colleagues observed,[234] diabetes may play a significant role in the increased number of noncancer-related deaths among survivors; however, its role in progressive cancer is still speculative.

Although there is one study that suggests that older breast cancer patients derive a cardioprotective benefit from their diagnosis and/or associated treatments (most likely tamoxifen),[246] most reports indicate that CVD is a major health issue among survivors, evidenced by mortality data that show that half of noncancer-related deaths are attributed to CVD.[10] Risk is especially high among men with prostate cancer who receive hormone ablation therapy, as well as patients who receive adriamycin and radiation treatment to fields surrounding the heart.[247] Although more research is needed to explore the potential benefits of lifestyle interventions specifically within survivor populations, the promotion of a healthy weight via a low saturated fat diet with ample amounts of fruits and vegetables and moderate levels of physical activity is recommended.[14,15]

Osteoporosis

Osteoporosis and osteopenia are prevalent conditions in the general population, especially among women. Despite epidemiologic findings that increased bone density and low fracture risk are associated with increased risk for breast cancer,[248–256] clinical studies suggest that osteoporosis is still a prevalent health problem among survivors.[257–260] Data of Twiss et al.[258] indicate that 80% of older breast cancer patients have T-scores less than –1 and thus have clinically confirmed osteopenia at the time of their initial appointment. Other cancer populations, such as premenopausal breast and prostate cancer patients, may possess good skeletal integrity at the onset of their disease, but are at risk of developing osteopenia that may ensue with treatment-induced ovarian failure or androgen ablation.

Decreased Functional Status

Previous studies indicate that functional status is lowest immediately after treatment and tends to improve over time; however, the presence of pain and co-occurring diseases may affect this relationship.[261] In the older cancer survivor, regardless of duration following diagnosis, the presence of comorbidity, rather than the history of cancer per se, correlates with impaired functional status.[262] Cancer survivors have almost a twofold increase in having at least one functional limitation; however, in the presence of another comorbid condition, the odds ratio increases to 5.06 (95% CI, 4.47–5.72).[263] These findings have been confirmed by other studies in diverse populations of cancer survivors.[264–266] A cost analysis by Chirikos et al.[266] indicates that "the economic consequence of functional impairment exacts an enormous toll each year on cancer survivors, their families and the American economy at large."

Grading of Late Effects

The assessment and reporting of toxicity, based on the toxicity criteria system, plays a central role in oncology. Grading of late effects can provide valuable information for systematically monitoring the development and/or progression of late effects.[267] Although multiple systems have been developed for grading the adverse effects[4] of cancer treatment, there is, to date, no universally accepted grading system.[3] In contrast to the progress made in standardizing acute effects, the use of multiple late effects grading systems by different groups hinders the comparability of clinical trials, impedes the development of toxicity interventions, and encumbers the proper recognition and reporting of late effects. The wide adoption of a standardized criteria system can facilitate comparisons between institutions and across clinical trials.

[4]Any new finding or undesirable event that may or may not be attributed to treatment.

Some adverse events are clinical changes or health problems unrelated to the cancer diagnosis or its treatment.

A definitive assignment of attribution cannot always be rendered at the time of grading.

Multiple systems have been developed and have evolved substantially since being first introduced more than 20 years ago.[268] Garre et al. developed a set of criteria to grade late effects by degree of toxicity as follows: grade 0 (no late effect), grade 1 (asymptomatic changes not requiring any corrective measures, and not influencing general physical activity), grade 2 (moderate symptomatic changes interfering with activity), grade 3 (severe symptomatic changes that require major corrective measures and strict and prolonged surveillance), and grade 4 (life-threatening sequelae).[269] The SPOG (Swiss Pediatric Oncology Group) grading system has not been validated so far. It also ranges from 0 to 4: grade 0, no late effect; grade 1, asymptomatic patient requiring no therapy; grade 2, asymptomatic patient, requires continuous therapy, continuous medical follow-up, or symptomatic late effects resulting in reduced school, job, or psychosocial adjustment while remaining fully independent; grade 3, physical or mental sequelae not likely to be improved by therapy but able to work partially; and grade 4, severely handicapped, unable to work independently).[270]

The National Cancer Institute Common Toxicity Criteria (CTC) system was first developed in 1983. The most recent version, CTCAE v3.0 (Common Terminology Criteria for Adverse Events version 3.0) represents the first comprehensive, multimodality grading system for reporting *both* acute and late effects of cancer treatment. This new version requires changes in two areas: (1) application of adverse event criteria (e.g., new guidelines regarding late effects, surgical and pediatric effects, and issues relevant to the impact of multimodal therapies); and (2) reporting of the *duration* of an effect. This instrument carries the potential to facilitate the standardized reporting of adverse events and a comparison of outcomes between trials and institutions.

It is important to be aware that tools for grading late effects of cancer treatment are available, to validate them in larger populations, and to examine their utility in survivors of adult cancers. Oncologists, primary care physicians, and ancillary providers should be educated and trained to effectively monitor, evaluate, and optimize the health and well-being of a patient who has been treated for cancer. Additional research is needed to provide adequate knowledge about symptoms that persist following cancer treatment or those that arise as late effects, especially among survivors diagnosed as adults. Prospective studies that collect data on late effects will provide much needed information regarding the temporal sequence and timing of symptoms related to cancer treatment. It may be clinically relevant to differentiate between onset of symptoms during treatment, immediately posttreatment, or months later. Continued, systematic follow-up of survivors will result in information about the full spectrum of damage caused by cytotoxic and/or radiation therapy and possible interventions that may mitigate these adverse effects. We also need to examine the role of comorbidities on the risk for, and development of, late effects of cancer treatment among, especially, adult cancer survivors. Practice guidelines for follow-up care of cancer survivors and evaluation and management of late effects need to be developed so that effects can be mitigated when possible. Clearly, survivors can benefit from guidelines established for the primary prevention of secondary cancers as well as continued surveillance.[271,272]

Follow-Up Care for Late and Long-Term Effects

Optimal follow-up of survivors includes both ongoing monitoring and assessment of persistent and late effects of cancer treatment and the successful introduction of appropriate interventions to ameliorate these sequelae. The achievement of this goal is challenging, and inherent in that challenge is the recognition of the importance of preventing premature mortality from the disease and/or its treatment and the prevention or early detection of both the physiologic and psychologic sources of morbidity. The prevention of late effects, second cancers, and recurrences of the primary disease requires watchful follow up and optimal utilization of early detection screening techniques. Physical symptom management is as important in survivorship as it is during treatment, and effective symptom management during treatment may prevent or lessen lasting effects.

Regular monitoring of health status after cancer treatment is recommended, because this should (1) permit the timely diagnosis and treatment of long-term complications of cancer treatment; (2) provide the opportunity to institute preventive strategies such as diet modification, tobacco cessation, and other lifestyle changes; (3) facilitate screening for, and early detection of, a second cancer; (4) timely diagnosis and treatment of recurrent cancer; and (5) the detection of functional or physical or psychologic disability.

There has been no consensus on overall recommendations for routine follow-up after cancer therapy for *all* cancer survivors. A recent review by Kattlove and Winn can help guide oncologists in providing quality continuing care for their patients—care that spans a broad spectrum of medical areas ranging from surveillance to genetic susceptibility.[273] Health promotion is a key concern of patients once acute management of their disease is complete. Increasingly, cancer survivors are looking to their oncology care providers for counsel and guidance with respect to lifestyle change that will improve their prospects of a healthier life and possibly a longer one as well. Although complete data regarding lifestyle change among cancer survivors have yet to be determined, and there remains an unmet need for behavioral interventions with proven efficacy in various cancer populations,[274] the oncologist can nonetheless make use of extant data to inform practice and also should be attentive to new developments in the field.

Follow-up care and monitoring for late effects is usually done more systematically and rigorously for survivors of childhood cancer while they continue to be part of the program or clinic where they were treated. The monitoring of adult cancer sites for the development of late effects, particularly outside the oncology practice, is neither thorough nor systematic. It is important that survivors of both adult and childhood cancers be monitored for the late and long-term effects or treatment, as discussed in preceding sections, at regular intervals.

It is now recognized that cancer survivors may experience various late physical and psychologic sequelae of treatment and that many healthcare providers may be unaware of actual or potential survivor problems.[275] Until recently, there were no clearly defined, easily accessible risk-based guidelines for cancer survivor follow-up care. Such clinical practice guidelines can serve as a guide for doctors, outline appropriate

methods of treatment and care, and address specific clinical situations (disease-oriented) or use of approved medical products, procedures, or tests (modality-oriented). In response to this growing mandate, the Children's Oncology Group has now developed and published its guidelines for long-term follow-up for Survivors of Childhood, Adolescent, and Young Adult Cancers.[275] These risk-based, exposure-related clinical practice guidelines are intended to promote earlier detection of and intervention for complications that may potentially arise as a result of treatment for pediatric malignancies, and are both evidence based (utilizing established associations between therapeutic exposures and late effects to identify high-risk categories) and grounded in the collective clinical experience of experts (matching the magnitude of risk with the intensity of screening recommendations). Importantly, they are intended for use beginning 2 or more years following the completion of cancer therapy and are not intended to provide guidance for follow-up of the survivor's primary disease.

Of great significance to survivors of adult cancer, using the best available evidence, the American Society of Clinical Oncology (ASCO) expert panels have also identified and developed practice recommendations for posttreatment follow-up of specific cancer sites (breast and colorectal; source: www.asco.org). In addition, ASCO has also created an expert panel tasked with the development of follow-up care guidelines geared toward the prevention or early detection of late effects among survivors diagnosed and treated as adults.

To facilitate optimal follow-up during the posttreatment phase, the patient's age at diagnosis, side effects of treatment reported or observed during treatment, calculated cumulative doses of drugs or radiation, and an overview of late effects most likely for a given patient given the treatment history should be summarized and kept on file. A copy of this summary should be provided to the patient or to the parent of a child who has undergone treatment for cancer. The importance of conveying this detailed treatment history to primary care providers should be clearly communicated, especially if follow-up will occur in the primary/family care setting. Finally, screening tests that may help detect subclinical effects that could become clinically relevant in the future should be listed.

Recommendations for regular, ongoing follow-up of cancer survivors are summarized in Table 6.2. For the prevention or early detection of second malignant neoplasms occurring as a late effect of treatment, providers should remain ever vigilant for the possibility. A detailed history and physical examination is always appropriate, in conjunction with screening at age-appropriate intervals or as outlined by consensus panel recommendations.

Physicians, caregivers, and the family must be able to hear and observe what the patient is trying to communicate, reduce fear and anxiety, counter feelings of isolation, correct misconceptions, and obtain appropriate symptom relief. Practitioners inheriting care for child or adult survivors need to understand the effects of cytotoxic therapies on the growing child or the adult at varying stages/ages of life and be knowledgeable about interventions that may mitigate the effects of these treatments.

Patient education should guide lifestyle and choices for follow-up care, promote adaptation to the disease or relevant sequelae, and help the patient reach an optimal level of wellness and functioning, both physical and psychologic, within the context of the disease and treatment effects.

Research Implications of Long-Term and Late Effects of Cancer

Cancer survivorship research continues to provide us with a growing body of evidence regarding the unique and uncharted consequences of cancer and its treatment among those diagnosed with this disease. It is becoming an acknowledged fact that most cancer treatment options available and in use today will affect the future health and life of those diagnosed with this disease. Adverse cancer treatment-related sequelae thus carry the potential to contribute to the ongoing burden of illness, health care costs, and decreased length and quality of survival.

Data and results from ongoing survivorship studies, examining outcomes among both adult and pediatric cancer survivors, are continuing to demonstrate that (a) there may be long latencies for potentially life-threatening late effects (e.g., cardiac failure secondary to the cardiotoxic effects of cancer treatment); (b) both late and chronic toxicities (e.g., fatigue, sexual dysfunction, cognitive impairment, neuropathies) are persistent, worsen over time, and carry significant potential to adversely affect the health and well being of survivors; (c) early interventions may hold the promise of reducing adverse outcomes; and (d) there may be a continued need for extended follow-up of survivors to prevent, detect early, control, or manage adverse sequelae of cancer or its treatment.

Among childhood cancer survivors, residual endocrine disorders have been shown to be as high as 40%.[276] A recent study found the cumulative frequency of congestive heart failure to be 17.4% at 20 years after diagnosis[277, (5)] and that risk factors such as female gender, higher cumulative doxorubicin doses, and lung and left abdominal irradiation increased the likelihood of heart failure in this population, variables that may affect practice in terms of initial cancer treatment, recommendations for posttreatment follow-up care, and interventions (behavioral, medical, or pharmacologic) to decrease future risk. Others have reported that there may be an increased risk of fetal malposition and premature labor among girls who received flank radiation therapy as part of their treatment for Wilm's tumor, and, among their offspring, an elevated risk for low birth weight, premature birth (less than 36 weeks gestation), and congenital malformations. These risks carry distinct implications for the obstetrical management of female survivors of Wilm's tumor.[278] Finally, data continue to show that survivors of acute lymphoblastic leukemia are at significant risk of being overweight or obese when compared to sibling controls.[125] Because premature coronary artery disease has been reported in this population, these findings underscore the importance of lifestyle and health promotion interventions.

Studies have also begun to demonstrate the deleterious impact of cancer treatment among those diagnosed with this disease as adults. Even after adjustment for age, baseline functional health status, and multiple covariates, long-term breast

[(5)]Among survivors of Wilm's tumor treated with doxorubicin.

TABLE 6.2. Follow-up care and surveillance for late effects.

Follow-up visit	*Content of clinic visit*	*Suggested evaluative procedures and ancillary actions*
Chemotherapy treatment cessation visit	1. Review complete treatment history 2. Calculate cumulative dosages of drugs 3. Document regimen(s) administered 4. Radiation ports, dosage, machine 5. Document patient age at diagnosis/ treatment 6. Side effects during treatment 7. Identify likely late effects 8. Baseline "grading" of late effects (Garre or SPOG)	Develop late effect risk profile Summarize all information in previous column Provide copy to patient (or parent if minor child) Instruct that this summary should be provided to primary care or other healthcare providers Keep copy of summary in patient chart
General measures at every visit	1. Detailed history 2. Complete physical examination 3. Review systems 4. Meds, maintenance, prophylactic antibiotics 5. Education: GPA, school performance 6. Employment history 7. Menstrual status/cycle 8. Libido, sexual activity 9. Pregnancy and outcome	Evaluate symptomatology, patient reports of issues Review any intercurrent illnesses Evaluate for disease recurrence, second neoplasms Systematic evaluation of long-term (persistent) and late effects (see specific measures) Grade long-term and late effects: Garre or SPOG criteria CBC; urinalysis; other tests depending on exposure history and late effect risk profile
Specific measures to evaluate late effects Relevance differs by: 1. Age at diagnosis/treatment 2. Specific drugs, regimens 3. Combinations of treatment modalities 4. Dosages administered 5. Expected toxicities (based on mechanics of action of cytotoxic drugs (cell-cycle-dependent; proliferation kinetics) 6. Exceptions occur to the theoretical assumption that least susceptible organs/tissues are those that replicate slowly or not at all (vinca, methotrexate, adriamycin) 7. Combinations of radiation/ chemotherapy more often associated with late effects	Growth: includes issues such as short stature, scoliosis, hypoplasia	Monitor growth (growth curve); sitting height, parental heights, nutritional status/diet, evaluate scoliosis, bone age, growth hormone assays, thyroid function, endocrinologist consult; orthopedic consult
	Cardiac	EKG, echo, afterload reduction, cardiologist consult Counsel against isometric exercises if high risk, advise ob/gyn risk of cardiac failure in pregnancy
	Neurocognitive	History and exam Communicate: school, family, special education Compensatory remediation techniques Neuropsychology consult; CT or MRI; CSF; basic myelin protein Written instructions, appointment cards
	Neuropathy	History/exam: neurologic exam, sensory changes hands/feet, paresthesias, bladder, gait, vision, muscle strength Neurologist consult
	Gonadal toxicity	History for primary vs. secondary dysfunction, gonadal function (menstrual cycle, pubertal development/delay, libido); hormone therapy; interventions (bromocriptine) Premature menopause: hormone replacement unless contraindicated; DXA scans for osteoporosis; calcium Endocrinologist consult Reproductive technologies
	Pulmonary	Chest X-ray; pulmonary function tests; pulmonologist consultation
	Urinary	Urinalysis; BUN/creatinine; urologist if hematuria
	Thyroid	Annual TSH; thyroid hormone replacement; endocrinologist
	Weight history	Evaluate dietary intake (food diary)/physical activity Nutritionist and/or endocrinologist consult
	Lymphedema	History/exam: swelling, sensations of heaviness/fullness
	Fatigue	Rule out hypothyroidism; anemia, cardiac/pulmonary sequelae; evaluate sleep habits Evaluate physical fitness and activity levels Regular physical activity unless contraindicated
	Surgical toxicity	Antibiotic prophylaxis (splenectomy)
	Gastrointestinal/hepatic	Liver function, hepatitis screen, gastroenterologist consult
Screening for second malignant neoplasms	Screening guidelines differ by age	Follow guidelines for age-appropriate cancer screening (mammogram, Pap smear, FOBT/flexible sigmoidoscopy)
	Oncologist consult	Mammogram at age 30 if history of mantle radiation for Hodgkins Screen for associated cancers in HNPCC family syndrome Screen for ovarian cancer if history of breast cancer and BRCAI II.
Assess/manage comorbidities	Osteoporosis; heart disease; arthritis, etc.	History/exam; be cognizant of risk; appropriate consult

Evaluations are suggestions only. Relevance will differ by treatment history and late effect risk profile.

Source: Data from Aziz (2002, 2003).[2,6]

cancer survivors are more likely to experience persistent significant declines in *physical* health status when compared to cancer-free controls, with younger or socially isolated survivors faring worse than those middle-aged or older in both physical and psychosocial dimensions.[279] These findings have been substantiated by another recent study where breast cancer survivors were found to be at significantly higher risk of physical declines in health status compared to age-matched controls.[280]

Outcomes of cancer and its treatment may be even more complex among medically underserved or ethnoculturally diverse populations. It has been reported that African-American survivors experience poorer functional health and consistently higher levels of comorbidities, decreased physical functioning, and general health vulnerability after cancer diagnosis and treatment compared to age-matched Caucasian patients.[281] From an economic standpoint, survivors working at the time of diagnosis may experience a significant reduction in annual market earnings,[6] the adverse economic impact being worse among survivors with the greatest declines in health status.[282] Long reported as a late effect among pediatric survivors, the adverse neurocognitive impact of cancer treatment is now increasingly reported as a potentially devastating outcome among adult survivors. Breast and lymphoma survivors exposed to systemic chemotherapy are at increased risk for neurocognitive deficits affecting memory, concentration, and attention. Diffuse white and gray matter changes have been reported in magnetic resonance imaging studies, and early data indicate that APOEe4 may be a potential genetic marker for risk.[283,284] Sexual dysfunction continues to be a persistent finding among both men and women years after cancer treatment.[285,286] Finally, the extent to which women's daily living is affected by lymphedema is not recognized routinely by healthcare providers even today.[287]

There are promising findings from intervention studies among both adult and childhood cancer survivors. Daily consumption of aspirin may result in a significant reduction in relative risk of death from breast cancer.[7] Dexrazoxane (DEXRA or Zinecard) administered during active treatment may prevent or reduce acute cardiac injury associated with doxorubicin therapy.[288,289] Methylphenidate (Ritalin) may provide at least a short-term benefit in childhood cancer survivors who experience clinically significant learning problems and deficits in attention and memory.[290]

Home-based educational interventions can help to improve cancer knowledge, self-efficacy (coping), and awareness of resources among both white and African-American breast cancer survivors.[291]

Self-reported depression burden may significantly influence the severity and number of side effects experienced by breast cancer survivors, and self-help interventions may reduce fatigue, pain, and nausea burden in women with breast cancer.[292] Last but not least, cognitive-behavioral stress management interventions may successfully reduce the prevalence of moderate depression and increase generalized optimism and positive reframing, lending support to the importance of examining positive responses to traumatic events.[293]

Thus, research that examines the effects of cancer and its treatment among individuals diagnosed with the disease and their family members is critical if we are to help patients make decisions about treatment options that could affect their future. Cancer survivorship research carries the potential to enable providers of care to tailor therapies to maximize cure while minimizing adverse treatment-related effects. The development and dissemination of evidence-based interventions may help us to reduce cancer morbidity as well as mortality and facilitate adaptation among cancer survivors. Finally, knowledge gained from survivorship research could help improve quality of care, control costs, and equip the next generation of physicians, nurses, and other healthcare professionals to provide not just the science but also the art of comprehensive cancer medicine.

Conclusions

A large and growing community of cancer survivors is one of the major achievements of cancer research during the past three decades. Both length and quality of survival are important endpoints. Many cancer survivors are at risk for, and develop, physiologic late effects of cancer treatment that may lead to premature mortality and morbidity. As in the past when treatments were modified to decrease the chance of developing toxicities among survivors of childhood cancer, the goal of future research and treatment should also be to evaluate late effects systematically and further modify toxicities without diminishing cures. Interventions and treatments that can ameliorate or manage effectively both persistent and late physical effects of treatment should be developed and promoted for use in this population. Oncologists, primary care physicians, and ancillary providers should be educated and trained to effectively monitor, evaluate, and optimize the health and well-being of a patient who has been treated for cancer.

Additional research is needed to provide adequate knowledge about symptoms that persist following cancer treatment or those that arise as late effects. Prospective studies that collect data on late effects prospectively are needed as most of the literature on late effects is derived from cross-sectional studies in which it is not clear if the symptom began during treatment or immediately after treatment. Continued, systematic follow-up of survivors will provide information about the full spectrum of damage caused by cytotoxic or radiation therapy and possible interventions that may mitigate the effects. Interventions, therapeutic or lifestyle, that can treat or ameliorate these late effects need to be developed. Practice guidelines for follow-up care of cancer survivors and evaluation and management of late effects need to be developed so that effects can be mitigated when possible.

Our knowledge about the late effects of cancer treatment, in large part, comes from studies conducted among survivors of pediatric cancer. We need to explore further the impact cancer treatment on late effects in survivors diagnosed as adults. We also need to examine the role of comorbidities on the risk for, and development of, late effects of cancer treatment among these adult cancer survivors.

[6]Compared to age-matched cancer free controls.
[7]Holmes MA. Personal communication.

Although there has been considerable research on the late outcomes among survivors of cancer, future research must be directed toward identification of risks associated with more-recent treatment regimens, as well as the very late occurring outcomes resulting from treatment protocols utilized three or more decades ago. As treatment- and patient-related factors impact the subsequent risk of late-occurring adverse outcomes, clear delineation of those survivors who are at high risk of specific adverse outcomes is essential for the rational design of follow-up guidelines, prevention, and intervention strategies.

Each person with cancer has unique needs based on the extent of the disease, effects of treatment, prior health, functional level, coping skills, support systems, and many other influences. This complexity requires an interdisciplinary approach by all health professionals that is organized, systematic, and geared toward the provision of high-quality care. This ambience may facilitate the adaptation of cancer survivors to temporary or permanent sequelae of the disease and its treatment.

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