Long-term Complications Following Childhood and Adolescent Cancer: Foundations for Providing Risk-based Health Care for Survivors

Kevin C. Oeffinger, MD; Melissa M. Hudson, MD

ABSTRACT  Survivors of childhood and adolescent cancer are one of the higher risk populations seen by health care professionals. The curative therapy administered for the cancer also affects growing and developing tissues. Following chemotherapy, radiation therapy, and surgery, many survivors will experience chronic or late-occurring health problems, often not becoming clinically apparent until decades after therapy. Survivors face an increased risk of morbidity, mortality, and diminished quality of life associated with their previous cancer therapy. Risk is further modified by the survivor’s genetics, lifestyle habits, and comorbid health conditions. Over their lifetime, survivors will see health care professionals from an array of specialties and disciplines. The aim of this review is threefold: (1) to convey a sense of the risk faced by survivors to clinicians unfamiliar with the population; (2) to provide an up-to-date tool for clinicians, regardless of specialty or discipline, when providing care for a survivor; and (3) to complement the recently completed recommendations for screening, prevention, and management of childhood cancer survivors. (CA Cancer J Clin 2004;54:208–236.) © American Cancer Society, 2004.

INTRODUCTION

One of the growing challenges in medicine is providing appropriate health care for survivors of childhood and adolescent cancer. They have an excess risk for early mortality due to second cancers and cardiac or pulmonary disease. Studies estimate that two thirds of survivors have at least one chronic or late-occurring complication (late effect) of their cancer therapy, with about one third having serious or life-threatening complications. Nearly one half of young adult survivors of childhood cancer have at least one major adverse outcome of their health status as a result of their cancer therapy. The incidence of most late effects increases with age, often becoming clinically apparent decades after therapy.

This high-risk population, currently numbering about 270,000 in the United States, interfaces with many health care professionals, including oncologists, medical and pediatric specialists, surgeons, primary care physicians, nurses, psychologists, and social workers. Table 1 provides the distribution of survivors by cancer group. Examples are innumerable: the pregnant Ewing’s sarcoma survivor referred by an obstetrician to a cardiologist for shortness of breath; the primary care physician evaluating a leukemia survivor for dyslipidemia and insulin resistance; a surgeon assessing a breast mass in a Hodgkin disease (HD) survivor who had mantle radiation; the school nurse working with the family of a medulloblastoma survivor with seizures and cognitive limitations. The challenge arises from the heterogeneity of this population treated with evolving cancer therapies amid a rapidly advancing understanding of the late effects of therapy.

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Faced with these risks and challenges, how can the health care delivered to these relatively young survivors be optimized? Many of the late effects can be lessened by prevention or by early diagnosis with therapeutic intervention. In the past 10 years, the concept of risk-based health care of survivors has evolved. The term “risk-based health care,” coined by Meadows, Oeffinger, and Hudson, refers to a conceptualization of lifelong health care that integrates the cancer and survivorship experience in the overall health care needs of the individual. A systematic plan for lifelong screening, surveillance, and prevention that incorporates risks based on the previous cancer, cancer therapy, genetic predispositions, lifestyle behaviors, and comorbid health conditions should be developed for all survivors. The fundamental tenets of risk-based health care are provided in Table 2. Possibly up to one third of this population experience relatively few minor complications and will face minimal long-term risks. It is difficult to fully appreciate risk, however, because the effect of chemotherapy, radiation therapy, and surgery on the aging of different organ systems will only become evident as the population ages.

Apart from academic centers, few health care professionals see more than a handful of survivors, each with different cancers, treatment exposures, and health risks. Thus, it is a daunting task for the clinician to deliver appropriate care. The aims of this review are to (1) convey a sense of the risk faced by survivors to clinicians unfamiliar with the population; (2) provide an up-to-date tool for clinicians, regardless of specialty or discipline, when providing care for a survivor; and (3) complement the recently completed recommendations for screening, prevention, and management of childhood cancer survivors described in the next section. Recognizing the diversity of readership of this journal, we have attempted to balance the details of late effects while maintaining the “big picture,” with the intent of providing a useful foundation for delivering risk-based health care to this vulnerable population.

### TABLE 1 Percent Distribution of Cancer Groups at Diagnosis in 2000 and Estimated Percent Distribution in Five-year or More Cancer Survivors Based Upon 1992 to 1999 Survival Rates, Ages 0 to 19*

<table>
<thead>
<tr>
<th>Cancer Group</th>
<th>Distribution at Cancer Diagnosis (2000) (%)</th>
<th>Five-year Survival Rates (1992 to 1999) (%)</th>
<th>Predicted Distribution of Five-year or More Survivors† (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>24.4</td>
<td>67.9</td>
<td>21.3</td>
</tr>
<tr>
<td>Brain and other nervous</td>
<td>18.5</td>
<td>70.8</td>
<td>16.8</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>7.7</td>
<td>79.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>7.1</td>
<td>72.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>6.5</td>
<td>94.2</td>
<td>7.9</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>4.8</td>
<td>74.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>4.8</td>
<td>68.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Other</td>
<td>26.2</td>
<td>91.4</td>
<td>30.8</td>
</tr>
</tbody>
</table>

*Adapted from Ries LAG, Eisner MP, Kosary CL, et al.*

†Predicted distribution calculated by using 1992 to 1999 five-year survival rates and 2000 incidence data.

### TABLE 2 Basic Tenets of Risk-based Health Care of Childhood Cancer Survivors

- Longitudinal care that is considered a continuum from cancer diagnosis to eventual death, regardless of age
- Continuity of care consisting of a partnership between the survivor and a single health care provider who can coordinate necessary services
- Comprehensive, anticipatory, proactive care that includes a systematic plan of prevention and surveillance
- Multidisciplinary team approach with communication between the primary health care provider, specialists of pediatric and adult medicine, and allied/ancillary service providers
- Health care of the whole person, not a specific disease or organ system, that includes the individual’s family and his or her cultural and spiritual values
- Sensitivity to the issues of the cancer experience, including expressed and unexpressed fears of the survivor and his or her family/spouse

Adapted from Oeffinger KC.
Organizational Approach of the Review

In presenting this information, one can approach late effects from three different vantage points: the specific type of cancer, the organ system affected, or the therapeutic exposure. Each has its advantages and limitations. We have chosen to organize this review by therapeutic exposures and believe this approach will be useful to clinicians regardless of specialty or discipline. By knowing the treatment exposures, the clinician can then determine what late effects the survivor faces. This review does not presume to be exhaustive; rather, it describes the more common or serious problems experienced by survivors. Because risk that is associated with one exposure may be modified by other therapies, where appropriate, these modifying risks are included.

This review is intended to complement the recently released “Children’s Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers,” which can be found on the Children’s Oncology Group Web site (http://www.survivorshipguidelines.org). These guidelines were produced through a multidisciplinary effort, cochaired by one of the authors (MMH) and Wendy Landier, RN, MSN, CPNP. A Web-based interactive and user-friendly format of these guidelines, targeted for health care professionals and survivors, is under development.

Childhood Cancer Survivor Study

A major contributor to the literature is the Childhood Cancer Survivor Study (CCSS). Briefly, this longitudinal cohort study, supported through the National Cancer Institute and directed through the University of Minnesota, is tracking the outcomes of over 14,000 long-term survivors of childhood cancer. Five-year or more survivors who were diagnosed with cancer at one of 26 participating institutions from 1970 to 1986 were eligible for enrollment. Survivors were diagnosed before the age of 21 with one of the following: leukemia, central nervous system (CNS) tumor, HD, non-Hodgkin lymphoma (NHL), Wilms tumor, neuroblastoma, soft tissue sarcoma, or bone tumor. The participating institutions abstracted extensive information regarding the cancer diagnosis and treatment exposures. For comparisons with many of the outcomes, a random sample of siblings was enrolled. The primary limitation of CCSS is that many of the outcomes are self-reported. The main strength of the CCSS is the large geographically and ethnically diverse population with extensive demographic and treatment exposure data, allowing in-depth analysis of factors associated with various outcomes. As this cohort is followed longitudinally, reports from CCSS will continue to enhance our understanding of the cancer and survivor experience and long-term effects of chemotherapy, radiotherapy, and surgery.

PSYCHOSOCIAL ASPECTS OF SURVIVORSHIP

The psychosocial outcomes of surviving cancer as a child or adolescent are complex. We reported that among 9,535 young adult survivors in CCSS, 17% had depressive, somatic, or anxious symptoms. About 10% reported moderate to extreme pain as a result of their cancer therapy, and 13% expressed frequent fears related to their cancer experience. Interestingly, though nearly one half reported fairly significant changes in their health status, including physical impairments and limitations in activity, only 10% reported that they thought their health was fair or poor. Illustrating this discordant finding was the 29-year-old T-cell lymphoma survivor with severe restrictive lung disease and moderate anthracycline-induced cardiomyopathy who reported that her health was great.

Zebrack and Zeltzer have described this phenomenon of survivors experiencing posttraumatic stress concurrent with feelings of resilience and enhanced quality of life. Kazak, Hobbie, and colleagues have explored the dimensions of posttraumatic symptoms in survivors and their families and have developed screening tools.

To the clinician, it may be difficult to determine whether somatic complaints such as fatigue, lethargy, and chronic pain are physical or psychological in nature. While it is impor-
tant to be aware of the increased prevalence of depressive and posttraumatic symptoms in survivors, it is also important to avoid attributing somatic complaints to nonorganic causes without proper evaluation. Thus, it is crucial to consider psychosocial issues when evaluating cancer survivors.

RADIATION THERAPY

Evolution of Radiation Therapy

Radiation therapy has long been known to be effective in killing cancer cells, with the first cancer patient cured with ionizing radiation occurring in 1899. The therapeutic use of radiation to destroy the tumor while sparing the surrounding tissue has depended on the technological advances of methods of delivery and imaging. With these advances, the ability to focus the energy of the ionizing beam on a specific location substantially reduced damage to the surrounding tissues while maintaining effectiveness in causing cancer cell death.

The developing and growing tissues of children and adolescents are particularly sensitive to the effects of radiation. Late effects of radiation therapy may be evident soon after therapy (eg, cognitive dysfunction or pericarditis) or decades later (eg, second malignant neoplasms). The incidence and severity of radiation-related late effects are influenced by the organs and tissues included in the treatment field, type of radiation administered, daily fractional and cumulative radiation dose, and age at treatment. Improvements in the delivery of radiation therapy in the past 10 years combined with multimodal risk-adapted therapeutic approaches may result in fewer late effects attributable to this treatment modality.

The following three sections describe the primary late effects associated with radiation therapy delivered to the brain, chest, and abdomen/pelvis. Total body irradiation (TBI) is described in the bone marrow transplantation section. For reference, the Gray (Gy) is the international unit of absorbed radiation dose, with 1 Gy equivalent to 1 Joule/kg or, in the older literature, to 100 rad. Table 3 provides selected late effects associated with radiation.

Regardless of the region irradiated, the skin and the musculoskeletal system are often affected. Radiation used in the treatment of childhood cancer is associated with an increased risk for melanoma, squamous cell carcinoma, and basal cell carcinoma in the radiation field. Musculoskeletal changes are also common after radiation. In the early days of radiation therapy, this sometimes resulted in fairly dramatic asymmetric growth of the spine or other structures. However, even with contemporary radiation therapy, survivors may have changes in their musculoskeletal system leading to pain or problems with function.

Cranial Radiation Therapy

Background and General Considerations

Radiation to the brain has been used in the treatment of brain tumors, acute lymphoblastic leukemia (ALL), head and neck soft tissue sarcoma, and retinoblastoma. As the long-term effects of brain radiation have become known, particularly cognitive dysfunction, more recent treatment protocols have either eliminated use (low and standard risk ALL) or are attempting to lower doses (some brain tumors) while maintaining equivalent efficacy.

Higher dose whole brain or local field radiation continues to be an integral part of treating most brain tumors. Conventional therapy for medulloblastoma and germ cell tumors includes 36 Gy craniospinal radiotherapy (CS-RT), with a 15 to 20 Gy boost to the posterior fossa. Current trials are assessing the five-year survival rate of lower dose CS-RT (23.4 Gy) with a 32.4 Gy boost to the posterior fossa. High-dose local field radiation (tumor plus margin) is used in the treatment of glial tumors and craniopharyngiomas.

For many years, whole brain radiation or cranial radiotherapy (CRT) was the primary method of preventing CNS relapse in patients with ALL. From the late 1960s to the early 1980s, 24 Gy CRT was the standard therapy for all children treated for ALL. Because of the
recognition of cognitive dysfunction associated with CRT, other methods of CNS prophylaxis are now used in the treatment of standard and low-risk ALL patients. Those with a higher risk for recurrence are still treated with CRT but with lower doses (12 to 18 Gy).

Ten percent of rhabdomyosarcoma occurs in the head and neck region. Radiation to the tumor site, generally in higher doses of 40 to 50 Gy, is administered in addition to chemotherapy. Children with nonrhabdomyosarcoma soft tissue sarcomas receive similar doses of radiation. Retinoblastoma that has extended beyond the retina to the orbit or to the cut edge of the optic nerve is treated with chemotherapy and 40 Gy local field radiation.

**TABLE 3** Selected Late Effects* Following Radiation in Survivors of Childhood and Adolescent Cancer

<table>
<thead>
<tr>
<th>Radiation Field</th>
<th>Late Effect(s)</th>
<th>Additional Risk Factors†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial radiotherapy</td>
<td>Neurocognitive deficits</td>
<td>Most marked for ≥ 36 Gy</td>
</tr>
<tr>
<td></td>
<td>Growth hormone deficiency</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Seizures and strokes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second cancers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dental problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cataracts</td>
<td>Combined treatment with corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Panhyponpuitarism</td>
<td>Uncommon &lt; 40 Gy</td>
</tr>
<tr>
<td>Chest or mantle radiotherapy</td>
<td>Breast cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac disease:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valvular disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pericardial disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Thyroid disease:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thyroid cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease:</td>
<td>Combined therapy with:</td>
</tr>
<tr>
<td></td>
<td>Reduced diffusion capacity</td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td>Restrictive lung disease</td>
<td>Busulfan</td>
</tr>
<tr>
<td></td>
<td>Obstructive lung disease</td>
<td>Carmustine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lomustine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smoking</td>
</tr>
<tr>
<td>Abdominal/Pelvic radiotherapy</td>
<td>Lung cancer</td>
<td>Combined therapy with:</td>
</tr>
<tr>
<td></td>
<td>Chronic enteritis</td>
<td>Cisplatin/carboplatin</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal malignancy</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td></td>
<td>Renal insufficiency</td>
<td>Aminoglycosides or amphotericin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunosuppressants or cyclosporine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combined therapy with:</td>
</tr>
<tr>
<td></td>
<td>Bladder disease:</td>
<td>cyclophosphamide or</td>
</tr>
<tr>
<td></td>
<td>Fibrosis</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic cystitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gonadal dysfunction:</td>
<td>Combined therapy with</td>
</tr>
<tr>
<td></td>
<td>Ovarian failure</td>
<td>cranial irradiation</td>
</tr>
<tr>
<td></td>
<td>Testicular failure</td>
<td></td>
</tr>
<tr>
<td>Any radiation</td>
<td>Skin cancer:</td>
<td>All of the above</td>
</tr>
<tr>
<td></td>
<td>Basal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal changes</td>
<td></td>
</tr>
<tr>
<td>Total body irradiation</td>
<td></td>
<td>All of the above</td>
</tr>
</tbody>
</table>

*Table 3 includes late effects discussed in the text and is not exhaustive. A complete listing of all known late effects by therapeutic exposure is provided in the “Children’s Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers” at www.survivorshipguidelines.org.
†For most late effects associated with radiation, risk is higher for the following groups: (1) higher dose of radiation; (2) younger age at radiation therapy; and (3) older methods and techniques of radiation therapy.
Cognitive Dysfunction

The most common late effect of moderate-to high-dose whole brain radiation is diminished intellectual capacity.19 This dose-related outcome is most evident in survivors of medulloblastoma who were treated with 36 Gy CS-RT. Deficits in full-scale intelligence quotient (FSIQ), verbal intelligence quotient (IQ), visual-spatial abilities, attention-concentration, nonverbal memory, and somatosensory functioning have been reported.20–22 In a series of 120 children with medulloblastoma treated from 1967 to 1987, Hoppe-Hirsch et al. reported that by five years following therapy, 42% had an FSIQ of less than 80.23 By 10 years after therapy, 75% of survivors had an FSIQ of less than 80, including 46% who were below an FSIQ of 60. The CCSS reported that 18% of 18- to 24-year-old brain tumor survivors had not completed high school.24 Recent studies suggest that treatment of medulloblastoma with lower dose whole brain radiation (23.4 Gy) and a higher boost to the posterior fossa is associated with less neuropsychological toxicity.25,26

Brain tumor survivors treated at a younger age are particularly susceptible to cognitive dysfunction following CS-RT.20,21,27 In a review of 22 studies of children with brain tumors, survivors treated at a younger age had a 14-point greater deficit in IQ as compared with those treated later in childhood.20 In the CCSS, about 70% of brain tumor survivors diagnosed before the age of six required special education services in school.24 They were 19 times more likely to have reported these services compared with the sibling group.

Although not as devastating as higher dose whole brain radiation for brain tumors, past treatment with 24 Gy CRT for ALL is associated with cognitive dysfunction. A meta-analysis of over 30 retrospective and prospective studies of ALL survivors reported that 24 Gy CRT resulted in a mean decrease in full-scale IQ of 10 points.28 Verbal IQ scores were affected more than performance IQ, and changes were noted to be progressive. Although more than one half of patients had mild to moderate learning problems, outcomes were highly variable, and some patients experienced 20 to 30 point losses, while others had no discernible changes. Deficits have also been noted in measures of visual-spatial abilities, attention-concentration, nonverbal memory, and somatosensory functioning.28–31 Female survivors and those treated with CRT before four years of age are likely to have more severe dysfunction.28–31 Treatment with 18 Gy CRT is associated with less neuropsychological toxicity than 24 Gy.32

The Children’s Cancer Group investigated the impact of treatment on scholastic performance of 593 adult survivors of ALL in comparison with 409 sibling controls.33 Survivors treated with 24 Gy CRT were much more likely to enter special education or learning disabled programs. In general, survivors were as likely to finish high school and enter college as the controls, but those treated with 24 Gy or treated before the age of six years were less likely to enter college. There were no gender differences in educational achievements.

Neuropathologic changes following whole brain radiation include leukoencephalopathy, mineralizing microangiopathy, subacute necrotizing leukomyelopathy, and intracerebral calcifications, commonly with subsequent cerebral atrophy and microcephaly.34 In a recent series of studies, Mulhern and colleagues have associated changes with FSIQ with the volume of white matter loss determined by quantitative neuroimaging.35,36 This may provide a model to better predict neurocognitive outcomes and identify those at highest risk.

Endocrine Dysfunction

Neuroendocrine dysfunction, such as growth hormone deficiency (GHD), is a common dose- and site-related sequelae following radiation to the brain. In 1,607 brain tumor survivors enrolled in CCSS, 43% reported one or more endocrine conditions.37 GHD is the most common endocrinopathy following cranial radiation. In 144 brain tumor survivors treated with radiation, Livesey et al. reported that 140 had evidence of GHD.38 Survivors of ALL treated with 24 Gy CRT have a decrease in median height of about 5 to 10 cm.39,40 Treatment with 18 Gy CRT affects the final height to a lesser degree.41 Female
patients and patients treated at a younger age (less than five years of age) have the greatest decrement. Treatment with growth hormone in these patients usually results in near normalization of final height, unless the spinal axis has also been irradiated. GHD in adults is associated with an increase in prevalence of dyslipidemia, insulin resistance, and cardiovascular mortality. Deficiency of gonadotropins, thyroid stimulating hormone, and adrenocorticotropic are rarely seen in survivors treated with less than 40 Gy radiation to the hypothalamic–pituitary axis.

Obesity

Moderate doses of CRT (24 Gy) are associated with obesity, particularly in female patients treated at a young age. In an analysis of 1,765 adult survivors of childhood ALL enrolled in the CCSS, female survivors treated with ≥20 Gy were two to three times more likely to be obese in comparison with siblings of childhood cancer survivors. Those who were treated with this dose range of CRT before the age of five were almost four times as likely to be obese as the sibling comparison group. Compared with male siblings, male ALL survivors treated with ≥20 Gy were almost twice as likely to be obese. Lower dose CRT (10 to 19 Gy) or chemotherapy alone was not associated with being obese. A recent small study using dual x-ray absorptiometry suggests that ALL survivors treated with lower dose CRT (15 to 18 Gy) are at increased risk for body fatness. In brain tumor survivors treated with higher doses of whole brain radiation, only female survivors treated at a younger age appear to be at increased risk for obesity.

Obesity that develops in the adolescent or young adult years is strongly associated with several common adult health problems, including adult-onset diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, endometrial cancer, osteoarthritis, and possibly breast and colon cancer. Two small studies suggest that survivors of ALL treated with CRT may have an increased prevalence of cardiovascular risk factors and that this may in part be secondary to radiation-associated obesity.

Other Late Effects Associated with Cranial Radiation

Less common but serious outcomes associated with radiation include seizures and cerebrovascular accidents. Second neoplasms are infrequent following CRT for ALL. However, with the higher doses of radiation used for brain tumors, there is an increased risk for meningiomas and glial tumors. Less serious though significant late effects include cataracts and dental abnormalities with a higher risk for periodontal disease. CRT also potentiates the hearing loss associated with cisplatin.

Cranial radiation, particularly in younger patients, significantly impacts long-term functional and psychosocial status. This was well illustrated in a recent extended follow-up study of 856 ALL survivors who had attained at least 10 years of event-free survival. Significant differences in socioeconomic indicators were observed in the irradiated group compared with the nonirradiated group and US population. The irradiated group had unemployment rates that were higher than those of the corresponding population. Irradiated female survivors also had lower marital rates than that in the corresponding age- and sex-matched general population.

Chest and Mantle Radiation Therapy

Background and General Considerations

Radiation to the chest or mantle is used in the treatment of HD, NHL, and metastases to the lungs (eg, soft tissue sarcoma, Wilms tumor). The group most often exposed to the highest average doses of radiation are survivors of HD. Because of this, the majority of studies assessing risk of late effects following chest radiation have focused on HD survivors. Mantle radiation was the mainstay for treatment of Stage I or II supradiaphragmatic HD from the 1960s through the 1980s. The mantle field encompasses the primary lymph node regions of the neck, supraclavicular, infraclavicular, axillary, and mediastinal areas. This field also exposes the developing breast tissue and heart to significant doses of ionizing radiation. Gener-
ally, radiation doses to the mantle ranged from 35 to 44 Gy. More recently, modified mantle radiotherapy with a lower total dose (15 to 25 Gy) to involved nodes has been used in combination with multiagent chemotherapy. The dose of radiation administered to the mediastinum or lungs for other primary malignancies or metastatic disease depends on the cancer type.

Problems following radiation involving the chest are common. As a note of caution, many of the HD studies have included survivors diagnosed at all ages, from childhood through the geriatric years. Because most late effects are modified by the age at diagnosis, the median age of HD survivors is provided in parentheses where appropriate. It is presumed that the incidence of late effects will decrease with more recent protocols that involve lower doses that minimize the effects on normal developing tissues.

**Breast Cancer Following Radiation**

Female survivors who were treated with chest or mantle radiation for a pediatric malignancy face a significantly increased risk of breast cancer. Ionizing radiation exposure to the breast can result from any of the following types of radiation therapy: mantle, chest, mediastinum, lung, and spinal (craniospinal). In a recent report by Bhatia et al., the 30-year cumulative incidence of breast cancer in female HD survivors following radiation was 17%.59 The cumulative incidence by age 40 years was 14%, increasing to 20% by age 45 years. Female patients treated with mantle radiation before the age of 21 are at significantly higher risk of breast cancer in comparison with those treated in their adult years.60,61 However, a difference in risk when radiation was administered in the adolescent versus prepubescent years has not been reported in recent studies.

The risk for breast cancer begins to increase about eight years after radiation.59,60,62 Women in this group are young at breast cancer diagnosis, often less than 40 years of age. Importantly, five-year survival rates in this group are strongly associated with stage of disease at time of diagnosis, and thus early diagnosis should confer improved outcomes.63–65 Mammography appears to detect most breast cancers in women with previous chest or mantle radiation.63,64,66

**Radiation-associated Cardiac Disease**

Much of the heart is exposed in chest, mantle, and spinal radiation fields, resulting in subsequent premature coronary artery, valvular, and pericardial disease.67–73 Childhood cancer survivors in CCSS who were treated with chest or spinal radiation had more than a twofold increase in relative risk for cardiac–related death in comparison with the standard US population.1 Hull et al. estimated that by 20 years after radiation, 16% would have significant cardiovascular morbidity.71 Similarly, a Dutch study of HD survivors reported a cumulative risk for ischemic heart disease of 21% at 20 to 25 years after radiation.72 An excellent review of radiation–associated cardiovascular disease was recently provided by Adams et al.73

Radiation-associated coronary artery disease is the most common cardiac outcome following radiation to the chest. In a follow-up of 415 HD survivors (median age at HD diagnosis, 25 years), 10% developed coronary heart disease.71 Similarly, 5.5% of 326 HD survivors (median age at HD diagnosis, 26 years) who had mantle radiation subsequently developed coronary artery disease.68 More recent methods of shielding the heart and equally weighting the anterior and posterior fields appear to decrease this risk. However, even with current shielding techniques, the proximal coronary arteries are within the standard mantle field.

Chest radiation is also associated with valvular disease, with the left-sided valves predominating.73 Hull et al. reported that 6% of their HD population developed clinically significant valvular disease, with aortic stenosis being the most common outcome.71 Long-term problems related to pericardial disease or dysrhythmias are less common.

**Radiation-associated Pulmonary Disease**

Acute radiation pneumonitis is an uncommon outcome with contemporary therapy.74 However, asymptomatic reductions in lung function, including diffusion capacity or abnormal restric-
tive or obstructive patterns, are common. Of 25 HD survivors treated with standard mantle radiation before the age of 35, 60% had an abnormal chest radiograph at a mean follow-up of nine years. Of the 19 who had pulmonary function testing, 89% had an abnormality, with 72% having a reduced diffusion capacity. None of the patients were symptomatic. Mefferd and colleagues assessed pulmonary function in 34 asymptomatic HD survivors who had been treated before the age of 18 with low-dose (15 to 25 Gy), involved-field radiation and bleomycin. By two years following treatment, 55% had an abnormal carbon monoxide diffusing capacity. Six of twenty survivors had restrictive changes, while two had obstructive disease. Similar findings were reported by Nysom et al. in a study of 41 survivors of childhood HD or NHL. For the majority of survivors who had radiation to the chest region, it is not known how the generally mild reductions in carbon monoxide diffusing capacity or mild restrictive or obstructive disease will affect the patient with comorbid heart or lung problems associated with aging.

Mertens and colleagues studied self-reported pulmonary problems in 12,390 long-term survivors in CCSS. The cumulative incidence of pulmonary fibrosis by 20 years after chest radiation was 3.5%. Chest radiation was associated with chronic cough, exercise-related dyspnea, and an abnormal chest wall.

Lung cancer is also associated with chest radiation, though it is relatively infrequent in the young adult survivor unless he or she also smokes.

Abdominal and Pelvic Radiation Therapy

Radiation Effects on the Gastrointestinal Tract and Liver

Childhood cancer survivors treated with abdominal or pelvic radiation are at risk for a variety of late health problems involving the gastrointestinal (GI) tract, liver, spleen, kidneys, and other genitourinary tract structures including the gonads. Following contemporary therapy for pediatric malignancies, chronic or delayed radiation injury of the GI tract is relatively uncommon. Radiation-related GI toxicity has been most commonly described in long-term survivors of genitourinary solid tumors or in survivors treated with allogeneic bone marrow transplantation for a hematologic malignancy. GI tract complications following radiation result from chronic mucosal inflammation that interferes with absorption and digestion of nutrients (enteritis) or predisposes to scarring (fibrosis) of intraabdominal tissues. Other cancer-related complications (eg, chronic infection, graft-versus-host disease [GVHD], or short bowel syndrome)
may exacerbate chronic radiation enteritis or fibrosis.

The most common clinical sequelae of fibrosis include partial or complete bowel obstruction from strictures or adhesions. This complication rarely develops in individuals treated with radiation who have not had abdominal surgery. The incidence of small bowel fibrosis is about 5% after 40 to 50 Gy and rises to 40% when doses exceed 60 Gy. Chronic GI tract injury is uncommon if radiation is administered over four to 4.5 weeks to cumulative doses below 42 Gy. Although radiation would be expected to enhance the risk of late postsurgical small bowel obstruction, this complication has rarely been observed in long-term childhood cancer survivors. Children irradiated at lower doses for Wilms tumor also uncommonly develop chronic GI toxicity. Chronic enteritis may occur in association with or independent of fibrosis and result in malabsorption, bowel ulceration/perforation, or fistula formation.

In the absence of other predisposing conditions, such as viral hepatitis, persistent or late onset hepatopathy after contemporary radiation is uncommon, suggesting complete resolution of acute hepatic radiation injury. The liver generally has good tolerance to radiation doses up to 30 to 35 Gy using conventional dose fractionation. The risk of hepatic injury increases significantly with doses exceeding 35 Gy, but smaller volumes of the liver can be safely irradiated to higher doses. Younger age at treatment, prior partial hepatectomy, and concomitant use of radiomimetic chemotherapy like dactinomycin and doxorubicin may increase the risk of radiation injury. Delayed and chronic hepatic radiation toxicity is rare. Hepatic radiation and a variety of chemotherapeutic agents, particularly agents used in conditioning regimens before hematopoietic stem cell transplantation, have been implicated in the causation of veno-occlusive disease. This complication appears to resolve in the majority of survivors, although long-term outcomes after veno-occlusive disease have not been established.

Radiation Effects on the Spleen

Individuals who received splenic radiation at doses of 30 Gy are also at increased risk for functional asplenia and should be managed similar to asplenic survivors (see below in Splenectomy); low-dose (less than 25 Gy) splenic radiation does not adversely affect splenic reticuloendothelial function.

Radiation Effects on the Genitourinary Tract

Chronic radiation injury of the kidneys may manifest as tubular or glomerular dysfunction and hypertension associated with renal artery stenosis or hyperreninemia. In adults with normal baseline renal function treated with conventional fractionation, the threshold dose for renal injury is 15 Gy; children may present with injury at doses as low as 12 to 14 Gy. Treatment with radiomimetic chemotherapy like doxorubicin and dactinomycin may enhance this risk, as can combination therapy with other nephrotoxic antineoplastic or supportive care agents. Reduction in renal mass following nephrectomy may also exacerbate radiation injury through chronic hyperfiltration of the remnant nephrons.

Fibrosis induced by pelvic radiation may adversely affect bladder capacity and function. The reported incidence is higher when cumulative radiation doses are 45 Gy or more. Clinical symptoms associated with this complication include dribbling, nocturnal enuresis, and frequency. Cystitis may be seen after radiation and specific chemotherapeutic agents like cyclophosphamide and ifosfamide and viral agents, especially adenovirus, may cause hemorrhagic cystitis. The incidence of hemorrhagic cystitis is described cases of colorectal and gastric cancer in adults surviving a childhood malignancy. The risk of GI cancers reported in large cohort studies of childhood cancer survivors was significantly elevated, with these malignancies developing at much younger ages compared with the general population. While radiation has been implicated as the primary predisposing risk factor in these cases, alkylating agent chemotherapy may enhance this risk.
5% if radiation doses to the bladder are limited to less than 40 Gy. Distal urinary tract obstruction, infection, concurrent treatment with radiomimetic agents, and viral infections may exacerbate this condition. In addition, cyclophosphamide and radiation have been implicated in the development of bladder malignancies.102,105

Radiation Effects on the Gonads

Radiation produces adverse effects on gonadal function that vary by age, gender, and cumulative dose. In male patients, the sperm production is reduced in a dose-dependent manner with fractionated exposures of 0.1 to 6 Gy.106,107 Azoospermia may be reversible at doses of 1 to 3 Gy; doses in excess of 3 Gy typically produce irreversible azoospermia that is associated with elevation of follicle stimulating hormone (FSH) and testicular atrophy.106 Prepubertal testicular germ cells are also radiosensitive.108 Radiation injury to Leydig cells is directly related to the dose delivered and inversely related to age at treatment.109,110 Most prepubertal boys treated with 12 Gy or less of fractionated testicular radiation produce normal amounts of testosterone, although elevated plasma concentrations of luteinizing hormone (LH) observed in this group suggest subclinical injury. Prepubertal boys treated with 24 Gy for testicular leukemia uniformly have delayed onset of puberty requiring androgen therapy.110 Leydig cell failure will occur in 50% of adolescent and young adult men treated with radiation doses in excess of 33 Gy.111

Radiation to the abdomen, pelvis, and spine is associated with an increased risk of ovarian failure, especially if the ovaries are in the treatment field. The ovaries of younger patients are more resistant to radiation injury than are those of older women. Radiation doses in excess of 20 Gy produce permanent ovarian failure in the majority of female childhood cancer patients.112 Ovarian dysfunction may develop at lower doses if radiation is used in combination with alkylating agent chemotherapy. Survivors treated with combined modality regimens including abdominal or pelvic radiation and alkylators may have fertility affected by the onset of premature menopause.113 Elevations of FSH in young women treated with spinal radiation for ALL and brain tumors are consistent with radiation-induced ovarian dysfunction.114,115 However, FSH levels normalize over time, and the majority of girls treated with doses of 18 to 24 Gy experience puberty and menarche without the need for hormonal replacement therapy.114,115 Girls treated for abdominal or pelvic solid tumors or lymphoma have a very high risk of premature ovarian failure. In prepubertal girls, doses in the range of 20 to 30 Gy may be associated with failure to undergo or complete pubertal development.112 Ovarian transposition may preserve ovarian function in young girls and adolescents who require pelvic radiation therapy.116

CHEMOTHERAPY

Evolution of Chemotherapy

The integration of anticancer drugs into treatment regimens previously relying on surgery and radiation therapy was instrumental in the achievement of long-term disease control for many pediatric malignancies. The combined modality approach provided systemic chemotherapy to eradicate metastatic disease with surgery and/or radiation therapy for local disease control. Investigations of children with ALL were among the first to establish the superiority of using combinations of drugs rather than single agents.117 Combination chemotherapy increased antitumor response by providing different mechanisms of antitumor activity against naturally resistant tumor cells and by reducing the development of acquired resistance.118 Combination chemotherapy may be associated with increased side effects if agents have a similar spectrum of toxicity. Conversely, patients may have better tolerance if agents with differing toxicity profiles are used together. Pediatric oncologists have organized combined modality therapy trials for a variety of malignancies that permit reduction or omission of one modality (eg, radiation therapy) based on a complete response to another. The successful outcome of these studies was followed by risk-adapted treatment approaches that reserved more intensive modalities for patients determined to be at higher risk of treatment failure based on clinical or biologic features. Knowledge regarding the
risk profiles for the unique toxicities associated with specific chemotherapeutic agents has been influential in therapy modifications implemented in contemporary treatment regimens. Treatment toxicities related to specific classes of chemotherapeutic agents are reviewed in the following section. Table 4 summarizes selected late effects following chemotherapy.

Alkylating Agents

Classical alkylators include commonly used anticancer drugs like mechlorethamine (nitrogen mustard), the oxazaphosphorines (cyclophosphamide and ifosfamide), melphalan, the nitrosoureas (lomustine, carmustine), and busulfan. These agents are highly carcinogenic, mutagenic, and teratogenic.

Gonadal Dysfunction

Potential late toxicity common to all of the alkylators is a dose-related risk of gonadal injury. Because of their greater complement of follicles, the ovaries of prepubertal and adolescent girls are more resistant to alkylator-induced damage compared with adults. The majority of female childhood cancer patients treated with standard combination chemotherapy will retain or recover ovarian function following completion of therapy. However, higher cumulative doses of alkylators, particularly in combination with abdominal/pelvic radiation, increase the risk of early menopause. Treatment with dose-intensive alkylating agent therapy for myeloablative conditioning before hematopoietic stem cell transplantation is associated with a considerable risk of premature ovarian failure. Girls treated with high-dose busulfan (600 mg/m²) have a particularly high incidence of ovarian failure.

In boys, alkylator-induced Leydig cell failure requiring androgen replacement therapy is uncommon, although transient and subclinical dysfunction is frequently observed based on studies demonstrating LH elevation. Conversely, damage to germ cells and infertility are very common following alkylator therapy. Treatment with six cycles of mechlorethamine, vincristine, procarbazine, and prednisone chemotherapy produces permanent azoospermia in most cases; the rate of recovery of spermatogenesis is significantly higher if treatment is restricted to three or fewer cycles. Several studies have correlated recovery of spermatogenesis with cumulative cyclophosphamide dose. Recovery of spermatogenesis occurred in 83% of men treated with less than 9.5 g/m² of cyclophosphamide for NHL. Restriction of cyclophosphamide doses to less than 7.5 g/m² is associated with preservation of fertility in 70% of sarcoma survivors. Variations in the threshold dose of cyclophosphamide have been attributed to combination treatment including other gonadotoxic agents. Pelvic radiation may also contribute to germ cell depletion in combined modality regimens including lower cumulative doses of alkylators. Dose relationships with ifosfamide have not been as well studied, but doses in the range of 42 to 60 g/m² were associated with higher risk of azoospermia in osteosarcoma survivors.

Secondary Acute Myeloid Leukemia

Alkylating agent therapy has also been linked to a dose-related risk of secondary acute myeloid leukemia (s-AML). Alkylator-associated s-AML is characterized by a mean latency of five to seven years, a prodromal myelodysplastic phase, and abnormalities of chromosomes 5 and 7. The risk of s-AML plateaus to less than 2% after 10 years from diagnosis. In cohort studies of HD survivors, the risk of alkylator-related s-AML has been associated with older age at treatment, history of splenectomy, presentation with advanced disease, treatment with high cumulative doses of alkylating agents, and history of relapse. Nitrogen mustard is a more potent leukemogen than cyclophosphamide, as evidenced by s-AML 15-year cumulative incidence rates of 4% to 8% after mechlorethamine, vincristine, procarbazine, and prednisone-based therapy compared with less than 1% after cyclophosphamide, vincristine, prednisone, and procarbazine-based therapy. Consequently, pediatric regimens that limit the total dose of alkylating agents or substitute other less leukemogenic alkylators, such as cyclophosphamide for mechlorethamine, have dramatically reduced the incidence of s-AML.
# Selected Late Effects* Following Chemotherapy in Survivors of Childhood and Adolescent Cancer

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Late Effect(s)</th>
<th>Additional Risk Factors†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td></td>
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</tr>
<tr>
<td>Mechlorethamine</td>
<td>Hypogonadism, infertility, and early menopause</td>
<td>Radiation involving brain or gonads (cranial, craniospinal, abdomen, pelvis, testes)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
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<td>Ifosfamide</td>
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<td>Melphalan</td>
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<td>Chlorambucil</td>
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<td>Lomustine</td>
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<td>Carmustine</td>
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<td>Busulfan</td>
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<td>Thiotaipa</td>
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<td>Procarbazine</td>
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<tr>
<td>Acute myeloid leukemia and myelodysplasia</td>
<td>Combined with multiple alkylators</td>
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<tr>
<td>Pulmonary fibrosis‡</td>
<td>Combined with other pulmonary toxic therapy,‡ including bleomycin, chest radiation, spinal radiation (&gt; 30 Gy), or total body irradiation</td>
<td></td>
</tr>
<tr>
<td>Bladder disease:§</td>
<td>Hemorrhagic cystitis, bladder fibrosis, dysfunctional voiding, cancer</td>
<td>Combined with pelvic radiation§</td>
</tr>
<tr>
<td>Glomerular toxicity¶</td>
<td>Younger age at treatment¶</td>
<td>Neoplastic renal impairment¶</td>
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<tr>
<td>Tubular toxicity:¶</td>
<td>Combined with other nephrotoxic therapy:¶</td>
<td></td>
</tr>
<tr>
<td>Renal tubular acidosis, Fanconi’s syndrome, hypophosphatemic rickets</td>
<td>Cisplatin/carboplatin, aminoglycosides, amphotericin, immunosuppression, or abdominal radiation</td>
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<tr>
<td>Cisplatin/Carboplatin</td>
<td>Ototoxicity:</td>
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<tr>
<td>Doxorubicin</td>
<td>Sensorineural hearing loss</td>
<td>Combined with head/neck radiation, aminoglycosides, or loop diuretics</td>
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<tr>
<td>Daunorubicin</td>
<td>Tinnitus</td>
<td>Renal dysfunction</td>
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<tr>
<td>Idarubicin</td>
<td>Vertigo</td>
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<tr>
<td>Mitoxantrone</td>
<td>Renal toxicity:</td>
<td>Combined with other nephrotoxic therapy, including ifosfamide, aminoglycosides or amphotericin, immunosuppression or cyclophosphamide, or abdominal radiation</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Glomerular injury</td>
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<tr>
<td>Methotrexate</td>
<td>Tubular injury</td>
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<tr>
<td>Anthracyclines</td>
<td>Renal injury</td>
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<tr>
<td>Bleomycin</td>
<td>Renal insufficiency</td>
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<tr>
<td>Cardiomyopathy or arrhythmia</td>
<td>Younger age at treatment (less than five years of age)</td>
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<tr>
<td>Daunorubicin</td>
<td>Females</td>
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<tr>
<td>Doxorubicin</td>
<td>Higher dose (≥ 300 mg/m²)</td>
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<tr>
<td>Idarubicin</td>
<td>Combined with chest radiation</td>
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<tr>
<td>Mitoxantrone</td>
<td>Combined with cyclophosphamide or amsacrine</td>
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<tr>
<td>Epirubicin</td>
<td>Longer time since treatment</td>
<td></td>
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<tr>
<td>Bleomycin</td>
<td>Interstitial pneumonitis or pulmonary fibrosis</td>
<td>Younger age at treatment</td>
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<tr>
<td></td>
<td>Combined with other pulmonary toxic therapy, including busulfan, nitrosoureas (lomustine/carmustine), chest radiation, spinal radiation (≥ 30 Gy), or total body irradiation</td>
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</tbody>
</table>

(cont)
Alkylator-associated Pulmonary Disease

Pulmonary toxicity has been most commonly linked to the nitrosoureas and busulfan and infrequently to high-dose cyclophosphamide and ifosfamide. Pulmonary fibrosis following carmustine administration varies in clinical manifestation, time to presentation, and outcome. Symptoms may develop acutely or insidiously over many years after therapy, with some cases exhibiting a very delayed onset of fatal pulmonary dysfunction. In the non-transplant setting, up to 30% of patients treated with carmustine doses between 80 and 240 mg/m² every six to eight weeks for more than two years (cumulative doses of 700 to 1,800 mg/m²) developed pulmonary fibrosis. A marked increase in pulmonary fibrosis appears at doses exceeding 1,500 mg/m². Pulmonary fibrosis has also been observed in 16% to 40% of transplant recipients treated with cytotoxic conditioning agents including carmustine at doses of 500 to 600 mg/m²; the incidence of fibrosis declines considerably when doses are limited to less than 300 to 450 mg/m². Female patients appear to be more susceptible to this complication than do male patients. Lung injury associated with busulfan is characterized by diffuse interstitial fibrosis and bronchopulmonary dysplasia; this complication is rare if doses are restricted to less than 500 mg/m². Chronic administration of melphalan and high-dose infusions of cyclophosphamide and ifosfamide have rarely been associated with pulmonary toxicity.

Alkylator-associated Genitourinary Disease

Genitourinary tract complications have been commonly reported after treatment with cyclophosphamide and ifosfamide. Both agents have been associated with a dose-related risk of hemorrhagic cystitis, which may be mild (dysuria and frequency) or severe (bladder hemorrhage) in presentation. This toxic effect has been attributed to the urinary metabolite of the activated oxazaphosphorine, acrolein. Incidence rates range from 5% to 10% for cyclophosphamide and 20% to 40% following ifosfamide. Adequate hydration, diuresis, and mesna uroprotection has dramatically reduced the risk of this complication.

Ifosfamide renal injury may manifest as proximal tubular injury, proteinuria, and reduced glomerular filtration. Ifosfamide-induced proximal renal tubular dysfunction has been associated with a Fanconi-like syndrome that predisposes to hypophosphatemic rickets. Clinical manifestations include phosphaturia, hypophosphatemia, glycosuria,

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Late Effect(s)</th>
<th>Additional Risk Factors†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Osteopenia</td>
<td>Combined with methotrexate, cranial or cranio-spinal radiation, other head/neck radiation, or high-dose radiation to bone</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Osteoporosis</td>
<td>Other conditions: hypogonadism, premature ovarian failure, growth hormone deficiency, or hyperthyroidism</td>
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<tr>
<td>Dexamethasone</td>
<td>Avascular necrosis (osteonecrosis)</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Older age at treatment (over 10 years of age)</td>
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<td></td>
<td></td>
<td>Combined with high-dose radiation to any bone</td>
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<tr>
<td></td>
<td></td>
<td>Weekly or twice weekly administration</td>
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<td></td>
<td></td>
<td>Less than five years from exposure</td>
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<tr>
<td>Epipodophyllotoxins</td>
<td>Acute myeloid leukemia</td>
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</tbody>
</table>

*Table 4 includes late effects discussed in the text and is not exhaustive. A complete listing of all known late effects by therapeutic exposure is provided in the “Children’s Oncology Group (COG) Long-term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers” at www.survivorshipguidelines.org.
†For most late effects, there is a dose relationship, with higher doses conferring higher risk.
‡Applies to lomustine, carmustine, and busulfan only.
§Applies to cyclophosphamide and ifosfamide only.
¶Applies to ifosfamide only.
aminoaciduria, elevation of serum alkaline phosphatase, hypokalemia, renal tubular acidosis, defective concentrating capacity, and reduced glomerular filtration rate. Literature from cohort studies correlates the risk of ifosfamide nephrotoxicity to age at treatment, cumulative dose, concomitant or prior treatment with other nephrotoxic agents or modalities, pre-existing renal impairment, and reduction of renal mass (ie, by nephrectomy). Patients at highest risk are younger at treatment (five years of age or less) and those treated with cumulative doses of 60 g/m² or more. Acute reversible subclinical nephrotoxicity occurs in the majority of patients, whereas chronic nephrotoxicity has ranged from 1.4% to 30% in series of childhood cancer survivors. In a prospective study of childhood cancer patients treated with ifosfamide chemotherapy, Fanconi syndrome occurred up to three years after completion of therapy and was always preceded by the development of a generalized subclinical tubulopathy. Long-term follow-up of childhood cancer survivors treated with ifosfamide showed persistent deficits in renal function with interindividual variability 10 years after treatment. The general consequences of renal injury, including hypertension, growth impairment, bony demineralization, and reduced renal drug excretion, should also be considered in patients receiving ifosfamide and other nephrotoxic agents.

**Anthracyclines**

**Anthracycline-associated Cardiomyopathy**

Anthracyclines, including doxorubicin and daunomycin, have a wide range of clinical activity against pediatric cancers, including acute leukemia, lymphoma, bone and soft tissue sarcoma, Wilms tumor, and neuroblastoma. About 40% to 50% of childhood cancer survivors were treated with an anthracycline, making it one of the more common exposures. Acute cardiotoxicity during treatment with an anthracycline is an infrequent and dose-related problem, occurring in less than 1% of children with cancer. More common, however, is a late-onset anthracycline-induced cardiomyopathy, characterized by a thinning of the wall of the left ventricle and elevated afterload. Over time, this can lead to a stiff and poorly compliant left ventricle, ultimately resulting in congestive heart failure (CHF). It is particularly important to realize that left ventricular dysfunction secondary to an anthracycline may not become apparent until 15 to 20 years following therapy.

Kremer and colleagues recently completed an excellent systematic review of the literature assessing the frequency of subclinical cardiotoxicity in long-term survivors of childhood cancer. Of 25 published studies of original research, 14 had serious methodological limitations. In the six studies with an acceptable validity score that used fractional shortening as the primary measure of left ventricular dysfunction, the range of reported frequency of subclinical cardiotoxicity for those who were treated with a cumulative dose greater than 300 mg/m² was 15.5% to 27.8%. For those treated with a cumulative dose below 300 mg/m², the range of abnormal left ventricular function was 0% to 15.2%. In four of the studies reporting abnormal afterload (defined as more than two standard deviations compared with controls), the range of reported frequency was 19% to 52% for those treated with over 300 mg/m². Although most survivors with late-onset subclinical left ventricular dysfunction do not have signs of cardiotoxicity during therapy with an anthracycline, those that do are at increased risk for late-occurring cardiomyopathy. Other risk factors for late-onset cardiomyopathy include higher anthracycline dose, longer duration of follow-up, female sex, early age at treatment, and previous chest or mantle radiation.

Although most survivors who develop echocardiographic evidence of left ventricular dysfunction will likely remain asymptomatic, longitudinal studies suggest that a significant proportion will experience progressive changes and progress to CHF. Earlier, small studies with relatively short intervals of follow-up estimated that by five to 10 years following therapy, 5% to 10% of survivors treated with an anthracycline will develop CHF. Three recent studies support these estimates and provide further evidence of the primary risk factor, the cumula-
tive dose of the anthracycline. Green et al. studied children treated with doxorubicin on National Wilms’ Tumor Studies and reported a cumulative frequency of CHF of 4.4% at 20 years after diagnosis. However, in children who were treated with an anthracycline for a first or subsequent relapse (increased cumulative dose), the cumulative frequency of CHF was 17.4% at 20 years. The relative risk of CHF by cumulative dose of doxorubicin was 3.3 per 100 mg/m². In follow up of 607 children treated with an anthracycline, Kremer and colleagues reported a cumulative incidence of CHF of 4.8% at 15 years. In an interesting prospective longitudinal study, Sorensen and colleagues measured serial echocardiograms in 101 ALL survivors and 83 Wilms tumor survivors. With an interval of about four years between echocardiograms, there was deterioration in cardiac performance in those who had received more than 250 mg/m² of an anthracycline. It was encouraging that in those exposed to less than 250 mg/m², there was no further deterioration.

One additional high-risk group that has received anecdotal attention is pregnant women who were treated with an anthracycline for childhood cancer. During the latter stages of pregnancy, the cardiac volume increases. The cardiac workload in labor can increase fairly abruptly, leading to overt symptomatology in women with left ventricular dysfunction. There have been several case reports of the abrupt onset of CHF in female survivors during the peripartum period. Hinkle and colleagues reported their recent anecdotal experience in 40 pregnant anthracycline-treated survivors. In their nonrepresentative sample, 30% developed symptomatic heart disease, including CHF and ventricular tachycardia. Recognizing the selection bias of this sample, these findings are quite provocative.

Time will be needed to better estimate the incidence of progressive changes and symptomatic disease in this population. Until then, the question of management of survivors with asymptomatic deterioration of left ventricular function will remain controversial. Angiotensin-converting enzyme (ACE) inhibitors have improved morbidity and mortality in other populations of patients with a cardiomyopathy. There are, however, some theoretical risks with such therapy in the childhood years. ACE inhibitors, while lowering the afterload in the short term, may also limit the cardiac growth potential by inhibiting cardiac growth factors, leading to further thinning of the left ventricular walls relative to body-surface area and ultimately an increased afterload. Lipshultz et al. reported on the retrospective evaluation of 18 children who had regular echocardiograms while on enalapril for late-onset anthracycline-induced cardiomyopathy. Over the first six years of enalapril therapy, there was progressive improvement in left ventricle dimensions, afterload, and shortening fraction. However, the parameters deteriorated between six and 10 years of therapy. All six children who had CHF at the start of therapy had either died or undergone cardiac transplantation. The role of ACE inhibitors and beta-blockers in asymptomatic survivors with cardiac dysfunction remains in question.

**Antimetabolites**

Antimetabolite therapy with methotrexate, mercaptopurine, and cytarabine form the cornerstone of ALL therapy. Antimetabolites are also used in the treatment of NHL, osteosarcoma, chronic myelogenous leukemia, and the histiocytoses.

**Peak Bone Mass, Bone Metabolism, and Osteoporosis**

It appears that a significant percentage of survivors of childhood cancer, including males, are at risk for a prevalent disease of middle to later life—osteoporosis. Risk appears to be multifactorial, with methotrexate, corticosteroids, and CRT as the primary culprits. Because it is difficult to differentiate the influence of these three exposures on the risk, the topic is discussed here.

Several well-designed, small- to medium-sized cross-sectional studies of childhood cancer survivors, with median ages at evaluation ranging from 12 to 25 years, consistently showed reduction in bone mineral density, bone mass content, and/or age-adjusted bone mass. In an ongoing
prospective cohort study, Atkinson et al. reported that by six months of therapy for ALL, 64% of children had a reduction from baseline measures of bone mass content, and by the end of two years of therapy, 83% were osteopenic.\textsuperscript{181}

A variety of other treatments used for childhood cancer can reduce peak bone mass and/or interfere with bone metabolism. Some chemotherapeutic agents, such as corticosteroids and methotrexate, appear to directly alter bone metabolism during treatment, thus reducing peak bone mass.\textsuperscript{179,182} Alkylating agents, notably cyclophosphamide and ifosfamide, appear to alter gonadal endocrine function, leading to subclinical or premature ovarian failure or Leydig cell dysfunction, thus promoting bone loss.\textsuperscript{128,183} Cranial irradiation for CNS tumors, ALL, T-cell lymphoma, and soft tissue sarcomas can cause subclinical hypothalamic/pituitary dysfunction resulting in inadequate growth hormone secretion and/or hypogonadotropic hypogonadism.\textsuperscript{182,184} Older methods of pelvic irradiation for Wilms tumors and genitourinary soft tissue sarcomas that did not adequately protect the gonads resulted in primary gonadal dysfunction and ovarian/ testicular failure. Hence, cancer treatment predisposes many survivors to bone mineral deficiency and osteopenia/osteoporosis by a direct effect on bone accretion or secondarily through pituitary-hypothalamic or gonadal dysfunction. The prevalence of osteoporosis in the survivor population needs further study.

Corticosteroids

Corticosteroids are used as an anticancer agent in the treatment of acute lymphoblastic leukemia, NHL, HD, histiocytic disorders, and brain tumors. In addition, they are frequently used to manage a variety of cancer related complications including increased intracranial pressure, chemotherapy-induced nausea and vomiting, anorexia, and hypercalcemia. Glucocorticoids induce apoptosis by binding to intracellular glucocorticoid receptors; continuous binding of the receptor is necessary to produce this effect, accounting for the preferred schedule of continuous thrice daily administration.\textsuperscript{185} Corticosteroids may cause acute effects involving a variety of organ systems.

The most common of these toxicities include centripetal weight gain, immunosuppression, myopathy, altered glucose metabolism, osteopenia, avascular necrosis, behavioral and mood disturbances, and hypertension.\textsuperscript{186}

Osteonecrosis and Corticosteroids

Osteonecrosis (avascular necrosis) is a well-known complication of corticosteroid therapy that has been observed with increasing frequency due to the use of more potent glucocorticoids in recent trials for ALL.\textsuperscript{187–190} Risk factors for this complication include age older than 10 years, glucocorticoid therapy with dexamethasone, and multiple courses of glucocorticoids; both genders are at risk.\textsuperscript{187–189} The five-year cumulative incidence of osteonecrosis in a recent investigation of high-risk ALL patients was 7%; notably, 31% of affected patients required surgical intervention, and 62% also developed bone fractures. Screening by magnetic resonance imaging in predisposed populations has demonstrated a considerable incidence of asymptomatic radiographic abnormalities of unclear clinical significance.\textsuperscript{187,190} Ongoing studies aim to evaluate whether anti-leukemia efficacy will be compromised in high-risk patients with reduced cumulative corticosteroid doses.\textsuperscript{188}

Heavy Metals

Cisplatin and carboplatin are the most frequently used nonclassical alkylators. Their most frequently observed late effects include nephrotoxicity, ototoxicity, and neurotoxicity. A dose-related nephrotoxicity is observed following platinum that may manifest as azotemia or tubular injury with electrolyte wasting (especially hypomagnesemia requiring electrolyte supplementation).\textsuperscript{191–193} Pathologic changes predominantly develop in the proximal and distal tubular epithelium and collecting ducts.\textsuperscript{194,195} Renal tubular dysfunction typically presents acutely and often persists following completion of therapy.\textsuperscript{196,197} The most severe cisplatin-related tubulopathy includes hypocalciuria, renal magnesium deficiency, and hypokalemic metabolic alkalosis. Renal injury may be enhanced if cisplatin is
combined with other nephrotoxic chemotherapeutic agents (especially ifosfamide) or renal radiation.\textsuperscript{198}

At cumulative doses of 300 to 600 mg/m\textsuperscript{2}, cisplatin commonly causes a sensory peripheral neuropathy manifested as paresthesias, dysesthesias, and disturbances of position and vibration.\textsuperscript{192,199–201} Acute neurotoxicity usually resolves, but as many as 20% to 60% of patients report persistent paresthesias after completion of therapy.\textsuperscript{200} The risk of irreversible cisplatin-induced, high-frequency hearing loss is increased after 400 mg/m\textsuperscript{2}.\textsuperscript{202–204} Younger age, cranial radiation, and history of brain tumor significantly increase the severity of hearing loss at lower cumulative doses of cisplatin.\textsuperscript{203} Combination treatment with ifosfamide may also exacerbate cisplatin-related hearing loss.\textsuperscript{205} Nephrotoxicity, ototoxicity, and neuropathy may be observed after carboplatin but typically to a milder degree than in cisplatin.\textsuperscript{206}

**Epipodophyllotoxins**

Late toxicity of epipodophyllotoxins (etoposide and teniposide) comprises a distinctive s-AML characterized by a brief time of onset from primary diagnosis, absence of a preceding myelodysplastic phase, monoblastic and myelomonoblastic histology, and translocations involving the \textit{MLL} gene at chromosome band 11q23.\textsuperscript{207–209} Studies of childhood leukemia patients suggest a relationship between intermittent weekly or twice weekly dosing schedules of epipodophyllotoxins resulting in transforming mutations of myeloid progenitor cells.\textsuperscript{208–210} Extensive evaluation of s-AML cases following epipodophyllotoxin administration for pediatric solid tumors failed to show a relationship between leukemogenic activity and cumulative dose of epipodophyllotoxins when used in the context of multiagent chemotherapy regimens including alkylating agents, doxorubicin, and dactinomycin.\textsuperscript{207} However, the risk of leukemogenesis following cumulative etoposide doses of 5.0 gm/m\textsuperscript{2} or less was not in excess of that associated with other agents used in solid tumor regimens.\textsuperscript{207} These data suggest relative safety in using limited doses of etoposide; however, continued reports of s-AML cases in pediatric trials with lower doses still raise concerns as to whether this agent should be avoided in favorable presentations.\textsuperscript{207}

**SURGERY**

**Evolution of Surgery in the Treatment of Childhood Cancer**

Historically, surgery has played an important role in the management of childhood malignancies. Initially, surgical interventions provided critical diagnostic and staging information and represented the primary component of curative therapy by local tumor control. Three subsequent factors strongly influenced the role of surgery in contemporary management of childhood cancers: (1) the development of effective systemic chemotherapy; (2) advancements in diagnostic imaging and radiation technology; and (3) appreciation of the long-term morbidity associated with aggressive surgical approaches. Induction of tumor regression with preoperative adjuvant chemotherapy made tumors more amenable to surgical resection and reduced the risk of metastatic disease.\textsuperscript{211,212} This approach significantly improved long-term survival and reduced surgical morbidity by subsequently spurring the development of organ and limb preservation surgeries. Innovations in radiation technology (eg, brachytherapy) permitted less disfiguring approaches to eradicate microscopic residual disease while minimizing normal tissue injury. New diagnostic imaging modalities, including computed tomography, magnetic resonance imaging, and nuclear imaging, provided more accurate noninvasive methods to assess disease stage, eliminating the morbidity associated with splenectomy\textsuperscript{213–215} or retroperitoneal lymph node dissection.\textsuperscript{216} Finally, appreciation of late surgical morbidity and mortality in the growing numbers of long-term survivors prompted the multimodal team approach used today in which the pediatric oncologist, surgeon, and radiation therapist make therapy recommendations after consideration of acute and long-term health risks. This section will review late treatment complications associated with specific surgical procedures used in the management of childhood malignancies.
Amputation and Limb-sparing Surgery

Removal of all gross and microscopic disease is required to prevent local recurrence of bone tumors. Amputation and limb-sparing surgery aim to accomplish this task through an en bloc excision of the tumor with a margin of normal uninvolved tissue. Each approach has advantages and disadvantages with regard to late functional outcomes. The incidence of late complications is related to the type of surgical procedure, the primary tumor site, and the age of the patient. Overall, more frequent complications have been observed in survivors who had limb-sparing procedures, but this morbidity is counterbalanced by the more acceptable cosmetic appearance provided by the limb-sparing procedure. Late complications unique to amputation include stump–prosthetic problems, chronic stump pain, phantom limb pain, and bone overgrowth. Survivors undergoing limb-sparing surgery may experience non-union, pathologic fracture, aseptic loosening, limb-length discrepancy, endoprosthetic fracture, poor joint movement, and stump-prosthesis problems. Severe complications after limb-sparing surgery may result in the need for amputation. Surprisingly, despite predictions that quality of life in survivors undergoing limb-sparing procedures would be superior to that of survivors treated with amputation, numerous studies have shown no improvement or only modest improvement in quality of life.

Exenteration and Organ Preservation Surgery

The approach to the management of genitourinary rhabdomyosarcoma in children has evolved from radical surgery, including pelvic exenteration with removal of pelvic organs, to multimodal therapy aimed at providing local disease control and preserving pelvic organs. Sequelae related to intensive multimodality therapy may be considerable, but preservation of bladder and urethral function can be accomplished in boys with prostate/bladder rhabdomyosarcoma without compromising disease control. Similarly, multimodality therapy also avoids the need for vaginectomy and hysterectomy in girls with vaginal tumors. In earlier Intergroup Rhabdomyosarcoma studies, total cystectomy with urinary diversion procedures was associated with frequent urinary tract infections, hydronephrosis, and the need for reoperation. Children treated with partial cystectomy may also experience functional bladder problems related to contracture or incontinence, which may be improved by bladder augmentation surgery. Clinicians should also consider that multimodal therapy with radiation and alkylators like cyclophosphamide that permit bladder preservation may increase the risk of genitourinary tract complications such as hemorrhagic cystitis.

Splenectomy

Staging laparotomy with a splenectomy and retroperitoneal node dissection was used in the evaluation of newly diagnosed HD patients from the 1960s into the 1980s. Advances in diagnostic imaging (computed tomography scans) and routine use of systemic chemotherapy gradually made surgical staging an unnecessary procedure. Thus, many HD survivors are asplenic and face a lifetime risk of overwhelming infection and sepsis. Long-term rates of infection have been difficult to estimate because of the introduction of pneumococcal and Haemophilus vaccines in recent years. The lifetime cumulative incidence of overwhelming sepsis following a splenectomy is about 2% to 4%, with a mortality rate of 1% to 2%. Survivors face an eightfold increased risk of bacteremia, generally with encapsulated organisms such as Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis. However, risk of bacteremia or parasitemia also includes other organisms such as Escherichia coli, Pseudomonas aeruginosa, Staphylococcus, Enterococcus, Salmonella, Capnocytophaga canimorsus, Babesia microti, and Plasmodium falciparum. Although antibiotic prophylaxis with penicillin (in the nonallergic individual) is recommended through childhood, continued long-
term prophylaxis through the adult years is controversial.237,238 Concerns about misuse of antibiotics and potential colonization with drug-resistant organisms have dissuaded most from universally recommending antibiotic prophylaxis in the adult asplenic population.236 However, it is quite important for the health care professional to educate the asplenic HD survivor about the necessity of prompt evaluation for any febrile illness.

Administering vaccinations for pneumococcus, H influenzae, and meningococcus markedly decreases risk for serious or overwhelming sepsis. The pneumococcal vaccine, 23-valent pneumococcal polysaccharide vaccine (Pneumovax), may have been administered before the splenectomy, depending on the year of treatment and availability of the vaccine. A booster should have been given five years after the initial vaccine. In Europe, clinicians recommend a repeat pneumococcal vaccine every five years.237 In the United States, infectious disease experts have recommended this strategy only in the individual with an episode of pneumococcal sepsis.

**Nephrectomy**

Surgical removal of the primary tumor remains the cornerstone of the treatment of Wilms tumor. The long-term impact of nephrectomy has not been particularly significant. It appears that nephrectomy without radiation does not lead to hyperfiltration injuries of the remaining kidney.239 Renal failure following a unilateral nephrectomy is rare.100 There is a question about whether Wilms tumor survivors treated with a unilateral nephrectomy are at increased risk for the development of hypertension.240,241 However, because the interval from treatment to the time of blood pressure measurement in most studies is fairly short, this risk has not been well characterized. Because hypertension is one of the most commonly underrecognized and underdiagnosed diseases, accurate estimates of risk necessitate close follow-up of survivors into their second and third decade of life.

**BONE MARROW TRANSPLANTATION**

**Hematopoietic Stem Cell Transplantation**

The risk of complications following hematopoietic stem cell transplantation is related to previous treatment of the primary disease, the intensity of the conditioning regimen, the type of stem cell product and donor source, and complications in the posttransplant period. In particular, the long-term transplant recipient has enhanced risks for adverse effects related to conditioning chemotherapy and radiation, GVHD, and chronic immunosuppression. This section will review these unique late toxicities, adding to the adverse effects of the specific therapeutic modalities reviewed above.

**Late Complications Related to Transplant Conditioning**

Transplant conditioning with high-dose alkylators and TBI commonly causes endocrine dysfunction that may adversely affect growth, pubertal development, and reproductive function. After a median of 11 years following hematopoietic cell transplant, the prevalence of type 2 diabetes mellitus in 748 leukemia survivors was 9%.242 Survivors of stem cell transplantation are at increased risk of a variety of thyroid problems, including primary hypothyroidism, autoimmune thyroid disease, and thyroid carcinoma.243,244 Hypothyroidism is the most common treatment-related thyroid complication, and its frequency varies considerably based on the duration of follow-up and TBI fractionation.243–247 Single-dose TBI is associated with a higher incidence of hypothyroidism compared with fractionated TBI.243–247 Children conditioned with high-dose chemotherapy alone generally exhibit normal growth following transplantation in the absence of significant complications like GVHD.248–252 However, growth impairment and reduced final height are very common following transplant for hematologic and solid malignancies. In addition to GHD, other risk factors for poor growth include young age at treatment, TBI conditioning (particularly single dose),246,253 and prior cranial
radiation. Other sequelae of transplantation, including chronic GVHD and radiation-induced skeletal dysplasia, may also contribute to growth impairment in this population.

Transplant conditioning generally produces some degree of gonadal dysfunction; the risk of more severe and irreversible dysfunction is related to the age at treatment, the cumulative dose of alkylator chemotherapy, the use of TBI conditioning, and history of previous alkylators or cranial radiation. Ovarian function remained normal in female survivors with aplastic anemia conditioned with high-dose cyclophosphamide before as well as after the onset of puberty. However, premature ovarian failure may be a delayed consequence of high-dose alkylator conditioning. The risk of ovarian failure is very high after conditioning with busulfan and cyclophosphamide regardless of pubertal status. Recovery of ovarian function may occur in some patients, but the majority require long-term hormonal replacement therapy. After TBI conditioning, 50% of girls who underwent transplants before puberty retain sufficient ovarian function to enter puberty and menstruate.

TBI conditioning in girls older than 10 years universally causes premature ovarian failure. These patients require hormonal replacement therapy to progress through puberty and menstruate. Women who maintain fertility after TBI are at increased risk of adverse pregnancy outcomes including spontaneous abortion, preterm delivery, and delivery of low birth weight infants; an increased risk of congenital malformations has not been observed. Leydig cell function and testosterone production is usually preserved in young boys and adolescents conditioned with high-dose cyclophosphamide (200 mg/kg). However, germ cell damage is suggested by the presence of testicular atrophy and increased plasma levels of FSH and may be more common in male survivors treated during or after puberty. Regardless of their age at irradiation, most male survivors retain their ability to produce testosterone after TBI conditioning. Prepubertal boys generally have normal pubertal progression after this treatment. Eleva-

tion of LH plasma levels suggests some degree of Leydig cell dysfunction, although testosterone levels are generally appropriate for age. Germ cell dysfunction occurs in nearly all male patients treated with TBI.

In addition to endocrine dysfunction, long-term transplant recipients encounter increased risks for a variety of chronic organ specific toxicities. Prior treatment and other transplant-related complications (eg, chronic GVHD or chronic infection) may exacerbate specific toxicity. TBI conditioning produces a substantial risk of cataract development; fractionation of the TBI dose reduces this risk from 60% to a risk of 10% to 30%. Delayed cardiac abnormalities have been infrequently reported in small cohort studies of variably treated survivors. The multifactorial nature of the late cardiac events has not been thoroughly evaluated in long-term survivors who underwent transplants during childhood, but transplant-related cardiac effects may contribute to morbidity in aging survivors. In adults, chronic pulmonary toxicity is a common cause of posttransplant morbidity and mortality. Clinical manifestations include delayed interstitial pneumonitis, restrictive or obstructive lung disease, bronchiolitis obliterans, and bronchiolitis obliterans with organizing pneumonia. From the limited information available about long-term pulmonary complications following transplantation during childhood, a smaller proportion of children appear to have symptomatic chronic pulmonary toxicity, but the long-term implications of asymptomatic pulmonary dysfunction remain to be established in this population.

Liver disease in long-term survivors of childhood cancer treated with bone marrow transplantation may result from chronic GVHD, chronic infection, nodular regenerative hyperplasia from cytoreductive therapy, and drug-related liver injury. Severe chronic liver disease with cirrhosis represents an important late complication of hematopoietic stem cell transplantation that, in most cases, is due to chronic hepatitis C. Transplant-related renal dysfunction is most often described in the setting of acute toxicity and has typically been attributed to direct nephrotoxicity from radiation, nephrotoxic chemotherapy or other medication, tumor lysis, or intravascular transplantation.
depletion. Partial renal shielding during TBI reduces the risk of posttransplant radiation nephropathy. Bony complications reported in transplant survivors include avascular necrosis and osteoporosis. Finally, survivors of stem cell transplantation have higher risks of subsequent malignancies related to chronic immunosuppression and cumulative carcinogenic treatment exposures. In particular, the risk of NHL, epithelial tumors, myelodysplastic syndromes, and solid nonhematopoietic tumors is fourfold to sevenfold that of the general population.

Late Complications Related to the Transplant Process

Chronic GVHD is a multisystem disorder that is associated with significant morbidity and mortality. Chronic GVHD most commonly involves the same organ systems affected by acute GVHD—the skin, liver, and gastrointestinal tract. Chronic GVHD of the skin produces variegated pigmentation and dermal scarring resulting in a lichenoid and/or sclerodermatous lesions. Alopecia may develop with involvement of the hair follicles. Sclerodermatous changes of the mucous membranes and salivary glands cause xerostomia that predisposes to accelerated tooth decay and periodontal disease. GI effects include esophageal strictures, chronic diarrhea, and malabsorption. Approximately 80% of individuals with chronic GVHD have liver involvement, which typically manifests as disordered cholestasis and may rarely progress to primary biliary cirrhosis. Chronic GVHD involving the lungs is associated with obstructive or restrictive pulmonary disease and interstitial fibrosis. Chronic GVHD may also result in functional asplenia, delayed immune reconstitution, and immune-mediated cytopenias that increase the risk of infection. The eyes, kidneys, and peripheral nervous system may also exhibit pathological changes related to chronic GVHD. It should be remembered that the intensive immunosuppression required to control symptoms of chronic GVHD may enhance the risk of other transplant-related complications, especially fatal infections, nephrotoxicity, and skeletal toxicity.

Other Therapeutic Exposures: Blood Transfusion

Many children receiving high-intensity chemotherapy, notably those with acute leukemia, will require blood transfusions or the use of other blood products. Survivors treated before adequate blood donor screening for hepatitis C virus (HCV) was initiated in the early 1990s are at risk for chronic liver disease. Prevalence of circulating HCV-RNA in ALL patients treated before 1990 ranges from 6.6% to 49%, with an unknown and likely sizable percentage of survivors never having been tested or aware of their risk. Early studies of chronically infected childhood cancer survivors suggested that fibrosis developed more slowly in patients who acquired the infection when they were 20 years of age or younger. However, a recent report describing histologic outcomes after more prolonged follow-up (median, 19 years) of chronically infected survivors indicates progressive fibrosis and end-stage liver disease at rates similar to those seen in larger adult cohorts with transfusion-associated hepatitis and in hemophiliacs coinfected with human immunodeficiency virus and hepatitis B. More aggressive chronic infection has also been observed in survivors coinfected with hepatitis B and in those treated with hematopoietic stem cell transplantation. Reports of decompensated cirrhosis and hepatocellular carcinoma in childhood cancer survivors with chronic HCV suggest that this population is at increased risk of liver-related morbidity and mortality.

Summary

The extensive summation of late effects presented is a testimony to the complex issues that must be considered by clinicians supervising the health care of childhood cancer survivors. Although late treatment effects can be anticipated in most cases based on therapeutic exposures, the risk to an individual patient is modified by multiple factors. The cancer patient may present with premorbid health conditions that influence tolerance to therapy and augment the risk of treatment toxicity.
Cancer-related factors including histology, tumor site, and tumor genetics determine treatment modality and intensity. Host-related factors such as age at diagnosis/treatment, race, and gender may influence the risk of several treatment complications. Other sociodemographic factors such as household income, educational attainment, and socioeconomic status influence access to health insurance, remedial services, and appropriate risk-based health care. Organ senescence in aging survivors may accelerate presentation of health conditions in survivors with subclinical injury or organ dysfunction resulting from cancer treatment. Genetic or familial characteristics may also enhance susceptibility for treatment complications. Problems experienced during and after treatment may add further morbidity. Finally, health behaviors including tobacco and alcohol use, excessive sun exposure, and poor diet and physical inactivity may increase the risk of specific conditions predisposed by cancer treatment.

While much is known about factors predisposing to cancer-related morbidity and mortality in this growing population, there is still much to learn to translate this compendium of literature into interventions that will optimize care for pediatric malignancies with limited or no toxicity. This fact underscores the importance of long-term follow-up to accurately define health outcomes, characterize high-risk groups, and implement risk-reducing interventions.

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