# Survivorship: Childhood Cancer Survivors

Kevin C. Oeffinger, MD[a,b,*], Melissa M. Hudson, MD[c], Wendy Landier, MSN, NP[d]

**KEYWORDS**

• Childhood cancer • Neoplasm • Survivors • Late effects • Surveillance • Screening • Children's Oncology Group

## CASE EXAMPLES

P.H. is a 25-year-old Hispanic man diagnosed with acute lymphoblastic leukemia at the age of 7. Records from the treating oncologist indicate that he was treated with chemotherapy over a period of 3 years, and received daunorubicin 100 mg/m$^2$, doxorubicin 150 mg/m$^2$, L-asparaginase, cyclophosphamide, prednisone, dexamethasone, vincristine, cytarabine, thioguanine, mercaptopurine, and intrathecal methotrexate. He did not receive radiation therapy. He presents to your office for a routine physical examination. In addition to general health maintenance, what screening tests should he undergo at this time? What health counseling does he need regarding potential health risks that he faces as a result of his leukemia treatment in childhood?

K.C. is a 31-year-old Caucasian woman diagnosed with Hodgkin lymphoma, stage IIB at the age of 16 years. A cancer treatment summary from her treating institution indicates that she received combined-modality therapy over a period of 8 months, including chemotherapy (doxorubicin 210 mg/m$^2$, cyclophosphamide, prednisone, procarbazine, bleomycin, vincristine, vinblastine, and dacarbazine) and radiation (36 Gy to the mini-mantle field). She has not been seen by her oncologist in several years. K.C. is planning to get married soon and presents to your office with questions about

[a] Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
[b] Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
[c] Division of Cancer Survivorship, Department of Hematology, St Jude Children's Research Hospital, the University of Tennessee, College of Medicine, 262 Danny Thomas Place, Memphis, TN 38105, USA
[d] Department of Population Sciences, Division of Outcomes Research, City of Hope Comprehensive Cancer Center, 1500 E. Duarte Road, DPS-173 Duarte, CA 91010, USA
* Corresponding author. Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.
*E-mail address:* oeffingk@mskcc.org (K.C. Oeffinger).

Prim Care Clin Office Pract 36 (2009) 743–780
doi:10.1016/j.pop.2009.07.007 **primarycare.theclinics.com**
0095-4543/09/$ – see front matter 

her risk of infertility. In addition to addressing her stated concerns, what other health counseling should she be given at this time? What potential health risks does she face as a result of her cancer treatment? What screening tests and preventive measures are indicated for her at this time?

## BACKGROUND

The primary care clinician is integral in the delivery of preventive and acute health care for many childhood cancer survivors, particularly those who are in their young adult years. This high-risk population is relatively small but growing. In 1997, there were an estimated 270,000 childhood cancer survivors in the United States; 46% were 20 to 40 years old and 18% were older than 40 years.[1] About 1 in every 640 young adults between the ages of 20 and 39 years is a childhood cancer survivor. Many of these survivors face a significantly increased risk of late-occurring serious morbidity or premature mortality. Among those treated from the 1970s to the 1990s, about 75% will develop a chronic disease by 40 years of age, and more than 40% will develop a serious health problem (**Figs. 1** and **2**).[2–4]

The excess risk of premature death from a second cancer, cardiovascular disease, or pulmonary disease is elevated beyond 30 years after the original cancer diagnosis (**Fig. 3**).[5] Almost half of long-term survivors will have moderate to extremely diminished health status, including limitations in activity and functional impairment.[6,7] Although some serious problems occur during the cancer therapy or soon thereafter (long-term effects), the majority do not become clinically apparent until many years after the cancer was diagnosed (late effects).

Fortunately, the incidence and severity of many late effects of therapy can be reduced through prevention or early detection. For this reason, the Institute of Medicine recommends periodic monitoring of all childhood cancer survivors throughout their life span, including a systematic plan for screening, surveillance, and prevention that incorporates risks based on the previous cancer, cancer therapy, genetic predispositions, lifestyle behaviors, and comorbid health conditions.[1] Over the past 15 to 20 years, many centers that treat children with cancer have developed specialized Long-Term Follow-Up (LTFU) programs to deliver risk-based care. Through these programs, survivors and their families are educated about their long-term health risks, counseled about avoiding risky health behaviors, and monitored for late effects of cancer therapy. As part of this care, the LTFU staff prepares a cancer treatment summary for the patient, family, and the patient's physicians (**Fig. 4**).

To assist in the follow-up care of childhood cancer survivors, the Children's Oncology Group (COG), the National Cancer Institute-supported pediatric oncology clinical trials organization for North America, has developed risk-based guidelines for specific therapeutic exposures.[8] First released in 2003, the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* contain recommendations for screening for late complications that may occur as a result of therapeutic exposures used to treat pediatric malignancies. A hybrid of evidence-based and consensus-driven approaches was used to develop the guidelines. For each therapeutic exposure, the strength of evidence from the literature linking that exposure with an adverse outcome was considered, and a multidisciplinary panel of experts in the late effects of pediatric cancer made a consensus-based recommendation for periodic screening. The COG *Long-Term Follow-Up Guidelines* are periodically updated. **Fig. 5** is a snapshot from the current version 3. The COG has also developed an extensive collection of educational materials for patients, called *Health Links*, that complement a variety of survivorship topics addressed in the *Guidelines*.[9] The COG *Long-Term Follow-Up Guidelines*

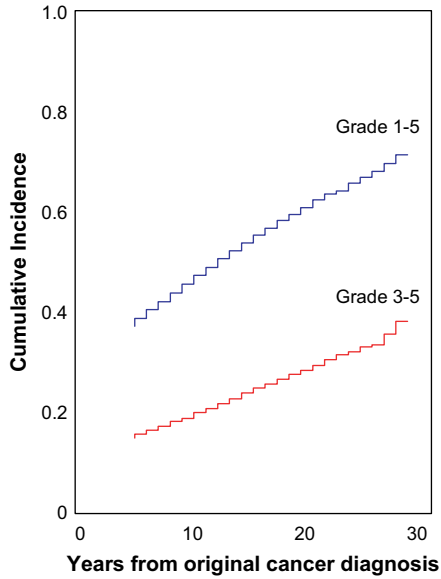



**Fig. 1.** Cumulative incidence of chronic health conditions among 10,397 adult survivors of pediatric cancer.[2] Footnote: Among the survivors of various types of childhood cancer, the severity of subsequent health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 3) as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). (*Reprinted from* Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355(15):1572–82; with permission.)

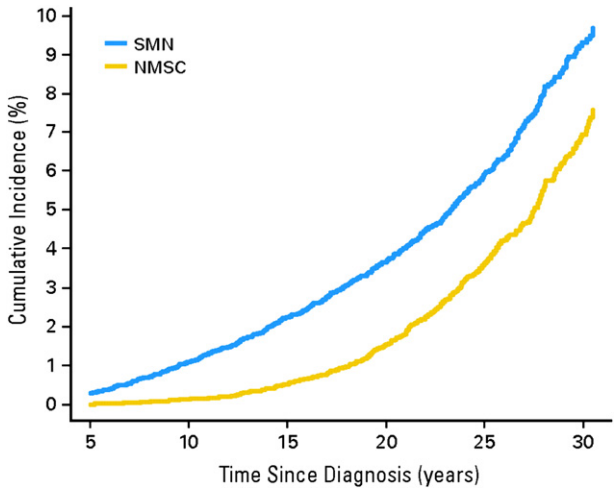



**Fig. 2.** Cumulative incidence of second malignant neoplasms (SMNs) and nonmelanoma skin cancer (NMSC) in childhood cancer survivors. At 30-year follow-up, the cumulative incidence of SMNs (*black plot*) and NMSC (*red plot*) continues to increase with time since 5 years after diagnosis of primary childhood cancer. (*Reprinted from* Meadows AT, Friedman DL, Neglia JP, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 2009;27(14):2356–62; with permission.)

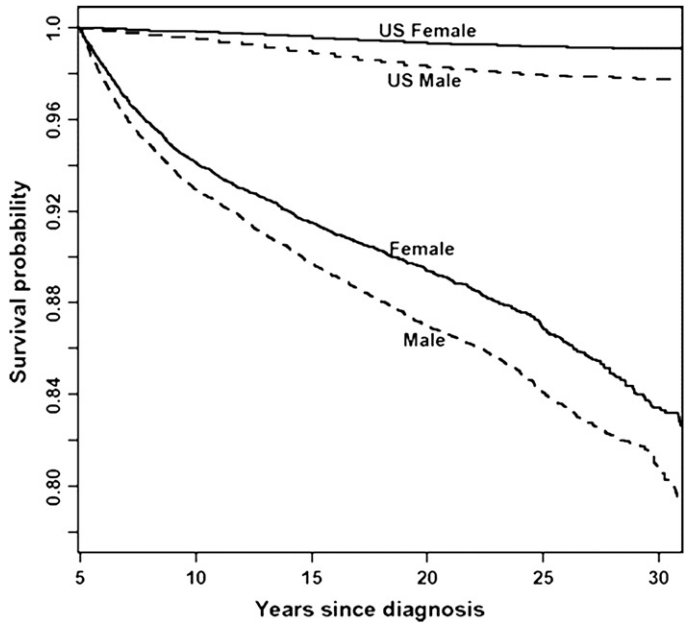



**Fig. 3.** Overall survival according to sex in the Childhood Cancer Survivor Study cohort and expected survival based on age-, year-, and sex-matched United States population mortality rates. (*Reprinted from* Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2008;100(19):1368–79; with permission.)

and related *Health Links* can be downloaded from www.survivorshipguidelines.org. Work is currently in progress to develop a web-based version of the COG *Long-Term Follow-Up Guidelines* that will generate individually tailored guidelines for survivors based on their specific therapeutic exposures.[10]

Unfortunately, despite this evolving infrastructure risk-based care is not the norm for most childhood cancer survivors, particularly those in their adult years who are at substantially increased risk of serious disease.[11,12] Whereas many cancer centers have established LTFU programs, some lack the resources and personnel to do so. Indeed, many of the existing LTFU programs have limited resources and few provide services for patients who are 25 years or older. Thus, the vast majority of adult survivors are not followed at a cancer center at a time when many experience increasing risk for second cancers, cardiac disease, and other serious health outcomes (**Fig. 6**).[13] Compounding this, most survivors who were treated in the 1970s and 1980s have never been seen in an LTFU program, do not have a cancer treatment summary, do not remember important details of their cancer therapy, and are generally unaware of their long-term risks.

## ROLE OF THE PRIMARY CARE CLINICIAN

Most long-term childhood cancer survivors will present to a primary care clinician for their routine health care needs or when they develop new signs and symptoms. Thus, it is imperative that the primary care clinician be familiar with this high-risk population. This task can be challenging. Childhood cancer survivors represent a very small

## SUMMARY OF CANCER TREATMENT
## (Abbreviated)

| DEMOGRAPHICS | | |
|---|---|---|
| Name: | Sex: | Date of Birth: |

| CANCER DIAGNOSIS | | |
|---|---|---|
| Diagnosis: | Date of Diagnosis: | Date Therapy Completed: |

CHEMOTHERAPY: ☐ Yes ☐ No *If yes, complete chart below*

| Drug Name | Additional Information† |
|---|---|
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |

† Anthracyclines: Include cumulative dose in mg/m$^2$ and age at first dose (see section 28 of Guidelines for isotoxic dose conversion); Carboplatin: Indicate if dose was myeloablative; Methotrexate and Cytarabine: Indicate route of administration (i.e., IV, IM, SQ, PO, IT, IO); IV Methotrexate and Cytarabine: Indicate if "high dose" (any single dose ≥1000 mg/m$^2$) or "standard dose" (all single doses <1000 mg/m$^2$)
Note: Cumulative doses, if known, should be recorded for all agents, particularly for alkylators and bleomycin.

RADIATION ☐ Yes ☐ No *If yes, complete chart below*

| Site/Field* | Total Dose** (Gy)*** |
|---|---|
| | |
| | |

* For chest, thoracic spine, and upper abdominal radiation, include age at first dose ** Total dose to each field should include boost dose, if given
*** Note: To convert cGy or rads to Gy, divide dose by 100 (example: 2400 cGy = 2400 rads = 24 Gy)

HEMATOPOIETIC CELL TRANSPLANT ☐ Yes ☐ No *If yes, answer question below*

Was this patient ever diagnosed with chronic graft-versus-host disease (cGVHD)? ☐ Yes ☐ No

SURGERY ☐ Yes ☐ No *If yes, complete chart below*

| Procedure | Site (if applicable) | Laterality (if applicable) |
|---|---|---|
| | | |
| | | |
| | | |

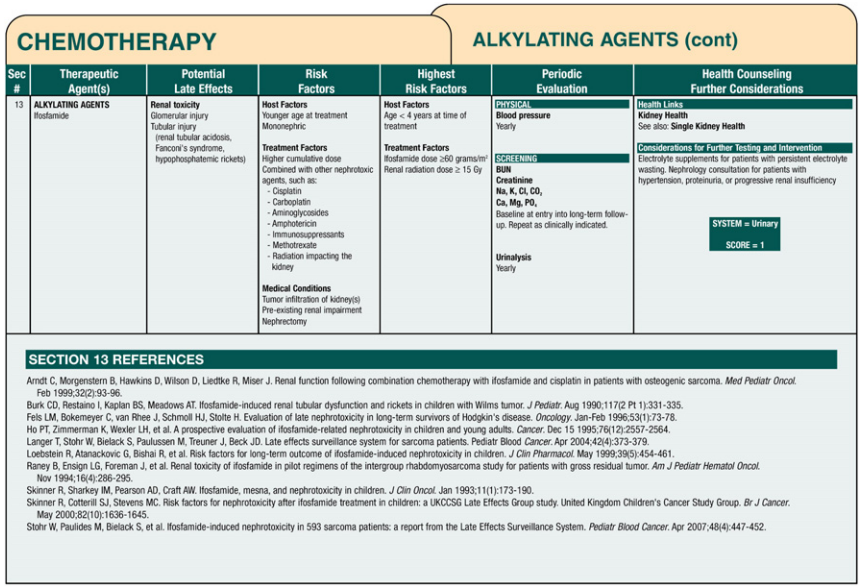
OTHER THERAPEUTIC MODALITIES ☐ Yes ☐ No *If yes, answer questions below*

| | |
|---|---|
| Did this patient receive radioiodine therapy (I-131 thyroid ablation)? | ☐ Yes ☐ No |
| Did this patient receive systemic MIBG (in therapeutic doses)? | ☐ Yes ☐ No |
| Did this patient receive bioimmunotherapy? | ☐ Yes ☐ No |

| Summary prepared by: | Date prepared: |
|---|---|

**Fig. 4.** Template for Cancer Treatment Summary. (*Reprinted from* The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adults Cancer, Version 3.0, Appendix I 2008; with permission.)

proportion of a primary care clinician's practice. In a routine year in a typical primary care practice, a clinician is likely to see less than 5 childhood cancer survivors, each with a different cancer treated with a different regimen. Recognizing the competing demands of a busy practice and the relative infrequency of seeing a childhood cancer survivor, it can be difficult to stay up to date with the health risks associated with specific cancer therapies, much less with the recommendations for surveillance. However, the primary care clinician can play a pivotal role in the health and well-being of a childhood cancer survivor by delivering risk-based health care. This article is intended to assist the primary care clinician in this role.



**CHEMOTHERAPY** — **ALKYLATING AGENTS (cont)**

| Sec # | Therapeutic Agent(s) | Potential Late Effects | Risk Factors | Highest Risk Factors | Periodic Evaluation | Health Counseling Further Considerations |
|---|---|---|---|---|---|---|
| 13 | **ALKYLATING AGENTS**<br>Ifosfamide | **Renal toxicity**<br>Glomerular injury<br>Tubular injury (renal tubular acidosis, Fanconi's syndrome, hypophosphatemic rickets) | **Host Factors**<br>Younger age at treatment<br>Mononephric<br><br>**Treatment Factors**<br>Higher cumulative dose<br>Combined with other nephrotoxic agents, such as:<br>- Cisplatin<br>- Carboplatin<br>- Aminoglycosides<br>- Amphotericin<br>- Immunosuppressants<br>- Methotrexate<br>- Radiation impacting the kidney<br><br>**Medical Conditions**<br>Tumor infiltration of kidney(s)<br>Pre-existing renal impairment<br>Nephrectomy | **Host Factors**<br>Age < 4 years at time of treatment<br><br>**Treatment Factors**<br>Ifosfamide dose ≥60 grams/m²<br>Renal radiation dose ≥ 15 Gy | **PHYSICAL**<br>**Blood pressure**<br>Yearly<br><br>**SCREENING**<br>**BUN**<br>**Creatinine**<br>**Na, K, Cl, CO,**<br>**Ca, Mg, PO,**<br>Baseline at entry into long-term follow-up. Repeat as clinically indicated.<br><br>**Urinalysis**<br>Yearly | **Health Links**<br>**Kidney Health**<br>See also: **Single Kidney Health**<br><br>**Considerations for Further Testing and Intervention**<br>Electrolyte supplements for patients with persistent electrolyte wasting. Nephrology consultation for patients with hypertension, proteinuria, or progressive renal insufficiency<br><br>**SYSTEM = Urinary**<br>**SCORE = 1** |

**SECTION 13 REFERENCES**


Arndt C, Morgenstern B, Hawkins D, Wilson D, Liedtke R, Miser J. Renal function following combination chemotherapy with ifosfamide and cisplatin in patients with osteogenic sarcoma. *Med Pediatr Oncol.* Feb 1999;32(2):93-96.

Burk CD, Restaino I, Kaplan BS, Meadows AT. Ifosfamide-induced renal tubular dysfunction and rickets in children with Wilms tumor. *J Pediatr.* Aug 1990;117(2 Pt 1):331-335.

Fels LM, Bokemeyer C, van Rhee J, Schmoll HJ, Stolte H. Evaluation of late nephrotoxicity in long-term survivors of Hodgkin's disease. *Oncology.* Jan-Feb 1996;53(1):73-78.

Ho PT, Zimmerman K, Wexler LH, et al. A prospective evaluation of ifosfamide-related nephrotoxicity in children and young adults. *Cancer.* Dec 15 1995;76(12):2557-2564.

Langer T, Stohr W, Bielack S, Paulussen M, Treuner J, Beck JD. Late effects surveillance system for sarcoma patients. Pediatr Blood *Cancer.* Apr 2004;42(4):373-379.

Loebstein R, Atanackovic G, Bishai R, et al. Risk factors for long-term outcome of ifosfamide-induced nephrotoxicity in children. *J Clin Pharmacol.* May 1999;39(5):454-461.

Raney B, Ensign LG, Foreman J, et al. Renal toxicity of ifosfamide in pilot regimens of the intergroup rhabdomyosarcoma study for patients with gross residual tumor. *Am J Pediatr Hematol Oncol.* Nov 1994;16(4):286-295.

Skinner R, Sharkey IM, Pearson AD, Craft AW. Ifosfamide, mesna, and nephrotoxicity in children. *J Clin Oncol.* Jan 1993;11(1):173-190.

Skinner R, Cotterill SJ, Stevens MC. Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study. United Kingdom Children's Cancer Study Group. *Br J Cancer.* May 2000;82(10):1636-1645.

Stohr W, Paulides M, Bielack S, et al. Ifosfamide-induced nephrotoxicity in 593 sarcoma patients: a report from the Late Effects Surveillance System. *Pediatr Blood Cancer.* Apr 2007;48(4):447-452.


COG LTFU Guidelines – Page 16 — Version 3.0 – October 2008

**Fig. 5.** Snapshot of the Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*, Section 13, Version 3.0 (Alkylating Agents: Ifosfamide—Renal Toxicity). (*Reprinted from* The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adults Cancer, Version 3.0, Appendix I 2008; with permission.)

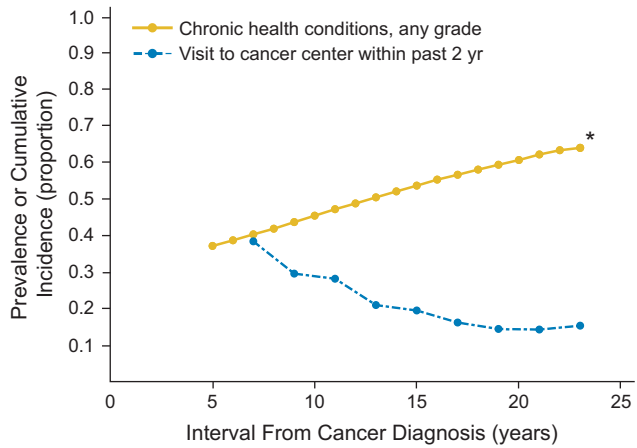



**Fig. 6.** Percentage of survivors with a visit to a cancer center in the past 2 years and cumulative incidence of any chronic condition by years since cancer diagnosis. (*Reprinted from* Nathan PC, Ford JS, Henderson TO, et al. Health behaviors, medical care, and interventions to promote healthy living in the Childhood Cancer Survivor Study cohort. J Clin Oncol 2009;27(14):2363–73; with permission.)

The long-term complications of childhood cancer treatment for which an individual survivor is at risk are determined by several factors, including cancer diagnosis, age at the time of treatment, chemotherapy and radiation received (including cumulative doses), genetic predisposition, and current health-related behaviors, such as tobacco and alcohol use, diet, and physical activity. To provide comprehensive care for the childhood cancer survivor, the primary care clinician must first determine what treatment each survivor received and for which complications the survivor is potentially at risk.

Communication between the survivor's treatment center and the primary care clinician should include a clear delineation of the role of the specialty center and the primary care practice in the continued care of the patient. This role delineation may vary depending on the particular circumstances of the individual survivor, including geographic and insurance considerations, as well as the magnitude of risk for late complications that each survivor faces. Regardless of the roles taken by the cancer center and the primary care clinician in caring for the childhood cancer survivor, ongoing communication between them is a crucial element in providing optimal survivorship care.

For survivors who return to the cancer center for regular comprehensive late effects evaluations, results of these evaluations should be communicated to the primary care clinician in a timely fashion. Any new health problems identified by the primary care clinician should similarly be communicated to the cancer center. For those patients primarily managed in the primary care setting, a communication channel should be maintained with the cancer center in order for the cancer center to convey new findings relevant to the survivors' care, such as new screening recommendations or newly emerging late effects for which additional monitoring is indicated. In addition, the primary care provider should communicate newly identified late complications back to the cancer center (with the survivors' permission) to assist in timely identification of posttreatment trends and treatment-related effects. To enable primary care clinicians to locate the appropriate ''late effects'' clinicians at a cancer center, the COG maintains an updated link to search by locale or center: http://www.childrensoncologygroup.org/Surveys/lateEffects/lateEffects.PublicSearch.asp.

## DEVELOPING RISK GROUPS TO GUIDE SURVIVORSHIP CARE

Treatment of most pediatric cancers today is ''risk-directed,'' aiming to provide the best chance for long-term survival while balancing potential short- and long-term toxicities. As a result, those with high-risk disease generally receive more intense therapy, and have greater potential for long-term complications, than those with lower-risk disease. Treatment received by pediatric cancer survivors therefore varies widely in terms of intensity, therapeutic modalities employed, and the potential for long-term complications.

### *Low-risk Group*

Survivors at lowest risk for long-term complications generally include those whose treatment involved surgery alone (eg, certain patients with limited stage neuroblastoma, thyroid carcinoma, or germ cell tumors) or limited chemotherapy associated with minimal long-term risk (eg, patients with low-stage Wilms tumor treated with nephrectomy, vincristine, and actinomycin-D). Risk for long-term complications in this group is low, and once appropriate information regarding potential health risks and indicated screening is obtained from the cancer center, follow-up care can often be provided in a primary care setting without the need for specialized oncologic follow-up, thus avoiding overmedicalization for survivors at lowest risk.

### *Intermediate-risk Group*

Survivors at moderate risk for long-term complications related to cancer treatment include the majority of patients, such as those who received standard treatments for leukemia, lymphoma, and many solid tumors. Patients in this group have not undergone hematopoietic cell transplantation (HCT) and have not received high doses of radiation therapy. Follow-up care for these patients can generally be shared between the cancer center and the primary care clinician.

### *High-risk Group*

Survivors at highest risk for late effects, such as those treated for central nervous system tumors, patients who received radiation therapy for treatment of Hodgkin lymphoma, and those who underwent HCT, should ideally receive their follow-up care in a cancer center by a multidisciplinary team specializing in the long-term complications of childhood cancer therapy. Annual evaluations for treatment-related complications may be handled at the cancer center. However, primary care for the majority of these patients, including management of intercurrent illnesses and ongoing management of comorbidities, is often provided in the community by primary care clinicians. Even for survivors at highest risk, shared care between the cancer center and the primary care clinician remains important.

## LATE EFFECTS OF CANCER THERAPY

The understanding of late effects has grown substantially over the last 3 decades. In the following sections a synopsis of key late effects, by major treatment exposures, is presented, although an exhaustive and detailed review of late effects is beyond the scope and purpose of this article. A brief historical perspective of the changes in therapy over time is also provided, and therapies used for different major cancer groups highlighted. Key screening recommendations from the COG *Long-Term Follow-Up Guidelines* are provided in **Table 1**. These recommendations and the review are focused on the long-term survivors and do not include recommendations for screening for recurrence of the primary disease. In addition, this article frequently refers to the Childhood Cancer Survivor Study (CCSS).[14] In brief, the CCSS is a retrospectively ascertained and prospectively followed cohort of over 14,000 long-term survivors of childhood cancer who were diagnosed between 1970 and 1986, and about 3600 of their siblings (without cancer). This endeavor, supported by the National Cancer Institute, has contributed greatly to the understanding of long-term outcomes of childhood cancer survivors.

## RADIOTHERAPY

Radiotherapy (RT) is critically important in the cure of many childhood cancers. However, the developing and growing tissues of children and adolescents are particularly sensitive to the effects of radiation. Late effects of RT may be evident soon after therapy (eg, cognitive dysfunction) or many years later (eg, coronary artery disease, 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. It is anticipated that improvements in the delivery of radiation therapy over the past 20 years, combined with multimodal risk-adapted therapeutic approaches, will result in fewer late effects attributable to this treatment modality.

The following 3 sections describe the primary late effects associated with RT delivered to the brain, chest, and abdomen/pelvis. Description of some outcomes related to total body irradiation (TBI), commonly used in preparation for an HCT, is integrated into the appropriate sections. For reference, the Gray (Gy) is the international unit of absorbed radiation dose, with 1 Gy equivalent to 1 J/kg. An older term that is sometimes seen in the medical record is a ''rad''. One rad is equal to 1 cGy (1 Gy = 100 cGy = 100 rads).

Regardless of the irradiated region, the skin and musculoskeletal system are often affected. Childhood cancer survivors who were treated with RT have an increased risk for melanoma, squamous cell carcinoma, and basal cell carcinoma in the radiation field,[15] in addition to musculoskeletal changes.[16] In the early days of RT, this sometimes resulted in dramatic asymmetric growth of the spine or other structures. However, even with contemporary RT, survivors may have pain or problems with function.

### *Cranial Radiotherapy*

Radiation to the brain is used to treat brain tumors, acute lymphoblastic leukemia (ALL), and head and neck soft tissue sarcoma. As the late effects of cranial RT have become known, more recent treatment protocols have either eliminated use (low- and standard-risk ALL) or are attempting to lower doses (brain tumors). Conventional therapy for posterior fossa tumors, such as medulloblastomas and ependymomas, includes 36 Gy craniospinal RT with a 15 to 20 Gy boost to the posterior fossa. Current trials are assessing the use of lower-dose craniospinal RT (18–23.4 Gy) with a 30.6 Gy boost to the posterior fossa. High-dose local field radiation (tumor plus margin) is used in the treatment of glial tumors and craniopharyngiomas. From the late 1960s to the early 1980s, 24 Gy cranial RT was standard therapy for all children with ALL. With contemporary therapy, only about 5% to 25% of ALL patients, primarily those with high-risk disease, are treated with cranial RT (12–18 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 along with chemotherapy. Children with nonrhabdomyosarcoma soft tissue sarcomas receive similar doses of radiation.

#### *Cognitive dysfunction following cranial radiotherapy*

Cognitive dysfunction following radiation to the brain is volume- and dose-related, and is generally apparent soon after therapy. Thus, children treated with higher doses of radiation to the whole brain (cranial RT), such as those with a medulloblastoma, are most impacted. Deficits include diminished full-scale intelligence quotient (FSIQ), verbal IQ, nonverbal memory, and visual-spatial abilities, and problems with attention-concentration and somatosensory functioning.[17] As a result of these cognitive deficits, brain tumor survivors treated with higher doses of cranial RT are less likely to complete high school, be employed, and live independently. Those treated at a younger age are particularly susceptible.[18] 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 compared with those treated later in childhood.[19] About 70% of brain tumor survivors diagnosed before the age of 6 years and treated between 1970 and 1986 required special education services in school.[20] Recent studies encouragingly suggest that treatment of medulloblastoma with lower-dose craniospinal RT (23.4 Gy) and a higher boost to the posterior fossa is associated with less neurocognitive toxicity.[21,22]

Though not as devastating as higher-dose cranial RT for brain tumors, treatment with 24 Gy cranial RT for ALL is also associated with cognitive dysfunction. A meta-

**Table 1**
**Overview of key screening recommendations from the Children's Oncology Group Long-Term Follow-Up Guidelines**

| Organ/System | Therapeutic Exposure | Potential Late Effect | Screening |
|---|---|---|---|
| Skin<br>Bones<br>Soft tissues | Any radiation | Skin, bone, and soft tissue malignancies | Physical examination of radiation field yearly |
| Brain<br>Neuroendocrine axis<br>Eyes<br>Ears | Head/brain radiation | Neurocognitive deficit | Neuropsychological evaluation 2 years following completion of treatment; repeat periodically as clinically indicated |
| | | Growth hormone deficiency, overweight/obesity, metabolic syndrome | Fasting glucose and lipid panel every 2 years |
| | Head/brain radiation at doses $\geq$40 Gy | Central gonadotropin deficiency | FSH, LH, estradiol or testosterone levels; baseline at age 13 (females) or age 14 (males) and as clinically indicated |
| | | Central adrenal insufficiency | 8 AM serum cortisol level yearly $\times$ 15 years post treatment |
| | Head/brain radiation; corticosteroids; busulfan chemotherapy | Cataracts, ocular complications | Yearly eye examination; ophthalmology evaluation every 1–3 years for patients who received radiation |
| | Head/brain radiation at doses $\geq$30 Gy; cisplatin chemotherapy; carboplatin chemotherapy in myeloablative doses | Hearing loss | Periodic auditory evaluation |
| Oral cavity | Any chemotherapy; radiation to the head/neck/oral cavity | Dental abnormalities | Dental examination and cleaning every 6 months |
| Thyroid | Head, neck and chest radiation impacting the thyroid | Thyroid nodules and cancer; hypothyroidism, hyperthyroidism | Physical examination of thyroid yearly; TSH, Free T4 yearly |
| Carotid and subclavian arteries | Radiation to carotid/subclavian arteries $\geq$40 Gy | Carotid and subclavian artery disease | Consider color Doppler ultrasound 10 years after radiation |

| | | | |
|---|---|---|---|
| Breast | Radiation to breast $\geq$20 Gy; screening may also be indicated in some cases for those who received total body irradiation alone in doses <20 Gy | Breast cancer | Clinical breast examination yearly until age 25, then every 6 months; mammogram with adjunct breast MRI yearly beginning 8 years after radiation or age 25, whichever occurs last |
| Lungs | Radiation involving lungs; bleomycin; nitrosourea chemotherapy | Pulmonary toxicity | Chest radiograph and pulmonary function testing 2 years following completion of treatment; repeat if clinically indicated |
| Heart | Anthracycline antibiotics<br>Radiation involving the heart (eg, chest, upper abdomen) | Cardiomyopathy; left ventricular dysfunction; congestive heart failure; arrhythmias; coronary artery disease (associated with radiation) | EKG 2 years following completion of treatment; Echocardiogram periodically depending on age at treatment and cumulative dose; Fasting glucose and lipid panel every 2 years in patients who received radiation; cardiology referral for evaluation of coronary artery disease risk in patients who received higher doses of radiation (eg, $\geq$40 Gy or $\geq$30 Gy in combination with anthracyclines) |
| Spleen | Radiation to left upper quadrant $\geq$40 Gy; splenectomy | Functional asplenia; asplenia | Blood culture and antibiotics as needed for fever |
| Hematologic | Alkylating agent and heavy metal chemotherapy; epipodophyllotoxins | Therapy-related AML and MDS | CBC with differential yearly for 10 years post therapy |
| Liver | Blood products before 1993 | Hepatitis C (exposure before 1993)<br>Hepatitis B (exposure before 1972) | Hepatitis C antibody; hepatitis B surface antigen and core antibody once following treatment |

(*continued on next page*)

**Table 1**
**(*continued*)**

| Organ/System | Therapeutic Exposure | Potential Late Effect | Screening |
|---|---|---|---|
| Bowel | Radiation to abdomen, pelvis, or thoracic spine $\geq$30 Gy; screening may also be indicated in some cases for those who received total body irradiation alone in doses <30 Gy | Colorectal cancer | Colonoscopy every 5 years beginning at age 35 years or 10 years after radiation, whichever occurs last |
| Kidneys | Ifosfamide, carboplatin, and cisplatin chemotherapy; abdominal radiation impacting the kidneys; nephrectomy | Renal toxicity | Blood pressure and urinalysis yearly<br>BUN, creatinine, and electrolytes 2 years following completion of treatment and as clinically indicated |
| Bladder | Cyclophosphamide chemotherapy; pelvic radiation impacting the bladder | Bladder malignancy; bladder fibrosis, dysfunctional voiding, hemorrhagic cystitis | Urinalysis yearly |
| Female reproductive | Alkylating agent and heavy metal chemotherapy; pelvic radiation | Ovarian failure; premature menopause; infertility | FSH, LH, estradiol at age 13 and as clinically indicated |
| Male reproductive | Alkylating agent and heavy metal chemotherapy; pelvic and testicular radiation (infertility associated with any dose; Leydig cell dysfunction/ failure associated with doses $\geq$20 Gy) | Infertility; Leydig cell dysfunction/ failure, hypogonadism | Semen analysis as indicated; FSH, LH, testosterone baseline at age 14 and as clinically indicated |

| | | | |
|---|---|---|---|
| Musculoskeletal | Any radiation from neck downward | Musculoskeletal growth problems | Physical examination yearly |
| | Chest/thorax radiation | Scoliosis/kyphosis | Physical examination yearly; more frequently during rapid periods of growth |
| | Antimetabolite chemotherapy; corticosteroids | Reduced bone mineral density | DEXA scan or quantitative CT 2 years following completion of treatment and as clinically indicated |
| | Corticosteroids | Osteonecrosis | Physical examination yearly; MRI as clinically indicated in patients with symptoms suggestive of osteonecrosis |
| | Amputation and limb-sparing surgery | Functional impairments | Yearly orthopedic evaluation |
| Psychological | Any cancer experience | Psychosocial and mental health disorders | Yearly psychosocial assessment |

*Abbreviations*: AML, acute myeloid leukemia; BUN, blood urea nitrogen; CBC, complete blood count; DEXA, dual energy x-ray absorptiometry; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MDS, myelodysplastic syndrome; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

analysis of more than 30 retrospective and prospective studies of ALL survivors reported that 24 Gy cranial RT resulted in a mean decrease in full-scale IQ of 10 points.[23] Verbal IQ scores were affected more than performance IQ and changes were noted to be progressive. Although more than half of patients had mild to moderate learning problems, outcomes were highly variable, and some patients experienced 20- to 30-point losses, whereas others had no discernible changes. Additional deficits have been noted in visual-spatial abilities, attention-concentration, nonverbal memory, and somatosensory functioning.[23,24] Females and those treated with cranial RT before 4 years of age are likely to have more severe dysfunction.[23,24] Treatment with 18 Gy cranial RT is associated with less neuropsychological toxicity than 24 Gy.[25]

When neurocognitive problems occur, children commonly present with school difficulties. Thus, primary care clinicians should be aware of this risk, recognize the school difficulties associated with prior cancer therapy, and have an approach to screening, intervention, and advocacy.

***Neuroendocrine dysfunction following cranial radiotherapy***

Neuroendocrine dysfunction is a common dose- and site-related late effect following radiation to the brain. Among 1607 brain tumor survivors in the CCSS, 43% reported at least one endocrine condition.[26] Growth hormone deficiency (GHD) is the most common endocrinopathy; and occurs more frequently with doses in excess of 18 to 20 Gy to the hypothalamic-pituitary axis (HPA). Risk factors for GHD include higher doses of radiation, younger age at exposure, and female gender.[27,28] Treatment with growth hormone in these patients usually results in near normalization of final height, unless the spinal axis has also been irradiated. Growth hormone deficiency in adults is associated with an increase in prevalence of dyslipidemia, insulin resistance, and cardiovascular mortality.[29] In a recent study of embryonal brain tumor survivors treated with a median dose of 44 Gy to the HPA, the cumulative incidence at 4 years from diagnosis was: GHD, 93%; thyroid-stimulating hormone (TSH) deficiency, 23%; adrenocorticotropic hormone (ACTH) deficiency, 38%; and primary hypothyroidism, 65%.[27] TSH and ACTH deficiency may not develop until several years after radiation.[27,30] Gonadotropin, TSH, and ACTH deficiency is uncommon among survivors treated with less than 40 Gy to the HPA.[27,30]

***Obesity following cranial radiotherapy***

Moderate-dose cranial RT (18–24 Gy) among ALL survivors is associated with obesity, particularly in females treated at a young age.[31,32] Female adult survivors of childhood ALL who were treated with 24 Gy cranial RT before 5 years old are 4 times more likely to be obese in comparison with women who have not been treated for a cancer.[31] In addition, women treated with 18 to 24 Gy cranial RT before the age of 10 years have a substantially greater rate of increase in their body mass index through their young adult years in comparison with women who were treated for ALL with only chemotherapy or with women in the general population.[32] It appears that these women also have a significantly increased visceral adiposity and associated insulin resistance.[33,34] These outcomes are attenuated in males. Among brain tumor survivors treated with higher doses of cranial RT, only females treated at a younger age seem to be at increased risk for obesity.[35]

***Other late effects associated with cranial radiotherapy***

Less common but serious outcomes associated with cranial RT include seizures and cerebrovascular accidents.[36,37] There is a dose-related increased risk for meningiomas and glial tumors.[38] Other late effects include cataracts, dental abnormalities and elevated risk of periodontal disease, and hearing loss.

### *Chest and Mantle Radiotherapy*

Radiation to the chest or mantle is used in the treatment of Hodgkin lymphoma (HL), non-Hodgkin lymphoma, and metastases to the lungs (eg, soft tissue sarcoma, Wilms tumor). The group most often exposed to the highest average doses of radiation is that of patients with HL. Thus, most studies assessing risk of late effects following chest radiation have focused on this group. Mantle RT was the mainstay of treatment for stage I or II supradiaphragmatic HL 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. In general, radiation doses to the mantle ranged from 35 to 44 Gy. More recently, modified mantle RT with a lower total dose (15–25 Gy) with volumes reduced to only the 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. Late effects are common following chest RT. It is presumed that the incidence of late effects will decrease with more recent protocols that involve lower doses and smaller volumes.

#### *Breast cancer following chest radiotherapy*

Women treated with chest RT for a pediatric malignancy face a significantly increased risk of breast cancer at a young age (**Fig. 7**). The risk of breast cancer begins to increase 8 years after the onset of radiation; the median age of breast cancer diagnosis ranges from 32 to 35 years.[39–41] Risk of breast cancer is greatest among women who were treated for HL with high-dose mantle RT. By age 45 years, it is estimated that 12% to 20% of women treated with moderate- to high-dose chest RT will be diagnosed with breast cancer.[39–41] As in the general population, breast cancer outcomes among childhood cancer survivors are strongly associated with stage at diagnosis.[42,43] Of note, treatment options for these women are often limited due to previous chest RT and possible exposure to anthracycline chemotherapy.

The COG recommends annual screening mammography and breast magnetic resonance imaging for women exposed to moderate- to high-dose chest RT ($\geq$20 Gy), starting at age 25 years or 8 years after radiation, whichever occurs last. However, as evidenced in a recent CCSS study, most women in this high-risk population are not being screened as recommended.[44] Among women aged 25 to 39 years, only 37% reported a screening mammogram within the past 2 years; 47% had never had a mammogram. Whereas 77% of women 40 to 50 years old reported a screening mammogram within the past 2 years, only 53% were being regularly screened (at least 2 mammograms within 4 years). The strongest predictor of mammography in women 25 to 39 years old was having a physician recommend the test, with the likelihood of reporting a mammogram 3 times higher among those who reported a physician recommendation than those who did not. Thus, it is important for clinicians to discuss this risk of breast cancer and the harms and benefits of screening with women who were treated with chest RT.

#### *Cardiovascular disease following chest radiotherapy*

Much of the heart is exposed in the mantle or mediastinal radiation field, increasing the risk for subsequent premature coronary artery, valvular, and pericardial disease. In addition, the carotid arteries are within the mantle field. Childhood cancer survivors in CCSS who were treated with chest RT had more than a threefold increase in relative risk for cardiac-related death in comparison with the standard United States

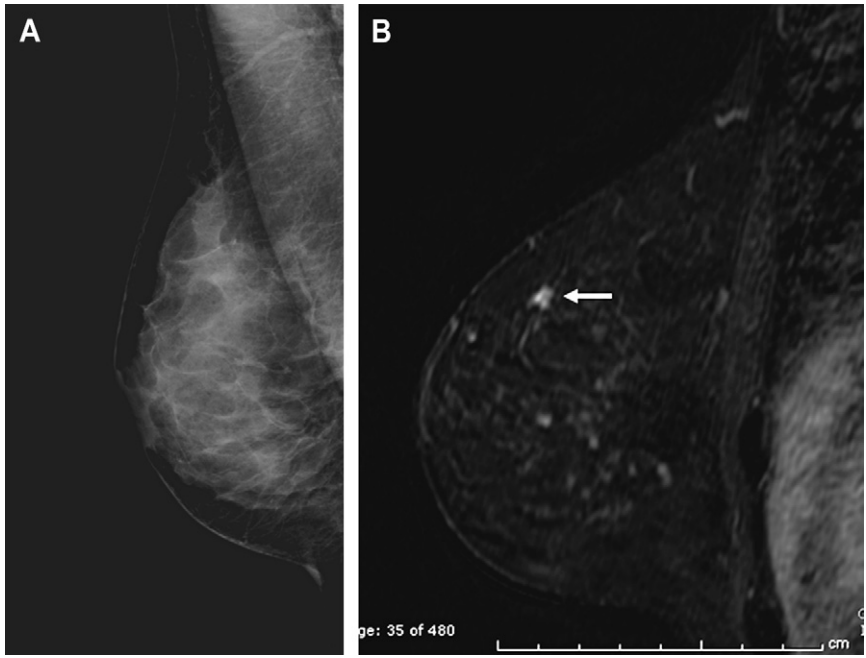



**Fig. 7.** 32 year-old woman treated for Hodgkin lymphoma with mantle radiation at age 18. (*A*) Mammogram showed dense breast tissue but no abnormality. (*B*) Magnetic resonance imaging shows a small irregular mass. Magnetic resonance biopsy revealed a 5-mm invasive ductal carcinoma. (*Reprinted from* Lee CH. The role of breast magnetic imaging in screening for breast cancer. PPO Updates 2008;22(5); with permission.)

population.[5] Hull and colleagues[45] estimated that by 20 years after radiation, 16% have significant cardiovascular morbidity.

Radiation-associated coronary artery disease (CAD) is the most common cardiac outcome following chest RT (**Fig. 8**). In a large British cohort study of HL survivors with an average of 11 years of follow-up, the standardized mortality risk from myocardial infarction was 3.2 for those who were treated with mediastinal RT.[46] By 20 years following RT, the cumulative incidence of symptomatic ischemic CAD is 21%[47]; by 30 years, the cumulative incidence of myocardial infarction is about 13%.[48] Traditional risk factors (smoking, hypercholesterolemia, diabetes) further increase risk.

More recent methods of shielding the heart and equally weighting the anterior and posterior fields seem to decrease the risk of cardiac late effects. However, even with current shielding techniques, the proximal coronary arteries are within the mediastinal field. Early identification of asymptomatic CAD, aggressive management of modifiable risk factors, and medical interventions may reduce morbidity and mortality. Of note, HL survivors may be somewhat unusual in their presentation with CAD, as they may not present with typical substernal chest pressure or pain because of a change in the pain perception after radiation.[49,50] Moreover, the vessels affected by mediastinal irradiation are proximal, including the left main artery and the left anterior descending artery, and thus the potential magnitude and seriousness of the myocardial infarction is greater.[50] Based on this evidence and because risk of coronary artery disease in these patients may be reduced with aggressive intervention and follow-up, screening for asymptomatic CAD in HL survivors has been recommended.[48,50] To date, there has been only one prospective study assessing screening in this population.

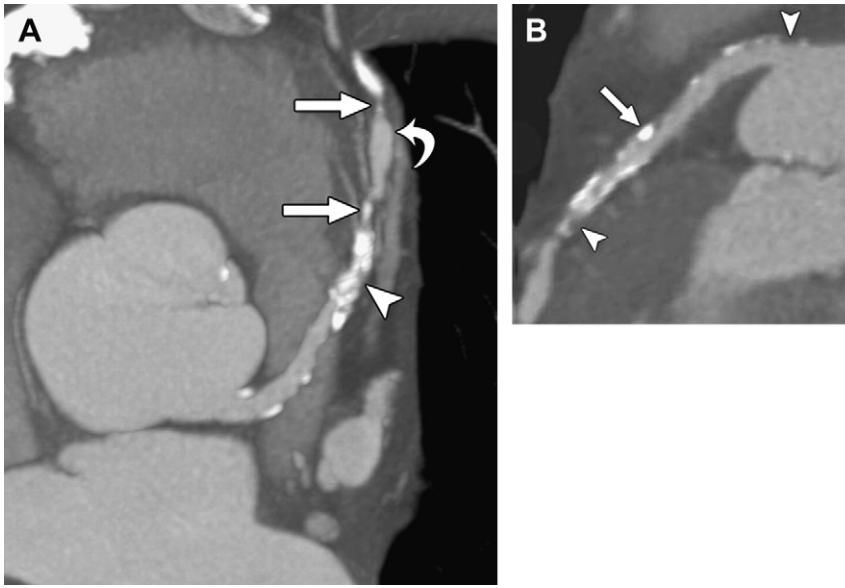



**Fig. 8.** 39-year-old man who had 45 Gy mantle field irradiation administered 25 years ago. (*A*) Curved reconstruction shows two areas of severe stenosis (*straight arrows*) in left anterior descending coronary artery (LAD) and multiple calcified plaques (*arrowhead*). More distal LAD has relatively wide diameter and might represent normal vessel or region of ectasia (*curved arrow*). (*B*) Curved reconstruction shows right coronary artery with soft plaques (*arrowheads*) and calcified plaque (*arrow*). (*Reprinted from* Rademaker J, Schoeder H, Ariaratnam NS, et al. Radiation-related coronary artery disease: coronary CT angiography findings and calcium scores in 9 asymptomatic patients with Hodgkin disease. Am J Roentgenol 2008;191:32–7; with permission.)

Heidenreich and colleagues[51] used 2 indirect methods of screening (stress echocardiography and radionucleotide perfusion scan) to detect CAD in 294 asymptomatic HL survivors. Twenty-one percent of the HL survivors had an abnormal test. Of these, 50% (or 11% of total) had CAD proven by conventional coronary angiography.

Chest RT is also associated with valvular disease, predominantly on the left side.[52] About 6% of HL survivors develop clinically significant valvular disease, with aortic stenosis being the most common outcome.[45] Long-term problems related to pericardial disease or dysrhythmias are less common. In addition, mantle RT is associated with an increased risk of carotid artery disease and stroke.[53,54]

***Pulmonary disease following chest radiotherapy***

Acute radiation pneumonitis is an uncommon outcome with contemporary therapy.[55] However, asymptomatic mild to moderate reductions in lung function, including diffusion capacity or abnormal restrictive or obstructive patterns, are common.[56] Concurrent therapy with bleomycin increases risk of a persistent decrease in diffusion capacity.[57,58] For the majority of survivors who had chest RT, it is not known how the generally mild reductions in the diffusion capacity or mild restrictive or obstructive disease will affect the patient with comorbid heart or lung problems associated with aging.

Mertens and colleagues[59] studied self-reported pulmonary problems in 12,390 long-term survivors in the CCSS. The cumulative incidence of pulmonary fibrosis by

20 years after chest RT was 3.5%. Chest RT was also associated with chronic cough, exercise-related dyspnea, and an abnormal chest wall. Lung cancer is also associated with chest RT, although it is infrequent in the young adult survivor unless he or she also smokes.[60,61]

#### *Thyroid disease following chest radiotherapy*

Thyroid disease, particularly hypothyroidism, is common following mantle or neck radiation. By 20 to 25 years after high-dose mantle radiation, the risk for hypothyroidism is about 40% to 50% and the risk for hyperthyroidism is about 3% to 5%.[62,63] Ionizing radiation penetrating the thyroid gland also frequently induces nodule development and occasionally, thyroid cancer (predominantly papillary or follicular carcinoma). The risk of thyroid cancer is not linearly related to the dose of radiation. Rather, risk increases through the low to moderate doses of radiation (10–25 Gy) and then decreases, due to radiation-induced cell death, at higher doses (>35 Gy).[64]

### *Abdominal and Pelvic Radiotherapy*

Abdominal and pelvic RT may lead to a variety of health problems involving the gastrointestinal (GI) tract, liver, spleen, kidneys, and other genitourinary tract structures including the gonads.

#### *Radiation effects on the gastrointestinal tract, liver, and spleen*

Long-term childhood cancer survivors treated with abdominal RT frequently complain of GI symptoms, including bloating, cramping, constipation, and loose stools. Often, these symptoms occur daily, and affect the patient's appetite and general quality of life. Although these symptoms can be vague, it is important to remain vigilant for a change in the pattern, as they may be related to an underlying malignancy. Childhood cancer survivors treated with abdominal or pelvic RT have an increased risk of colon cancer.[39,65,66] In addition, patients treated with abdominal (or chest) RT also have an excess risk of gastric and esophageal cancer. Recognizing that symptoms of gastroesophageal reflux disease are common in the general population, pediatric cancer survivors should be appropriately evaluated for new or changing symptoms. Enteritis and malabsorption are uncommon following contemporary radiation therapy. Small bowel obstruction similarly is rare in the patient treated with only radiation (without abdominal surgery).

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. Hepatic radiation and a variety of chemotherapeutic agents, particularly those used in conditioning regimens before HCT, have been associated with veno-occlusive disease (VOD).[67,68] This complication seems to resolve in the majority of survivors, although long-term outcomes following VOD are unknown.

Survivors who received splenic radiation at doses of 40 Gy or more (eg, for HL) are at increased risk for dysfunction and should be managed similarly to asplenic survivors (see later discussion "Splenectomy").[69]

#### *Radiation effects on the genitourinary tract*

Abdominal RT, particularly to the entire abdomen (eg, TBI, whole abdominal RT) may result in late-onset renal insufficiency and hypertension, particularly in patients also treated with potentially nephrotoxic chemotherapy, such as ifosfamide or cisplatin.[70,71] The hypertension is generally related to hyperreninemia and seems to respond to angiotensin-converting enzyme inhibitors,[72] although it may also be secondary to radiation-induced renal artery stenosis.[70]

Pelvic RT may cause bladder fibrosis leading to a reduced bladder capacity, altered function, and microscopic or gross hematuria.[73,74] Clinical symptoms associated with this complication include dribbling, nocturnal enuresis, and frequency.

***Radiation effects on the gonads***

Because the ovaries and the testicular germinal epithelium are sensitive to radiation, infertility and premature gonadal dysfunction are common among childhood cancer survivors treated with pelvic RT. More than 70% of women in the CCSS who had been treated with 20 Gy or more of radiation to the ovary had acute ovarian failure.[75] Doses less than 10 Gy were capable of inducing acute ovarian failure in women who received concomitant alkylating agents (eg, cyclophosphamide) or were 13 to 20 years old at exposure. Survivors at greatest risk for acute ovarian failure are those treated with TBI in preparation for an HCT. Virtually all women treated with TBI after 10 years of age will develop acute ovarian failure, compared with only 50% of those treated before 10 years.[76,77]

Female survivors treated with abdominal or pelvic RT who do not develop acute ovarian failure are at increased risk for premature menopause (eg, menopause before age 40 years) and having reduced ovarian reserve. For women treated with an alkylating agent plus abdominopelvic RT, the cumulative incidence of nonsurgical menopause approaches 30% by 40 years of age.[78] The consequences of ovarian failure and premature menopause extend beyond infertility and may include alterations in bone metabolism leading to osteoporosis, sexual dysfunction, and impaired body image.

In recent years, much attention has been given to preserving fertility in females undergoing cancer therapy during childhood. When radiation fields include the pelvis, the ovaries can be surgically transposed to a more protected location.[79,80] However, even after transposition of the ovaries, some women develop premature menopause secondary to chemotherapy. Those who become pregnant after pelvic RT have an elevated risk of miscarriages, preterm deliveries, and small-for-gestational-age (SGA) infants.[81,82] In the CCSS, low birth weight was reported for 25% of women who received uterine doses of 250 to 500 cGy and 36% of those who received doses greater than 500 cGy.[82] This higher dose of radiation to the uterus was also associated with an increased prevalence of SGA births (18%).

Even low-dose radiation to the testicles is associated with decreased spermatogenesis, with doses greater than 200 cGy invariably causing oligospermia or azoospermia.[83] Thus, males treated with TBI, with a fractionated dose of 12 to 15 Gy, are often rendered infertile.[84] Males with ALL who are treated with testicular RT for a testicular relapse will inevitably be azoospermic. Although modern techniques shield the testes, scatter from high-dose radiation to other fields (eg, pelvic, inguinal, or spinal radiation) can result in oligospermia or azoospermia.[85,86] Radiation injury to Leydig cells is directly related to the dose delivered and inversely related to age at treatment.[87,88] Most prepubertal boys treated with 20 Gy or less fractionated testicular RT 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 and require androgen therapy.[88] Leydig cell failure occurs in 50% of adolescent and young adult men treated with radiation doses in excess of 33 Gy.[89]

## CHEMOTHERAPY

### *Evolution of Chemotherapy*

Chemotherapy plays a critical role in the treatment of childhood cancer. Most childhood cancer survivors have received chemotherapy as part of their treatment, mainly

due to 2 considerations. (1) Radiation is used sparingly, if at all, in many childhood cancers due to the known potentially devastating late complications related to radiation in the growing child; therefore, chemotherapy is usually given in lieu of radiation whenever this is a viable option. (2) Due to the aggressive biologic nature of most childhood cancers, the disease is likely to be disseminated at the time of diagnosis and localized treatment is rarely a definitive option; therefore, chemotherapy is indicated in the majority of pediatric cancers. Chemotherapy was first employed in the treatment of childhood cancer in the 1940s with the introduction of antimetabolites.[90] In the 1950s, corticosteroids were introduced, followed by alkylating agents, anthracyclines, and vinca alkaloids in the 1960s, and epipodophyllotoxins and heavy metals in the 1970s. As children began to survive their cancers, long-term complications related to these agents emerged, and the relationships between these complications and cumulative dosage, age at therapy, and other salient risk factors were recognized.[91]

### *Alkylating Agent Chemotherapy*

#### *Gonadal dysfunction following alkylating agent chemotherapy*

Females whose therapy included an alkylating agent (eg, cyclophosphamide, ifosfamide, or a nitrosourea) are at risk for gonadal dysfunction. In the female, germ cell damage from alkylating agents has the potential to cause both infertility and loss of hormone production. The human ovary has a fixed set of primordial follicles at birth that is depleted as a result of normal menstrual cycles over each woman's lifetime, resulting in natural menopause at a median age of 51 years.[92] Once the supply of follicles is depleted, which may occur prematurely due to injury and reduced supply following gonadotoxic cancer therapy, ovarian failure occurs. The onset of ovarian failure can thus occur acutely—during or shortly after cessation of therapy—or it may take the form of premature onset of menopause.[92] The ovary is much more sensitive to radiation-induced injury than to chemotherapy-related damage during childhood, and young women who have received alkylating agent chemotherapy alone are less likely to experience acute ovarian failure than those with a history of pelvic or TBI. However, those treated with high doses of alkylating agents as a myeloablative preparatory regimen before HCT are at high risk for acute ovarian failure.[93] Premature menopause may occur in survivors who received intermediate and lower doses of alkylators. Factors associated with increased risk include higher cumulative doses of alkylating chemotherapy, older age at exposure, and treatment with radiation to the abdomen or pelvis.[94] For survivors with a history of alkylating agent chemotherapy, careful attention should be given to menstrual and reproductive history. Survivors should be counseled regarding their risk for premature menopause and the associated implications for family planning. Referral to a reproductive endocrinologist may be indicated for those currently menstruating but not yet ready to begin a family, as they may wish to further evaluate their risk or explore fertility preservation options. For survivors experiencing premature menopause, hormonal replacement therapy should be considered in light of the increased risk for reduction in bone mineral density and implications for cardiovascular health.

Unlike the female, male gonadal damage is compartmentalized such that the germinal epithelium, the site of spermatogenesis, is much more sensitive to the gonadotoxic effects of cancer therapy than are the slower growing Leydig cells that support hormone production. Spermatogenesis is therefore often adversely affected by alkylating agent chemotherapy, and the likelihood of infertility increases with higher cumulative doses.[85] Although spontaneous return of spermatogenesis can occur for several years following exposure to lower cumulative doses of alkylating agents,[95]

permanent sterility is generally seen in patients who received higher cumulative doses, and is inevitable for those who received testicular radiation.[86] Testosterone production is unlikely to be affected by exposure to alkylating agent chemotherapy alone, although subclinical Leydig cell dysfunction (as evidenced by elevated levels of LH) may occur. It is currently unknown whether subclinical dysfunction will lead to premature androgen deficiency in these survivors as they age.[96] Although elevated levels of follicle-stimulating hormone generally indicate impaired spermatogenesis, semen analysis is a more definitive determination of fertility status. Because recovery of spermatogenesis may sometimes occur in the first 10 years after therapy, testing should be repeated over time for those with oligospermia or azoospermia, and survivors should be counseled to use contraceptive measures unless pregnancy is desired. Leydig cell function should be evaluated via measurement of serum LH and testosterone levels at age 14 in at-risk survivors, and in those with clinical symptoms of androgen deficiency.

#### *Alkylating agent therapy-related acute myeloid leukemia*

Patients who have received treatment with alkylating agents are at increased risk for development of secondary therapy-related acute myeloid leukemia (t-AML), often preceded by a phase of myelodysplasia.[97] These therapy-related leukemias and myelodysplastic syndromes (MDS) are characterized by a relatively short latency period (peak risk 4–6 years after exposure)[98] and the presence of monosomy 5 or 7.[97] Risk is directly proportional to cumulative dose of alkylating agents, and reaches 8% at 10 years following exposure.[99] The period of risk generally does not exceed 15 years. Unfortunately, treatment of t-AML/MDS is difficult, and even with HCT, outcomes are generally inferior to those of patients with de novo AML.[100]

#### *Pulmonary disease following alkylating agent chemotherapy*

Alkylating agents, particularly BCNU (carmustine), CCNU (lomustine), cyclophosphamide, and busulfan, have been implicated in late-onset lung fibrosis and chronic pulmonary dysfunction among childhood cancer survivors.[101] Symptoms of pulmonary dysfunction may include chronic cough or dyspnea associated with exercise intolerance. Smoking exacerbates the risk for pulmonary dysfunction, and all at-risk survivors should be counseled regarding the importance of smoking cessation and avoidance.

#### *Genitourinary disease following alkylating agent chemotherapy*

Cyclophosphamide and ifosfamide have been implicated in late complications involving the bladder, including hemorrhagic cystitis and bladder fibrosis.[102,103] Cyclophosphamide has also been implicated in the rare development of bladder cancer.[104] Damage to the bladder occurs as a result of acrolein, a metabolic by-product of these alkylating agents that is excreted in the urine. Symptoms may include hematuria, frequency, dysuria, nocturia, and dysfunctional voiding. In addition, ifosfamide is associated with renal glomerular and tubular dysfunction,[105] potentially resulting in elevated levels of serum creatinine, decreased glomerular filtration rate, or salt-wasting tubular dysfunction requiring chronic electrolyte supplementation. Nephrology consultation should be considered for those with hypertension, proteinuria, or progressive renal insufficiency.

### *Anthracycline Chemotherapy*

#### *Anthracycline-associated cardiomyopathy*

Anthracyclines (eg, doxorubicin, daunorubicin) are antineoplastic agents that have played a significant role in advancing survival for many common pediatric

malignancies. These agents remain an essential component of contemporary therapy for 50% or more of children and adolescents diagnosed with cancer.[106] Anthracyclines have well-established cardiotoxicity that can manifest as asymptomatic left ventricular dysfunction, cardiomyopathy, congestive heart failure, and death.[107–109] With the use of contemporary pediatric regimens that limit cumulative anthracycline dose, early cardiotoxicity during or in the first year following treatment is rare.[110] However, late-onset anthracycline cardiotoxicity (eg, more than 1 year after completion of therapy) may occur, characterized by cardiac myocyte loss and failure of myocardial growth.[107] The resulting left ventricular wall thinning and elevated afterload can lead to a stiff, poorly compliant left ventricle and congestive heart failure that may present as late as 15 to 25 years after anthracycline therapy.[111]

Estimating risk for anthracycline injury in a given patient is confounded by the fact that investigations have differed in the methods used to evaluate and define cardiotoxicity. In a systematic review of well-designed studies that defined cardiotoxicity by episodes of clinical heart failure, the frequency of cardiotoxicity ranged from 0% to 16%.[108] Of concern is the increasing number of studies that have reported subclinical abnormalities of left ventricular systolic function in up to 57% of survivors evaluated by noninvasive testing methods.[109] These findings are problematic, because there is currently a lack of understanding regarding the long-term significance of these cardiovascular abnormalities in a relatively young population without clinically symptomatic cardiovascular disease.

Anthracycline cardiotoxicity has been reported at all dose levels; however, the risk increases at higher cumulative doses, younger age at first exposure, time from exposure, and among female survivors.[108,109] Among these risk factors, cumulative anthracycline dose is the most consistent and significant predictor of cardiotoxicity. Early studies established the cardiotoxic threshold dose of 550 mg/m$^2$ in adults[112]; however, numerous subsequent investigations demonstrated that children treated with lower cumulative anthracycline doses are at risk of subclinical cardiovascular dysfunction and clinically significant cardiomyopathy.[108,109,113,114] Currently available data from longitudinal studies indicate a definite risk of progressive cardiovascular dysfunction over time, particularly in survivors treated with cumulative anthracycline doses of 300 mg/m$^2$ or more.[111,115] As these cohorts age, the knowledge of long-term outcomes following contemporary risk-adapted regimens for favorable presentations of pediatric cancer (cumulative anthracycline doses less than 250 mg/m$^2$) will continue to evolve. Contrary to previous results advocating the relative safety of anthracycline therapy when doses are restricted to less than 250 mg/m$^2$,[114] St. Jude investigators noted an excess risk of abnormalities of cardiac function after treatment with cumulative anthracycline doses in the range of 100 to 200 mg/m$^2$.[113] Other studies evaluating the long-term impact of low-dose anthracycline exposure indicate that a significant proportion of survivors exhibit subclinical changes of cardiac dysfunction.[116,117] Whereas several investigations have failed to demonstrate long-term cardiac injury in survivors treated with anthracycline doses limited to 100 mg/m$^2$ or less,[113,118] cases of congestive heart failure have also been reported in survivors treated with low cumulative doses of anthracyclines.[108] Thus, it is likely that demographic (age, sex, race) and treatment factors (combined use of anthracyclines and chest RT) modify the risk of anthracycline cardiotoxicity. In addition, conditions that impose a significant increase on cardiac workload (eg, pregnancy, labor, and delivery) may precipitate the acute onset of symptomatic left ventricular dysfunction.[119]

### *Antimetabolite Chemotherapy*

Antimetabolite chemotherapy (eg, methotrexate, mercaptopurine, cytarabine) are antineoplastic agents predominantly used for treatment of pediatric hematological malignancies, especially acute lymphoblastic leukemia (ALL). Acute reversible toxicities are most commonly observed with these agents, but methotrexate-induced alteration of bone metabolism may impact long-term bone health by reducing bone mineral density and attainment of peak bone mass.

#### *Peak bone mass and osteoporosis following antimetabolite chemotherapy*

Maximal peak bone mass is an important factor influencing the risk of osteoporosis and fracture associated with aging. In healthy individuals, bone mass rises rapidly during puberty and typically peaks at the end of sexual development.[120] Methotrexate reduces bone mineral accretion during therapy; this effect may be exacerbated by the chronic use of corticosteroids, another class of agents routinely used in the treatment of hematological malignancies and in supportive care for a variety of pediatric cancers. Radiation-related endocrinopathies, such as GHD or hypogonadism, may contribute to ongoing bone mineral loss.[121,122] In addition, suboptimal nutrition and physical inactivity may further predispose to deficits in bone mineral accretion.

Most knowledge about cancer and its treatment effects on bone mineralization has been derived from studies of children with ALL. In this group, the leukemic process and possibly vitamin D deficiency may play a role in the alterations in bone metabolism and bone mass observed at diagnosis.[123] Antileukemic therapy causes further bone mineral density (BMD) loss,[124] which has been reported to normalize over time[125,126] or to persist for many years after completion of therapy.[127,128] Clinical factors predicting higher risk for low BMD include treatment with high cumulative doses of methotrexate (50 g/m$^2$), high cumulative doses of corticosteroids ($\geq$9 g/m$^2$), and use of more potent glucocorticoids like dexamethasone.[129] Investigations evaluating the contribution of cranial radiation to the risk of low BMD in childhood cancer survivors have yielded conflicting results.[127,130]

### *Corticosteroid Chemotherapy*

#### *Osteonecrosis and corticosteroids*

Osteonecrosis (also known as aseptic or avascular necrosis) is a rare but well-recognized skeletal complication observed predominantly in survivors of pediatric hematological malignancies treated with corticosteroids.[131,132] The condition is characterized by death of one or more segments of bone that most often affect weight-bearing joints, especially the hips and knees. Longitudinal cohort studies have identified a spectrum of clinical manifestations of osteonecrosis, ranging from asymptomatic spontaneously resolving imaging changes to painful progressive articular collapse requiring joint replacement.[133,134] Symptomatic osteonecrosis characterized by pain, joint swelling and reduced mobility typically presents during therapy. These symptoms may improve over time, persist, or progress in the years after completion of therapy. The reported prevalence of osteonecrosis affecting childhood cancer patients has varied from 1% to 15% based on the study population, treatment protocol, method of evaluation, and time from treatment.[131,135] The most important clinical risk factor for osteonecrosis is treatment with substantial doses of glucocorticoids, as is typical in regimens used for ALL, non-Hodgkin lymphoma, and HCT.[131,136] Delayed intensification therapies for childhood ALL featuring the more potent glucocorticoid, dexamethasone, have been speculated to enhance risk, because osteonecrosis was infrequently reported before this approach became

more widely used in the 1990s. However, currently available results suggest that cumulative corticosteroid dose may be a better predictor of this complication.[131,136] Osteonecrosis is more common in adolescents than in children, with the highest risk among those who are older than 10 years.[131,136] Osteonecrosis also occurs much more frequently in whites than in blacks.[131,137] Studies evaluating the influence of gender on the risk of osteonecrosis have yielded conflicting results, with some suggesting a higher incidence in females,[131,133] which has not been confirmed by others.[134,136] Genetic factors influencing antifolate and glucocorticoid metabolism have also been linked to excess risk of osteonecrosis among survivors.[137]

### *Heavy Metals*

The platinum analogues, cisplatin and carboplatin, are atypical alkylators and, as such, are associated with risks for gonadal dysfunction, renal dysfunction, and t-AML/MDS (as discussed for the alkylating agents) among childhood cancer survivors. In addition, the platinum analogues increase the risk of hearing loss,[138] peripheral sensory neuropathy,[139] and dyslipidemia.[140] Hearing loss associated with platinum chemotherapy is typically most severe in high-frequency ranges and progresses to the speech ranges with higher cumulative doses. More severely affected survivors (typically those who were younger during treatment and those who received high cumulative doses) will often need hearing aids or other assistive devices, special accommodations in the classroom, and the services of a speech or language professional. Those who are less severely affected are still likely to have problems hearing soft speech and high-pitched sounds, and may also have difficulty hearing in noisy environments. Peripheral sensory neuropathy is generally not late in onset but may persist beyond therapy, requiring physical or occupational therapy, and in some cases treatment by a specialist adept in the management of neuropathic pain. Patients with dyslipidemia are at risk for premature atherosclerotic cardiovascular disease and should be counseled about management with diet and exercise; lipid-lowering agents may also be indicated in these patients.

### *Epipodophyllotoxins*

Epipodophyllotoxin chemotherapy, such as etoposide and teniposide, are topoisomerase-II inhibitors that place patients at risk for t-AML. The cumulative risk for t-AML in patients treated with epipodophyllotoxins has been reported at 3.8% by 6 years after exposure.[141] The latency period of epipodophyllotoxin-associated t-AML is shorter than that of secondary leukemia associated with alkylating agents, and the myelodysplastic phase is notably absent. Mutations in the MLL gene associated with 11q23 rearrangements are typically seen.[98]

## SURGERY

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

Surgery has historically been an important diagnostic, staging, and therapeutic modality in the management of pediatric malignancies, especially solid tumors. However, the role of surgery in contemporary treatment regimens has changed significantly, concurrent with efforts to reduce long-term surgical morbidity. The development of effective combined-modality treatment protocols incorporating systemic chemotherapy and radiation not only reduced the risk of metastatic disease but also precluded the need for more radical surgical interventions to achieve local tumor control.[142] Advances in diagnostic imaging technology and recognition of long-term surgical morbidity resulted in the abandonment of aggressive surgical staging

procedures.[143,144] Progress in radiation technology facilitated the development of less disfiguring approaches to eradicate microscopic residual disease while minimizing normal tissue injury. These changes collectively contributed to improved childhood cancer survival, and reduced surgical morbidity by promoting the development of organ and limb preservation surgeries. The subsequent sections briefly review treatment complications associated with specific surgical procedures used in the management of pediatric and adolescent cancers.

### *Amputation and Limb-sparing Surgery*

Amputation and limb-sparing surgery prevent local recurrence of bone tumors by removal of all gross and microscopic disease. If optimally executed, both procedures accomplish an en bloc excision of tumor with a margin of normal uninvolved tissue. The type of surgical procedure, the primary tumor site, and the age of the patient affect the risk of postsurgical complications. Complications in survivors treated with amputation include stump-prosthetic problems, chronic stump pain, phantom limb pain, and bone overgrowth.[145] Although limb-sparing surgeries may offer a more aesthetically pleasing outcome, complications have been reported more frequently in survivors undergoing these procedures compared with those treated with amputation. Complications after limb-sparing surgery include nonunion, pathologic fracture, aseptic loosening, limb-length discrepancy, endoprosthetic fracture, poor joint movement.[145,146] On occasion, refractory complications develop after limb-sparing surgery and require amputation.[147,148] Several studies have compared functional outcomes after amputation and limb-sparing surgery, but results have been limited by inconsistent methods of functional assessment and small cohort sizes. Overall, data suggest that limb-sparing surgery results in better function than amputation, but differences are relatively modest.[145,148] Long-term quality of life outcomes among survivors undergoing amputation and limb-sparing procedures also have not differed substantially.[147]

### *Nephrectomy*

Nephrectomy remains the preferred procedure for local tumor control of childhood renal malignancies. Complications reported in children who have undergone nephrectomy include renal insufficiency, hyperfiltration injury, hypertension, and hydrocele. Compensatory hypertrophy of the remaining kidney typically occurs after nephrectomy, likely as an adaptation to increase glomerular filtration capacity.[149] Chronic glomerular hyperfiltration has been shown to cause focal glomerulosclerosis and interstitial injury[150] that may ultimately lead to a decline in renal function. Microalbuminuria, an indicator of glomerular hyperfiltration, has been observed in up to 84% of cases in postnephrectomy cohorts.[151] However, nephrectomy without radiation does not seem to lead to hyperfiltration injuries of the remaining kidney.[151] Diastolic hypertension has also been reported as a late complication of nephrectomy, but primarily in individuals who also received abdominal RT.[152] Clinicians should also be cognizant of other therapeutic interventions that may further impair renal function in children who have undergone nephrectomy, including nephrotoxic chemotherapy (eg, cisplatin, carboplatin, ifosfamide), supportive care medications (eg, aminoglycoside antibiotics, amphotericin, cyclosporine), and abdominal RT.

Renal failure following a unilateral nephrectomy is rare.[153] Survivors of Wilms tumor who develop chronic renal failure often have syndromes accompanying WT1 mutations or deletions that predispose to renal disease.[154,155] The National Wilms Tumor Study Group reported an overall incidence of end-stage renal disease (ESRD) of 1% for unilateral tumors and 12% for bilateral tumors. However, patients with

Denys-Drash syndrome, Wilms tumor aniridia syndrome, or associated genitourinary anomalies had ESRD risks as high as 90%.[156]

### *Exenteration and Organ-preservation Surgery*

For many years, the management of genitourinary rhabdomyosarcoma in children involved radical surgery to achieve local tumor control, including pelvic exenteration with removal of pelvic organs. Contemporary multimodal therapy aims to eradicate the primary tumor, treat or prevent metastatic disease, and preserve pelvic organs.[157–159] Intergroup Rhabdomyosarcoma Study Group investigations demonstrated that the use of primary chemotherapy optimizes preservation of bladder and urethral function in boys with prostate/bladder rhabdomyosarcoma without compromising disease control.[158,159] Conservative surgical intervention with primary chemotherapy and adjunctive radiation also avoids the need for vaginectomy and hysterectomy in girls with vaginal rhabdomyosarcoma tumors.[157] However, intensive multimodal therapy confers significant risks for treatment morbidity in long-term survivors.[160] Long-term complications reported after total cystectomy with urinary diversion procedures include chronic urinary tract infections, vesicoureteral reflux, hydronephrosis, renal dysfunction, reservoir calculi, neobladder perforation, and deficiencies of vitamin B12, folate, and carotene.[161,162] Treatment with partial cystectomy may also result in functional bladder problems related to contracture or incontinence.[158,162] Multimodal therapy including radiation and the oxazophorine alkylating agents cyclophosphamide and ifosfamide increases the risk of genitourinary tract complications, such as bladder fibrosis and hemorrhagic cystitis.[73]

### *Splenectomy*

Laparotomy including splenectomy and lymph node sampling was a routine staging procedure for Hodgkin lymphoma from the 1970s to 1990, especially in patients treated with radiation as a single modality. The procedure was abandoned as systemic chemotherapy was incorporated into pediatric protocols and advances in diagnostic imaging technology enabled more accurate intra-abdominal staging. Asplenic HL survivors remain at risk for infection and overwhelming postsplenectomy sepsis throughout their life span. The risk of bacteremia is increased eightfold after splenectomy, but vaccinations can reduce this risk.[163] Bacteremia most often results from infection with encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis.* Asplenic individuals are also at risk of infection with other organisms such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus*, *Enterococcus*, *Salmonella*, *Capnocytophaga canimorsus*, *Babesia microti*, and *Plasmodium falciparum*.[164] Daily antibiotic prophylaxis with penicillin (or an alternative agent in children with penicillin allergies) is recommended during childhood when infectious risks are substantially greater.[165] Long-term prophylaxis through the adult years remains controversial[166,167] because of concerns about inappropriate use of antibiotics and potential colonization with drug-resistant organisms.[164] However, all asplenic patients should be given guidelines to follow at the onset of febrile illnesses that emphasize the need for prompt medical evaluation. Due to the risk of rapidly invasive infections with encapsulated organisms, asplenic patients with a temperature of 38.3°C (101°F) or other signs of serious illness should be evaluated immediately a set of blood cultures should be obtained, a long-acting, broad-spectrum parenteral antibiotic (eg, ceftriaxone) administered, and the status monitored closely while awaiting blood culture results.

### OTHER THERAPEUTIC EXPOSURES: BLOOD TRANSFUSION

Childhood cancer survivors transfused before effective screening measures for hepatitis B virus (HBV) and hepatitis C virus (HCV) are at risk for transfusion-acquired hepatitis.[168] HBV screening was implemented in 1971 in the United States. HCV screening by the first-generation enzyme immunoassay (EIA) was initiated in 1990; a more sensitive second-generation EIA became available in 1992. Hence, in the United States, survivors who are at highest risk of HBV and HCV were exposed to blood/serum products before 1972 and 1993, respectively.

HBV typically has a more aggressive acute clinical course, but a relatively low rate of chronic infection.[168,169] In the United States and many other developed countries, routine vaccinations of children and adolescents against HBV has resulted in a low infection rate in the general population (<2%).[168] In contrast, acute infection with HCV is often mild or asymptomatic, but the rate of chronic infection approaches 80%.[169] At present, no vaccines are available to prevent infection, but the risk of transfusion-acquired HCV has declined significantly over the past 2 to 3 decades because of more stringent blood donor screening regulations.[170]

The prevalence of HCV infection (positive EIA or polymerase chain reaction [PCR]) in childhood cancer survivors ranges from 5% to 50% depending on the geographic location of the treating center.[171–173] PCR detection of viral RNA supports a high rate of chronic infection, ranging from 70% to 100%.[171,174] The rate of progressive fibrosis and end-stage liver disease seems to be comparable to those seen in adult cohorts with transfusion-associated hepatitis, and in hemophiliacs coinfected with human immunodeficiency virus and HBV.[171,175] Recognizing that some survivors are unsure of whether they received a transfusion or blood product during therapy, the COG recommends that all survivors who were treated before 1993 be screened for HCV.

### PSYCHOSOCIAL ASPECTS OF SURVIVORSHIP

Childhood cancer survivors are at risk for adverse psychosocial outcomes, including anxiety, depression, posttraumatic stress disorder (PTSD), academic and vocational difficulties, and barriers to health care access related to inability to obtain adequate health insurance. The late psychosocial consequences of childhood cancer therapy are dependent on many variables, including age at diagnosis, family functioning, intensity and duration of therapy, and treatment-specific sequelae, such as altered physical or cognitive functioning.[176]

Although most childhood cancer survivors appear to be experiencing good psychological health following their cancer treatment, certain subgroups may be at higher risk for adverse outcomes, particularly those with a history of brain tumors or acute lymphoblastic leukemia. In addition, survivors with a history of HL, sarcoma, and bone tumors have been found to be at increased risk for continuing cancer-related anxiety. This finding may be related to most of these survivors being adolescents at the time of their cancer diagnosis, and therefore having the capacity to understand the life-threatening implications of their illness at the time of diagnosis and throughout treatment and recovery.[6]

PTSD has also been identified as a consequence of childhood cancer and its treatment. PTSD may manifest as somatic complaints, depression, or anxiety in both survivors[177] and their family members.[178] In contrast, some survivors and families have reported posttraumatic growth (eg, positive psychosocial gains, such as enhanced self-concept and a new appreciation for life) related to the cancer experience.[179] Nevertheless, survivors and their families may benefit from psychosocial interventions

to assist with ongoing identification and management of therapy-related complications.

In terms of social and emotional adjustment, most childhood cancer survivors also appear to be doing well; however, differences in certain subgroups are apparent.[180] In one study, survivors who received higher-intensity treatments were less assertive in making and maintaining friendships, and reported greater feelings of isolation than their siblings.[181] Survivors of brain tumors, leukemia, and bone tumors report higher rates of employment difficulties, including unemployment, underemployment, and job discrimination,[182] which may be attributable to neurocognitive impairment or deficits in motor function. For these survivors, difficulties in obtaining health insurance coverage may be tied to employment problems and may limit access to adequate health care. Although disparities in health insurance coverage seem to be decreasing over time, the cost of premiums for adequate coverage may be prohibitive for some survivors.[183] Marital status has also been used to assess social well-being in childhood cancer survivors, because concerns about fertility and future health of both the survivor and any potential offspring may influence decisions about long-term relationships and marriage.[184] In general, survivors are less likely to be married than their siblings,[185] with the lowest rates of marriage occurring among those who received central nervous system-directed therapy and those with bone cancers.[186]

## SUMMARY

Late effects of therapy for childhood cancer are frequent and serious. Fortunately, many late effects are also modifiable. Proactive and anticipatory risk-based care can reduce the frequency and severity of treatment-related morbidity. The primary care clinician should be an integral component in risk-based care of survivors. Continued communication between the ''late effects'' staff at the cancer center and the primary care clinician is essential for optimum care of this high-risk population.

## ACKNOWLEDGMENTS

The authors appreciate the assistance with manuscript preparation provided by Stephanie Smith, MPH and the insightful comments of Emily Tonorezos, MD, MPH.

## REFERENCES

1. Hewitt M, Weiner SL, Simone JV, editors. Childhood cancer survivorship: improving care and quality of life. Washington, DC.: The National Academies Press; 2003. p. 20–36.
2. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 2007;297(24):2705–15.
3. Meadows AT, Friedman DL, Neglia JP, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 2009;27(14):2356–62.
4. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355(15):1572–82.
5. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2008;100(19):1368–79.

6. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. JAMA 2003;290(12):1583–92.
7. Ness KK, Mertens AC, Hudson MM, et al. Limitations on physical performance and daily activities among long-term survivors of childhood cancer. Ann Intern Med 2005;143(9):639–47.
8. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol 2004;22(24):4979–90.
9. Eshelman D, Landier W, Sweeney T, et al. Facilitating care for childhood cancer survivors: integrating Children's Oncology Group long-term follow-up guidelines and health links in clinical practice. J Pediatr Oncol Nurs 2004;21(5):271–80.
10. Poplack DG, Fordis M, Horowitz ME, et al. Improving the lives of childhood cancer survivors: development of a novel Internet resource for managing long-term health risks. In: Hewitt M, editor. Implementing cancer survivorship care planning. Washington, DC: The National Academies Press; 2007. p. 206–41.
11. Nathan PC, Greenberg ML, Ness KK, et al. Medical care in long-term survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2008;26(27):4401–9.
12. Oeffinger KC, Mertens AC, Hudson MM, et al. Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Fam Med 2004;2(1):61–70.
13. Nathan PC, Ford JS, Henderson TO, et al. Health behaviors, medical care, and interventions to promote healthy living in the Childhood Cancer Survivor Study cohort. J Clin Oncol 2009;27(14):2363–73.
14. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med Pediatr Oncol 2002;38(4):229–39.
15. Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2005;23(16):3733–41.
16. Fletcher BD. Effects of pediatric cancer therapy on the musculoskeletal system. Pediatr Radiol 1997;27(8):623–36.
17. Mulhern RK, Merchant TE, Gajjar A, et al. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol 2004;5(7):399–408.
18. Reimers TS, Ehrenfels S, Mortensen EL, et al. Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. Med Pediatr Oncol 2003;40(1):26–34.
19. Mulhern RK, Hancock J, Fairclough D, et al. Neuropsychological status of children treated for brain tumors: a critical review and integrative analysis. Med Pediatr Oncol 1992;20(3):181–91.
20. Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 2003; 97(4):1115–26.
21. Mulhern RK, Palmer SL, Merchant TE, et al. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. J Clin Oncol 2005;23(24):5511–9.
22. Ris MD, Packer R, Goldwein J, et al. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. J Clin Oncol 2001;19(15):3470–6.

23. Cousens P, Waters B, Said J, et al. Cognitive effects of cranial irradiation in leukaemia: a survey and meta-analysis. J Child Psychol Psychiatry 1988; 29(6):839–52.
24. Langer T, Martus P, Ottensmeier H, et al. CNS late-effects after ALL therapy in childhood. Part III: neuropsychological performance in long-term survivors of childhood ALL: impairments of concentration, attention, and memory. Med Pediatr Oncol 2002;38(5):320–8.
25. Waber DP, Tarbell NJ, Fairclough D, et al. Cognitive sequelae of treatment in childhood acute lymphoblastic leukemia: cranial radiation requires an accomplice. J Clin Oncol 1995;13(10):2490–6.
26. Gurney JG, Kadan-Lottick NS, Packer RJ, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer 2003;97(3):663–73.
27. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. J Clin Oncol 2008;26(7):1112–8.
28. Sklar CA. Growth and neuroendocrine dysfunction following therapy for childhood cancer. Pediatr Clin North Am 1997;44(2):489–503.
29. Hew FL, O'Neal D, Kamarudin N, et al. Growth hormone deficiency and cardiovascular risk. Baillieres Clin Endocrinol Metab 1998;12(2):199–216.
30. Rose SR, Danish RK, Kearney NS, et al. ACTH deficiency in childhood cancer survivors. Pediatr Blood Cancer 2005;45(6):808–13.
31. Oeffinger KC, Mertens AC, Sklar CA, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2003;21(7):1359–65.
32. Garmey EG, Liu Q, Sklar CA, et al. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2008;26(28):4639–45.
33. Janiszewski PM, Oeffinger KC, Church TS, et al. Abdominal obesity, liver fat, and muscle composition in survivors of childhood acute lymphoblastic leukemia. J Clin Endocrinol Metab 2007;92(10):3816–21.
34. Oeffinger KC, Adams-Huet B, Victor RG, et al. Insulin resistance and risk factors for cardiovascular disease in young adult survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 2009;27:3698–704.
35. Gurney JG, Ness KK, Stovall M, et al. Final height and body mass index among adult survivors of childhood brain cancer: Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2003;88(10):4731–9.
36. Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2006;24(33):5277–82.
37. Packer RJ, Gurney JG, Punyko JA, et al. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: Childhood Cancer Survivor Study. J Clin Oncol 2003;21(17):3255–61.
38. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98(21):1528–37.
39. Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 2003;21(23):4386–94.

40. Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Intern Med 2004; 141(8):590–7.
41. Taylor AJ, Winter DL, Stiller CA, et al. Risk of breast cancer in female survivors of childhood Hodgkin's disease in Britain: a population-based study. Int J Cancer 2007;120(2):384–91.
42. Cutuli B, Borel C, Dhermain F, et al. Breast cancer occurred after treatment for Hodgkin's disease: analysis of 133 cases. Radiother Oncol 2001;59(3):247–55.
43. Wolden SL, Hancock SL, Carlson RW, et al. Management of breast cancer after Hodgkin's disease. J Clin Oncol 2000;18(4):765–72.
44. Oeffinger KC, Ford JS, Moskowitz CS, et al. Breast cancer surveillance practices among women previously treated with chest radiation for a pediatric cancer. JAMA 2009;301(4):404–14.
45. Hull MC, Morris CG, Pepine CJ, et al. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA 2003;290(21):2831–7.
46. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. J Natl Cancer Inst 2007;99(3):206–14.
47. Reinders JG, Heijmen BJ, Olofsen-van Acht MJ, et al. Ischemic heart disease after mantlefield irradiation for Hodgkin's disease in long-term follow-up. Radiother Oncol 1999;51(1):35–42.
48. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007;109(5):1878–86.
49. Orzan F, Brusca A, Conte MR, et al. Severe coronary artery disease after radiation therapy of the chest and mediastinum: clinical presentation and treatment. Br Heart J 1993;69(6):496–500.
50. Adams MJ, Lipshultz SE, Schwartz C, et al. Radiation-associated cardiovascular disease: manifestations and management. Semin Radiat Oncol 2003;13(3):346–56.
51. Heidenreich PA, Schnittger I, Strauss HW, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. J Clin Oncol 2007; 25(1):43–9.
52. Adams MJ, Hardenbergh PH, Constine LS, et al. Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol 2003;45(1):55–75.
53. Bowers DC, McNeil DE, Liu Y, et al. Stroke as a late treatment effect of Hodgkin's disease: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2005; 23(27):6508–15.
54. King LJ, Hasnain SN, Webb JA, et al. Asymptomatic carotid arterial disease in young patients following neck radiation therapy for Hodgkin lymphoma. Radiology 1999;213(1):167–72.
55. Mah K, Van Dyk J, Keane T, et al. Acute radiation-induced pulmonary damage: a clinical study on the response to fractionated radiation therapy. Int J Radiat Oncol Biol Phys 1987;13(2):179–88.
56. Morgan GW, Freeman AP, McLean RG, et al. Late cardiac, thyroid, and pulmonary sequelae of mantle radiotherapy for Hodgkin's disease. Int J Radiat Oncol Biol Phys 1985;11(11):1925–31.
57. Mefferd JM, Donaldson SS, Link MP. Pediatric Hodgkin's disease: pulmonary, cardiac, and thyroid function following combined modality therapy. Int J Radiat Oncol Biol Phys 1989;16(3):679–85.
58. Ng AK, Li S, Neuberg D, et al. A prospective study of pulmonary function in Hodgkin's lymphoma patients. Ann Oncol 2008;19(10):1754–8.

59. Mertens AC, Yasui Y, Liu Y, et al. Pulmonary complications in survivors of childhood and adolescent cancer. A report from the Childhood Cancer Survivor Study. Cancer 2002;95(11):2431–41.
60. van Leeuwen FE, Somers R, Taal BG, et al. Increased risk of lung cancer, non-Hodgkin's lymphoma, and leukemia following Hodgkin's disease. J Clin Oncol 1989;7(8):1046–58.
61. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002;94(3):182–92.
62. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 1991;325(9):599–605.
63. Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2000;85(9):3227–32.
64. Sigurdson AJ, Ronckers CM, Mertens AC, et al. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. Lancet 2005;365(9476):2014–23.
65. Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. J Clin Oncol 2000;18(12):2435–43.
66. Bassal M, Mertens AC, Taylor L, et al. Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2006;24(3):476–83.
67. Tefft M. Radiation related toxicities in National Wilms' Tumor Study Number 1. Int J Radiat Oncol Biol Phys 1977;2(5–6):455–63.
68. Deeg HJ. Delayed complications after hematopoietic cell transplantation. In: Thomas ED, Blume KG, Forman SJ, editors. Hematopoietic cell transplantation. 2nd edition. Malden (MA): Blackwell Science; 1999. p. 776–88.
69. Coleman CN, McDougall IR, Dailey MO, et al. Functional hyposplenia after splenic irradiation for Hodgkin's disease. Ann Intern Med 1982;96(1):44–7.
70. Jones DP, Spunt SL, Green D, et al. Renal late effects in patients treated for cancer in childhood: a report from the Children's Oncology Group. Pediatr Blood Cancer 2008;51(6):724–31.
71. Cohen EP. Radiation nephropathy after bone marrow transplantation. Kidney Int 2000;58(2):903–18.
72. Moulder JE, Fish BL, Cohen EP. Treatment of radiation nephropathy with ACE inhibitors and AII type-1 and type-2 receptor antagonists. Curr Pharm Des 2007;13(13):1317–25.
73. Yeung CK, Ward HC, Ransley PG, et al. Bladder and kidney function after cure of pelvic rhabdomyosarcoma in childhood. Br J Cancer 1994;70(5):1000–3.
74. Hale GA, Marina NM, Jones-Wallace D, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. J Pediatr Hematol Oncol 1999; 21(2):115–22.
75. Chemaitilly W, Mertens AC, Mitby P, et al. Acute ovarian failure in the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2006;91(5):1723–8.
76. Sklar C. Maintenance of ovarian function and risk of premature menopause related to cancer treatment. J Natl Cancer Inst Monographs 2005;34:25–7.
77. Sklar C. Growth and endocrine disturbances after bone marrow transplantation in childhood. Acta Paediatr Suppl 1995;411:57–61 [discussion: 62].
78. Sklar CA, Mertens AC, Mitby P, et al. Premature menopause in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98(13):890–6.

79. Bisharah M, Tulandi T. Laparoscopic preservation of ovarian function: an underused procedure. Am J Obstet Gynecol 2003;188(2):367–70.
80. Williams RS, Littell RD, Mendenhall NP. Laparoscopic oophoropexy and ovarian function in the treatment of Hodgkin disease. Cancer 1999;86(10): 2138–42.
81. Green DM, Whitton JA, Stovall M, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 2002;187(4):1070–80.
82. Signorello LB, Cohen SS, Bosetti C, et al. Female survivors of childhood cancer: preterm birth and low birth weight among their children. J Natl Cancer Inst 2006; 98(20):1453–61.
83. Thomson AB, Wallace WH, Sklar CA. Testicular function. In: Wallace WH, Green DM, editors. Late effects of childhood cancer. London (UK): Arnold Publishers; 2004. p. 239–53.
84. Rovo A, Tichelli A, Passweg JR, et al. Spermatogenesis in long-term survivors after allogeneic hematopoietic stem cell transplantation is associated with age, time interval since transplantation, and apparently absence of chronic GvHD. Blood 2006;108(3):1100–5.
85. Howell SJ, Shalet SM. Spermatogenesis after cancer treatment: damage and recovery. J Natl Cancer Inst 2005;34:12–7.
86. Sklar CA, Robison LL, Nesbit ME, et al. Effects of radiation on testicular function in long-term survivors of childhood acute lymphoblastic leukemia: a report from the Children Cancer Study Group. J Clin Oncol 1990;8(12):1981–7.
87. Shalet SM, Tsatsoulis A, Whitehead E, et al. Vulnerability of the human Leydig cell to radiation damage is dependent upon age. J Endocrinol 1989;120(1):161–5.
88. Sklar C. Reproductive physiology and treatment-related loss of sex hormone production. Med Pediatr Oncol 1999;33(1):2–8.
89. Izard MA. Leydig cell function and radiation: a review of the literature. Radiother Oncol 1995;34(1):1–8.
90. Farber S, Diamond LK. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. N Engl J Med 1948;238(23):787–93.
91. Meadows AT, D'Angio GJ. Late effects of cancer treatment: methods and techniques for detection. Semin Oncol 1974;1(1):87–90.
92. Critchley HO. Ovarian and uterine function and reproductive potential. In: Wallace H, Green D, editors. Late effects of childhood cancer. London: Arnold; 2004. p. 225–38.
93. Sklar C, Boulad F, Small T, et al. Endocrine complications of pediatric stem cell transplantation. Front Biosci 2001;6:G17–22.
94. Bath LE, Wallace WH, Critchley HO. Late effects of the treatment of childhood cancer on the female reproductive system and the potential for fertility preservation. BJOG 2002;109(2):107–14.
95. Wallace WH, Shalet SM, Lendon M, et al. Male fertility in long-term survivors of childhood acute lymphoblastic leukaemia. Int J Androl 1991;14(5):312–9.
96. Kenney LB, Laufer MR, Grant FD, et al. High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer 2001;91(3):613–21.
97. Dann EJ, Rowe JM. Biology and therapy of secondary leukaemias. Best Pract Res Clin Haematol 2001;14(1):119–37.
98. Bhatia S, Sklar C. Second cancers in survivors of childhood cancer. Nat Rev Cancer 2002;2(2):124–32.

99. Pedersen-Bjergaard J, Larsen SO. Incidence of acute nonlymphocytic leukemia, preleukemia, and acute myeloproliferative syndrome up to 10 years after treatment of Hodgkin's disease. N Engl J Med 1982;307(16):965–71.
100. Godley LA, Larson RA. Therapy-related myeloid leukemia. Semin Oncol 2008; 35(4):418–29.
101. Hinkle AS, Proukou C, Chen Y. Pulmonary effects of antineoplastic therapy. In: Schwartz L, Hobbie W, Constine LS, et al, editors. Survivors of childhood and adolescent cancer: a multidisciplinary approach. New York: Springer; 2005. p. 161–79.
102. Levine LA, Richie JP. Urological complications of cyclophosphamide. J Urol 1989;141(5):1063–9.
103. Sarosy G. Ifosfamide—pharmacologic overview. Semin Oncol 1989;16(1 Suppl 3): 2–8.
104. Samra Y, Hertz M, Lindner A. Urinary bladder tumors following cyclophosphamide therapy: a report of two cases with a review of the literature. Med Pediatr Oncol 1985;13(2):86–91.
105. Burk CD, Restaino I, Kaplan BS, et al. Ifosfamide-induced renal tubular dysfunction and rickets in children with Wilms tumor. J Pediatr 1990; 117(2 Pt 1):331–5.
106. Krischer JP, Epstein S, Cuthbertson DD, et al. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience. J Clin Oncol 1997;15(4):1544–52.
107. Adams MJ, Lipshultz SE. Pathophysiology of anthracycline- and radiation-associated cardiomyopathies: implications for screening and prevention. Pediatr Blood Cancer 2005;44(7):600–6.
108. Kremer LC, van Dalen EC, Offringa M, et al. Frequency and risk factors of anthracycline-induced clinical heart failure in children: a systematic review. Ann Oncol 2002;13(4):503–12.
109. Kremer LC, van der Pal HJ, Offringa M, et al. Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol 2002;13(6):819–29.
110. Iarussi D, Indolfi P, Casale F, et al. Anthracycline-induced cardiotoxicity in children with cancer: strategies for prevention and management. Paediatr Drugs 2005;7(2):67–76.
111. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol 2005;23(12):2629–36.
112. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91(5):710–7.
113. Hudson MM, Rai SN, Nunez C, et al. Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. J Clin Oncol 2007;25(24):3635–43.
114. Sorensen K, Levitt GA, Bull C, et al. Late anthracycline cardiotoxicity after childhood cancer: a prospective longitudinal study. Cancer 2003;97(8):1991–8.
115. van Dalen EC, van der Pal HJ, Kok WE, et al. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. Eur J Cancer 2006;42(18):3191–8.
116. Levitt GA, Dorup I, Sorensen K, et al. Does anthracycline administration by infusion in children affect late cardiotoxicity? Br J Haematol 2004;124(4):463–8.
117. Poutanen T, Tikanoja T, Riikonen P, et al. Long-term prospective follow-up study of cardiac function after cardiotoxic therapy for malignancy in children. J Clin Oncol 2003;21(12):2349–56.

118. Rammeloo LA, Postma A, Sobotka-Plojhar MA, et al. Low-dose daunorubicin in induction treatment of childhood acute lymphoblastic leukemia: no long-term cardiac damage in a randomized study of the Dutch Childhood Leukemia Study Group. Med Pediatr Oncol 2000;35(1):13–9.
119. Pan PH, Moore CH. Doxorubicin-induced cardiomyopathy during pregnancy: three case reports of anesthetic management for cesarean and vaginal delivery in two kyphoscoliotic patients. Anesthesiology 2002;97(2):513–5.
120. Gilsanz V. Bone density in children: a review of the available techniques and indications. Eur J Radiol 1998;26(2):177–82.
121. van der Sluis IM, Boot AM, Hop WC, et al. Long-term effects of growth hormone therapy on bone mineral density, body composition, and serum lipid levels in growth hormone deficient children: a 6-year follow-up study. Horm Res 2002; 58(5):207–14.
122. van der Sluis IM, van den Heuvel-Eibrink MM, Hahlen K, et al. Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. Med Pediatr Oncol 2000;35(4):415–20.
123. van der Sluis IM, van den Heuvel-Eibrink MM, Hahlen K, et al. Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. J Pediatr 2002;141(2):204–10.
124. Arikoski P, Komulainen J, Riikonen P, et al. Reduced bone density at completion of chemotherapy for a malignancy. Arch Dis Child 1999;80(2):143–8.
125. Brennan BM, Mughal Z, Roberts SA, et al. Bone mineral density in childhood survivors of acute lymphoblastic leukemia treated without cranial irradiation. J Clin Endocrinol Metab 2005;90(2):689–94.
126. Kadan-Lottick N, Marshall JA, Baron AE, et al. Normal bone mineral density after treatment for childhood acute lymphoblastic leukemia diagnosed between 1991 and 1998. J Pediatr 2001;138(6):898–904.
127. Kaste SC, Jones-Wallace D, Rose SR, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. Leukemia 2001;15(5):728–34.
128. Warner JT, Evans WD, Webb DK, et al. Relative osteopenia after treatment for acute lymphoblastic leukemia. Pediatr Res 1999;45(4 Pt 1):544–51.
129. Mandel K, Atkinson S, Barr RD, et al. Skeletal morbidity in childhood acute lymphoblastic leukemia. J Clin Oncol 2004;22(7):1215–21.
130. Nysom K, Holm K, Michaelsen KF, et al. Bone mass after treatment for acute lymphoblastic leukemia in childhood. J Clin Oncol 1998;16(12):3752–60.
131. Mattano LA Jr, Sather HN, Trigg ME, et al. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. J Clin Oncol 2000;18(18):3262–72.
132. Sala A, Mattano LA Jr, Barr RD. Osteonecrosis in children and adolescents with cancer—an adverse effect of systemic therapy. Eur J Cancer 2007;43(4):683–9.
133. Arico M, Boccalatte MF, Silvestri D, et al. Osteonecrosis: An emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. Haematologica 2003;88(7):747–53.
134. Ribeiro RC, Fletcher BD, Kennedy W, et al. Magnetic resonance imaging detection of avascular necrosis of the bone in children receiving intensive prednisone therapy for acute lymphoblastic leukemia or non-Hodgkin lymphoma. Leukemia 2001;15(6):891–7.
135. Burger B, Beier R, Zimmermann M, et al. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)—experiences from trial ALL-BFM 95. Pediatr Blood Cancer 2005;44(3):220–5.

136. Strauss AJ, Su JT, Dalton VM, et al. Bony morbidity in children treated for acute lymphoblastic leukemia. J Clin Oncol 2001;19(12):3066–72.
137. Relling MV, Yang W, Das S, et al. Pharmacogenetic risk factors for osteonecrosis of the hip among children with leukemia. J Clin Oncol 2004;22(19):3930–6.
138. Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol 2005;23(34):8588–96.
139. Hilkens PH, ven den Bent MJ. Chemotherapy-induced peripheral neuropathy. J Peripher Nerv Syst 1997;2(4):350–61.
140. Ellis PA, Fitzharris BM, George PM, et al. Fasting plasma lipid measurements following cisplatin chemotherapy in patients with germ cell tumors. J Clin Oncol 1992;10(10):1609–14.
141. Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. N Engl J Med 1991;325(24):1682–7.
142. Trimble EL, Ungerleider RS, Abrams JA, et al. Neoadjuvant therapy in cancer treatment. Cancer 1993;72(11 Suppl):3515–24.
143. Heyn R, Raney RB Jr, Hays DM, et al. Late effects of therapy in patients with paratesticular rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. J Clin Oncol 1992;10(4):614–23.
144. Jockovich M, Mendenhall NP, Sombeck MD, et al. Long-term complications of laparotomy in Hodgkin's disease. Ann Surg 1994;219(6):615–21 [discussion: 621–4].
145. Nagarajan R, Neglia JP, Clohisy DR, et al. Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications? J Clin Oncol 2002;20(22):4493–501.
146. Kaste SC, Neel MN, Rao BN, et al. Complications of limb-sparing procedures using endoprosthetic replacements about the knee for pediatric skeletal sarcomas. Pediatr Radiol 2001;31(2):62–71.
147. Eiser C, Darlington AS, Stride CB, et al. Quality of life implications as a consequence of surgery: limb salvage, primary and secondary amputation. Sarcoma 2001;5(4):189–95.
148. Renard AJ, Veth RP, Schreuder HW, et al. Function and complications after ablative and limb-salvage therapy in lower extremity sarcoma of bone. J Surg Oncol 2000;73(4):198–205.
149. Bailey S, Roberts A, Brock C, et al. Nephrotoxicity in survivors of Wilms' tumours in the North of England. Br J Cancer 2002;87(10):1092–8.
150. Gutierrez-Millet V, Nieto J, Praga M, et al. Focal glomerulosclerosis and proteinuria in patients with solitary kidneys. Arch Intern Med 1986;146(4):705–9.
151. Bhisitkul DM, Morgan ER, Vozar MA, et al. Renal functional reserve in long-term survivors of unilateral Wilms tumor. J Pediatr 1991;118(5):698–702.
152. Finklestein JZ, Norkool P, Green DM, et al. Diastolic hypertension in Wilms' tumor survivors: a late effect of treatment? A report from the National Wilms' Tumor Study Group. Am J Clin Oncol 1993;16(3):201–5.
153. Ritchey ML, Green DM, Thomas PR, et al. Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. Med Pediatr Oncol 1996; 26(2):75–80.
154. Breslow NE, Norris R, Norkool PA, et al. Characteristics and outcomes of children with the Wilms tumor-Aniridia syndrome: a report from the National Wilms Tumor Study Group. J Clin Oncol 2003;21(24):4579–85.
155. Breslow NE, Takashima JR, Ritchey ML, et al. Renal failure in the Denys-Drash and Wilms' tumor-aniridia syndromes. Cancer Res 2000;60(15):4030–2.

156. Breslow NE, Collins AJ, Ritchey ML, et al. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol 2005;174(5):1972–5.
157. Andrassy RJ, Hays DM, Raney RB, et al. Conservative surgical management of vaginal and vulvar pediatric rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study III. J Pediatr Surg 1995;30(7):1034–6 [discussion: 1036–7].
158. Hays DM, Raney RB, Wharam MD, et al. Children with vesical rhabdomyosarcoma (RMS) treated by partial cystectomy with neoadjuvant or adjuvant chemotherapy, with or without radiotherapy. A report from the Intergroup Rhabdomyosarcoma Study (IRS) Committee. J Pediatr Hematol Oncol 1995;17(1):46–52.
159. Heyn R, Newton WA, Raney RB, et al. Preservation of the bladder in patients with rhabdomyosarcoma. J Clin Oncol 1997;15(1):69–75.
160. Spunt SL, Sweeney TA, Hudson MM, et al. Late effects of pelvic rhabdomyosarcoma and its treatment in female survivors. J Clin Oncol 2005;23(28):7143–51.
161. Kalloo NB, Jeffs RD, Gearhart JP. Long-term nutritional consequences of bowel segment use for lower urinary tract reconstruction in pediatric patients. Urology 1997;50(6):967–71.
162. Raney B Jr, Heyn R, Hays DM, et al. Sequelae of treatment in 109 patients followed for 5 to 15 years after diagnosis of sarcoma of the bladder and prostate. A report from the Intergroup Rhabdomyosarcoma Study Committee. Cancer 1993; 71(7):2387–94.
163. Ejstrud P, Kristensen B, Hansen JB, et al. Risk and patterns of bacteraemia after splenectomy: a population-based study. Scand J Infect Dis 2000;32(5):521–5.
164. Sumaraju V, Smith LG, Smith SM. Infectious complications in asplenic hosts. Infect Dis Clin North Am 2001;15(2):551–65, x.
165. Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. Br J Surg 1991;78(9):1031–8.
166. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. Working Party of the British Committee for Standards in Haematology Clinical Haematology Task Force. BMJ 1996;312(7028):430–4.
167. Waghorn DJ, Mayon-White RT. A study of 42 episodes of overwhelming postsplenectomy infection: is current guidance for asplenic individuals being followed? J Infect 1997;35(3):289–94.
168. Centers for Disease Control. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Morb Mortal Wkly Rep 1991;40(RR-13):1–25.
169. Centers for Disease Control. Recommendations for prevention and control of hepatitis C Virus (HCV) infection and HCV-related chronic disease. MMWR Morb Mortal Wkly Rep 1998;47(RR-19):1–39.
170. Donahue JG, Munoz A, Ness PM, et al. The declining risk of post-transfusion hepatitis C virus infection. N Engl J Med 1992;327(6):369–73.
171. Castellino S, Lensing S, Riely C, et al. The epidemiology of chronic hepatitis C infection in survivors of childhood cancer: an update of the St Jude Children's Research Hospital hepatitis C seropositive cohort. Blood 2004;103(7):2460–6.
172. Locasciulli A, Testa M, Pontisso P, et al. Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. Blood 1997;90(11):4628–33.
173. Paul IM, Sanders J, Ruggiero F, et al. Chronic hepatitis C virus infections in leukemia survivors: prevalence, viral load, and severity of liver disease. Blood 1999;93(11):3672–7.

174. Cesaro S, Petris MG, Rossetti F, et al. Chronic hepatitis C virus infection after treatment for pediatric malignancy. Blood 1997;90(3):1315–20.
175. Liang TJ, Rehermann B, Seeff LB, et al. Pathogenesis, natural history, treatment, and prevention of hepatitis C. Ann Intern Med 2000;132(4):296–305.
176. Lesko LM. Surviving hematological malignancies: stress responses and predicting psychological adjustment. Prog Clin Biol Res 1990;352:423–37.
177. Rourke MT, Hobbie WL, Schwartz L, et al. Posttraumatic stress disorder (PTSD) in young adult survivors of childhood cancer. Pediatr Blood Cancer 2007;49(2): 177–82.
178. Kazak AE, Barakat LP, Meeske K, et al. Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. J Consult Clin Psychol 1997;65(1):120–9.
179. Barakat LP, Alderfer MA, Kazak AE. Posttraumatic growth in adolescent survivors of cancer and their mothers and fathers. J Pediatr Psychol 2006;31(4): 413–9.
180. Reiter-Purtill J, Vannatta K, Gerhardt CA, et al. A controlled longitudinal study of the social functioning of children who completed treatment of cancer. J Pediatr Hematol Oncol 2003;25(6):467–73.
181. Spirito A, Stark LJ, Cobiella C, et al. Social adjustment of children successfully treated for cancer. J Pediatr Psychol 1990;15(3):359–71.
182. Pang JW, Friedman DL, Whitton JA, et al. Employment status among adult survivors in the Childhood Cancer Survivor Study. Pediatr Blood Cancer 2008;50(1): 104–10.
183. Park ER, Li FP, Liu Y, et al. Health insurance coverage in survivors of childhood cancer: the Childhood Cancer Survivor Study. J Clin Oncol 2005;23(36): 9187–97.
184. Zebrack BJ, Zeltzer LK. Living beyond the sword of Damocles: surviving childhood cancer. Expert Rev Anticancer Ther 2001;1(2):163–4.
185. Green DM, Zevon MA, Hall B. Achievement of life goals by adult survivors of modern treatment for childhood cancer. Cancer 1991;67(1):206–13.
186. Felder-Puig R, Formann AK, Mildner A, et al. Quality of life and psychosocial adjustment of young patients after treatment of bone cancer. Cancer 1998; 83(1):69–75.