Primary Care of Adult Survivors of Childhood Cancer

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There are approximately 300,000 survivors of childhood cancer in the United States, and most of them receive their medical care from primary care physicians. Adult survivors of childhood cancer are at considerable risk of long-term morbidity and mortality beyond the recurrence of their primary malignancy. Late adverse effects can impair organ function, stunt growth and development, and cause neurocognitive dysfunction and secondary malignancies. To address the need for systematic, comprehensive care of this expanding high-risk patient population, the Children's Oncology Group has developed long-term follow-up guidelines. Proper use of these guidelines will allow primary care physicians to understand a patient's individual risk, provide additional screening as needed, and identify late adverse effects of childhood cancer early. The foundation of the care of an adult survivor of a childhood cancer is a complete, accurate account of the patient's cancer and subsequent therapy in the form of a Summary of Cancer Treatment. A complete Summary of Cancer Treatment allows a primary care physician to use the long-term follow-up guidelines to create an individualized care plan. This article will review the late adverse effects of childhood cancer therapy and the transition of patients from pediatric oncologists to physicians in adulthood, and explain how primary care physicians can use these tools to provide appropriate care to adult survivors of childhood cancer. (*Am Fam Physician.* 2010;81(10):1250-1255.

▶ **Patient information:** A handout on staying healthy after childhood cancer, written by the authors of this article, is provided on page 1256.

More than 12,000 Americans younger than 20 years are diagnosed with cancer annually.[1] The treatment of childhood cancer has now progressed to the point that 80 percent of these persons will be alive five years after their initial diagnosis.[2] This means that there are approximately 300,000 survivors of childhood cancer in the United States, or approximately one out of every 1,000 Americans,[3] most between the ages of 20 and 34 years.[4]

Most adult survivors of childhood cancer receive their medical care from primary care physicians.[5] This group of physicians may be unfamiliar with the chronic issues these patients face and therefore may not be prepared to provide the appropriate long-term follow-up care. A survey of female childhood cancer survivors treated with chest radiation and, therefore, at an increased risk of breast cancer, found that more than 60 percent of those 25 to 40 years of age were not receiving screening mammograms at appropriate intervals.[6] Primary care physicians of childhood cancer survivors also need to perform surveillance for secondary cancers, identify late adverse effects of therapy, and attend to psychosocial needs.[3,7] To address the need for improved guidance, the Children's Oncology Group developed long-term follow-up guidelines for the comprehensive care of this expanding high-risk patient population.[7] Although the guidelines have not been shown to improve outcomes, they represent expert recommendations that allow primary care physicians to understand a survivor's risk, provide additional screening as needed, and identify late adverse effects of childhood cancer early. *Table 1* summarizes common late adverse effects by organ system.[3]

Risks of Long-Term Morbidity

Adult survivors of childhood cancer are at an increased risk of long-term morbidities in addition to the recurrence of their primary

Table 1. Potential Late Effects of Selected Therapeutic Interventions for Childhood Cancer According to Organ System

	Therapeutic Exposures			
Organ System	*Chemotherapy*	*Radiation Therapy Field*	*Surgery*	*Potential Late Effect*
Skin	—	All fields	—	Dysplastic nevi; skin cancer
Ocular	Busulfan; corticosteroids	Cranial; orbital/eye; TBI	Neurosurgery	Cataracts; retinopathy (XRT doses ≥ 30 Gy only); ocular nerve palsy (neurosurgery only)
Auditory	Cisplatin; carboplatin (in myeloablative doses only)	≥ 30 Gy to: cranial, ear/infratemporal, nasopharyngeal	—	Sensorineural hearing loss; conductive hearing loss (XRT only); Eustachian tube dysfunction (XRT only)
Dental	Any chemotherapy before development of secondary dentition	Head and neck fields that include the oral cavity or salivary glands (e.g., cranial, oropharyngeal, mantle, TBI)	—	Dental maldevelopment (tooth/root agenesis, microdontia, enamel dysplasia); periodontal disease; dental caries; osteoradionecrosis (XRT doses ≥ 40 Gy)
Cardiovascular	Anthracycline agents (e.g., doxorubicin, daunorubicin)	Chest (e.g., mantle, mediastinal); upper abdominal	—	Cardiomyopathy; congestive heart failure; arrhythmia; subclinical left ventricular dysfunction; XRT only: valvular disease, atherosclerotic heart disease, myocardial infarction, and pericarditis, pericardial fibrosis
Pulmonary	Bleomycin; busulfan; carmustine lomustine	Chest (mantle, mediastinal, whole lung); TBI	Pulmonary resection; lobectomy	Pulmonary fibrosis; interstitial pneumonitis; restrictive/obstructive lung disease; pulmonary dysfunction
Breast	—	Chest (mantle, mediastinal, axillary, whole lung); TBI	—	Breast tissue hypoplasia; breast cancer (XRT doses ≥ 20 Gy)
Gastrointestinal	—	Abdominal, pelvic (doses ≥ 30 Gy)	Laparotomy; pelvic/spinal surgery	Chronic enterocolitis; gastrointestinal tract strictures; adhesions/obstruction; fecal incontinence; colon cancer (XRT only; doses ≥ 30 Gy)
Liver	Antimetabolites (mercaptopurine, thioguanine, methotrexate)	Abdominal (doses ≥ 30 Gy)	—	Hepatic dysfunction; veno-occlusive disease (VOD); hepatic fibrosis, cirrhosis; cholelithiasis
Renal	Cisplatin; carboplatin; ifosfamide; methotrexate	Abdominal (including kidney)	Nephrectomy	Glomerular toxicity; tubular dysfunction; renal insufficiency; hypertension
Bladder	Cyclophosphamide; ifosfamide	Pelvic (including bladder); lumbar-sacral spine	Spinal surgery; cystectomy	Hemorrhagic cystitis; bladder fibrosis; dysfunctional voiding; neurogenic bladder; bladder malignancy (cyclophosphamide, XRT)

continued

This table briefly summarizes potential late effects for selected therapeutic exposures only; the complete set of long-term follow-up guidelines from the Children's Oncology Group, including screening recommendations, is available at http://www.survivorshipguidelines.org. XRT indicates radiation therapy; TBI, total body irradiation; IV, intravenous.

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Table 1. Potential Late Effects of Selected Therapeutic Interventions for Childhood Cancer According to Organ System *(continued)*

	Therapeutic Exposures			
Organ System	*Chemotherapy*	*Radiation Therapy Field*	*Surgery*	*Potential Late Effect*
Sexual/reproductive				
Males	Alkylating agents (e.g., busulfan, carmustine, lomustine, cyclophosphamide, mechlorethamine, melphalan, procarbazine)	Hypothalamic-pituitary; testicular; pelvic; TBI	Pelvic/spinal surgery; orchiectomy	Delayed/arrested puberty; hypogonadism; infertility; erectile/ejaculatory dysfunction
Females	Alkylating agents (e.g., busulfan, carmustine, lomustine, cyclophosphamide, mechlorethamine, melphalan, procarbazine)	Hypothalamic-pituitary; pelvic; ovarian; lumbar-sacral spine; TBI	Oophorectomy	Delayed/arrested puberty; premature menopause; infertility; uterine vascular insufficiency (XRT only); vaginal fibrosis/stenosis (XRT only)
Endocrine/ metabolic	—	Hypothalamic-pituitary; neck (thyroid)	Thyroidectomy	Growth hormone deficiency; precocious puberty; hypothyroidism; thyroid nodules/ cancer; XRT doses ≥ 40 Gy: hyperprolactinemia, central adrenal insufficiency, gonadotropin deficiency, and hyperthyroidism
Musculoskeletal	Corticosteroids; methotrexate	—	—	Osteopenia/osteoporosis; osteonecrosis
	—	All fields	—	Reduced/uneven growth; reduced function/mobility; hypoplasia, fibrosis; radiation-induced fracture (doses ≥ 40 Gy); scoliosis/kyphosis (trunk fields only); secondary benign or malignant neoplasm
	—	—	Amputation; limb sparing	Reduced/uneven growth; reduced function/mobility
Neurocognitive	Methotrexate (intrathecal administration or IV doses ≥ 1000 mg/m^2); cytarabine (IV doses ≥ 1000 mg/m^2)	Cranial; ear/ infratemporal; TBI	Neurosurgery	Neurocognitive deficits (executive function, attention, memory, processing speed, visual motor integration); learning deficits; diminished IQ
Central nervous system	Methotrexate, cytarabine (intrathecal administration or IV doses ≥ 1000 mg/m^2)	Doses ≥ 18 Gy to: cranial, orbital/eye, ear/infratemporal, nasopharyngeal	Neurosurgery	Leukoencephalopathy (spasticity, ataxia, dysarthria, dysphagia, hemiparesis, seizures [chemotherapy and XRT]); motor and sensory deficits; cerebrovascular complications (stroke, Moya Moya, occlusive cerebral; vasculopathy [XRT and surgery]); brain tumor (any XRT dose)
Peripheral nervous system	Plant alkaloids (vincristine, vinblastine); cisplatin, carboplatin	—	Spinal surgery	Peripheral sensory or motor neuropathy
Immunologic	—	Abdomen, left upper quadrant, spleen (doses ≥ 40 Gy)	Splenectomy	Life-threatening infection related to functional or anatomic asplenia (note: functional asplenia can also occur as a consequence of active chronic graft-vs-host disease after hematopoietic stem cell transplant)
Psychosocial	Any	Any	Any	Social withdrawal; educational problems; depression; anxiety; posttraumatic stress

malignancy. Late adverse effects of therapy are defined as acute or chronic diseases appearing five years or later after diagnosis of the primary cancer.[1] These adverse effects can impair organ function, stunt growth and development, cause neurocognitive impairment, and induce secondary malignancies. There are particular factors that place the survivor at increased risk of developing long-term morbidities. The role of the primary care physician is to screen for and identify these risk factors to prevent, diagnose, or treat specific late adverse effects. The long-term care plan for a survivor of childhood cancer should be an individualized plan based on the patient's risks of various late adverse effects.[3,7]

CANCER AND TREATMENT FACTORS

Over the past 30 years, cancer treatment has incorporated aggressive and combined use of chemotherapy, blood and serum products, radiation therapy, hematopoietic cell transplants, and surgery. Despite efforts to minimize complications, survivors remain at risk of developing late adverse effects from the therapies they initially received. The primary care physician caring for the childhood cancer survivor should ascertain the type and cumulative dose of chemotherapy and radiation therapy received, because both impose an increasing risk of long-term morbidities with increasing doses.

The specific morbidities associated with chemotherapy depend on the agents used for treatment. Alkylating agents can cause hypogonadism and infertility, acute myeloid leukemia, and pulmonary fibrosis. Agents that include metals (e.g., platinum) can cause renal dysfunction, ototoxicity, dyslipidemia, and peripheral neuropathies. The long-term sequelae of radiation therapy are influenced by the cumulative dose and location of the therapy. For example, abdominal radiation therapy for testicular cancer predisposes the survivor to increased risk of stomach, pancreatic, colon, kidney, and bladder cancers.[8] Radiation to any given area of the body can predispose the patient to skin cancers and other secondary malignancies, vascular damage, specific organ dysfunction, and impaired growth.[7,9,10] The combination of chemotherapy and radiation therapy can add greater risk than either therapy alone.[8]

The primary care physician must be aware of other childhood cancer therapies and their equally wide-ranging long-term effects. Hematopoietic cell transplant may leave a patient at risk of osteonecrosis, leukemia, and hepatic toxicity. Chronic graft-versus-host disease can cause xerophthalmia, xerostomia, chronic immune deficiencies, and functional asplenia. Surgery, even when curative, can leave permanent damage beyond the scars. For example, surgical patients who had an amputation may have residual phantom pain, functional limitations, and neuropathic pain. Pelvic and genitourinary surgeries can cause bowel or bladder incontinence, hypogonadism, and sexual dysfunction. Patients who have had neurosurgery may be at future risk of seizures, motor and sensory deficits, and neurocognitive impairment.[7] Even the time period during which the patient received treatment may carry greater risk for the cancer survivor. For instance, patients who received blood products before routine donor screening are at increased risk of developing human immunodeficiency virus and hepatitis B or C.[7]

PATIENT FACTORS

In addition to the patient's childhood cancer and its curative treatment, there are several patient-associated risk factors for future morbidity, including genetics, race, sex, age at diagnosis, and lifestyle behaviors. Genetics, including a known cancer-associated mutation (e.g., mutation of *TP53*) or a family history of cancer, can place a patient already exposed to carcinogenic therapies at heightened risk of developing second malignancies. Given a particular cancer therapy, race can place a survivor at increased risk; among all survivors treated with anthracyclines, black patients are at highest risk of developing cardiac toxicities.[9] Sex also has inherent risks for the childhood cancer survivor. Women tend to have a higher rate of late adverse effects than men, particularly in the areas of functional impairment, activity limitations, and anxiety.[11]

A patient's age at treatment of the primary cancer can affect the risk of future complications. Prepubertal patients undergoing whole body radiation therapy are more likely to develop osteoporosis than postpubertal patients.[12] Female leukemia survivors diagnosed before the age of four years are more than three times as likely to develop obesity when compared with age-matched control patients, whereas girls diagnosed after four years of age have an odds ratio of less than 2 for developing obesity.[13] Conversely, patients treated with corticosteroids after the age of 10 years are at greater risk of osteonecrosis.[7]

Lifestyle choices are the only modifiable risk factors for late adverse effects. Given the increased risk of cardiovascular disease and metabolic syndrome among cancer survivors, the primary care physician should encourage healthy eating habits, exercise, and smoking cessation within this population.[14] As a further example, patients who are smokers and whose childhood cancer was treated with cyclophosphamide are at a greater risk than nonsmokers of developing bladder cancer and other urinary tract diseases.[7]

Transition

The foundation of care of an adult survivor of childhood cancer is a complete, accurate account of the patient's cancer and subsequent therapy. Ideally, this information is systematically recorded during transition, which is the process of shifting from being a patient with childhood cancer to a childhood cancer survivor. This process is not merely a handoff from oncologist to primary care physician, but rather the deliberate movement of all of the medical and psychosocial concerns of the childhood cancer survivor.[15]

A consensus statement by the American Academy of Family Physicians, American Academy of Pediatrics, and American College of Physicians states that transition should be in a health care system that is "family-centered, continuous, comprehensive, coordinated, compassionate, culturally competent," and "as developmentally appropriate as it is technically sophisticated."[16] Central to successful transition is collaboration between oncologist and primary care physician, such as a shared-care model. Following completion of treatment, a survivorship care plan is developed in conjunction with or by the treating oncologist, which allows the primary care physician to direct care, both medically and psychosocially, while maintaining open, ongoing communication with the treating oncologist.[17,18]

Transition should be a deliberate, systematic process that includes the creation of a complete Summary of Cancer Treatment *(Table 2[7])*.[15,16] Ideally, this summary is made in conjunction with the treating pediatric oncologist. Further history (including relevant comorbidities), a review of systems and family history, and subsequent evaluations and screening contribute to each patient's cancer-specific survivorship care plan.[19] In adulthood, some patients will present to a primary care physician, potentially years after treatment, without such a summary. In this instance, every effort must be made to obtain as much history about the patient's cancer and treatment as possible to develop an appropriate long-term care plan.

Table 2. Summary of Cancer Treatment

Demographics: name, sex, date of birth
Cancer diagnosis: date of diagnosis, date therapy completed
Chemotherapy: drug name, cumulative dose, route of administration
Radiation: age at first dose, total dose
Hematopoietic cell transplant: history of chronic graft-versus-host disease?
Surgery: procedure, site
Other therapies (e.g., radioiodine therapy, systemic meta-iodobenzylguanidine, bioimmunotherapy)

Information from reference 7.

Developing an Individualized Care Plan

The Children's Oncology Group's long-term follow-up guidelines are available at http://www.survivorshipguidelines.org. Included are links to the complete guidelines, reference materials, Summary of Cancer Treatment form, Patient-Specific Guideline Identification Tool, Radiation Reference Guide, and health links specific to childhood cancer survivors.[7] The guidelines are applicable for patients beginning two years after completion of their treatment.[3]

The Patient-Specific Guideline Identification Tool is used along with the patient's Summary of Cancer Treatment to develop an individualized long-term follow-up approach. The Radiation Reference Guide directs readers to sections appropriate for those who received radiation as part of their cancer therapy. Based on the treatments and dosages the patient received, this tool will direct readers to the appropriate sections of the long-term follow-up guidelines. Next, the indicated sections of the long-term follow-up guidelines should be referenced to create an individualized follow-up plan. Each section of the guidelines covers the adverse effects of a specific therapy on a given organ or region of the body. These sections provide specific guidance on potential late adverse effects, risk factors, periodic evaluation, recommended screening tests, and other counseling considerations.

Case Scenario

A 22-year-old woman, new to your practice, presents for a well-woman examination. You uncover in her history that she was diagnosed with Hodgkin disease at age 10 years. She knows very little about her cancer or treatment except that she only received radiation therapy and was considered cured afterwards. She has not seen her treating oncologist nor had any follow-up care related to her cancer since she was 15 years old.

CASE SCENARIO RESOLUTION

You were able to obtain records indicating that your patient had stage IA Hodgkin lymphoma confined to the right supraclavicular region. She received a total of 35 Gy of radiation to the neck and chest (mini-mantle). She had complete resolution of her tumor and was found to be disease free at age 15 years, the time of her last visit with her pediatric oncologist. Using the Children's Oncology Group's long-term follow-up guidelines,[7] you determine

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
In addition to providing regular medical care, primary care physicians of childhood cancer survivors need to perform surveillance for secondary cancers, identify late adverse effects of therapy, and attend to psychosocial needs.	C	3, 7
The long-term care plan for a childhood cancer survivor should be individualized based on the patient's risks of various late adverse effects.	C	3, 7
The transition of childhood cancer survivors to adult primary care should be a deliberate, systematic process that includes the creation of a complete Summary of Cancer Treatment.	C	15, 16

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

that she is at continued risk for xerostomia, thyroid nodules, thyroid cancer, hypothyroidism, breast cancer, a variety of chronic lung diseases, and esophageal stricture. You determine that, in addition to routine visits, she should have yearly thyroid function testing. Because she has never had pulmonary function testing, you order a baseline examination. You educate her about her increased breast cancer risk, and, based on the guideline, you plan to perform yearly mammography plus breast magnetic resonance imaging starting at age 25 years.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of Defense, the U.S. Army Medical Corps, or the U.S. Army at large.

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