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Pediatric Oncology

Cancer Survivorship: A Pediatric Perspective

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LEARNING OBJECTIVES

After completing this course, the reader should be able to:

1. Quantify the magnitude of long-term complications and the burden of morbidity faced by cancer survivors.
2. Detail the relationship between therapeutic exposures and specific long-term complications, identify those at highest risk, and follow up these patients using standardized follow-up guidelines.
3. Evaluate and manage childhood cancer survivors.

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ABSTRACT

The last four decades have seen tremendous improvements in the survival of children diagnosed with cancer, with 5-year survival rates now at 80%. The burgeoning population of childhood cancer survivors creates an obligation to understand the health and well-being of these individuals. The use of cancer therapy at an early age can produce complications that may not become apparent until years later; it has been demonstrated quite conclusively that approximately two thirds of these survivors will experience at least one late effect and about one third will experience a late effect that is severe or life threatening. Long-term complications in childhood cancer survivors, such as impairment in growth and development, neurocognitive dysfunction, cardio-pulmonary compromise, endocrine dysfunction, renal impairment, gastrointestinal dysfunction, musculoskeletal sequelae, and subsequent malignancies, are not only related to the specific therapy employed, but may also be determined by individual host characteristics. This review describes some of the known late effects described in childhood cancer survivors in order to suggest reasonable starting points for evaluation of specific long-term problems in this unique and growing population. *The Oncologist* 2008;13:1181–1192

INTRODUCTION

Effective risk-based therapy for the management of childhood cancer in the setting of clinical trials has been the cornerstone of the tremendous progress in overall survival seen over the last four decades, with 5-year survival rates now at 80% [1]. This has resulted in a growing population of childhood cancer survivors—an estimated 270,000 survivors in the U.S. alone [2]. The demographics of childhood cancer

survivors reveal that, whereas one third of these individuals are <20 years of age, 46% are 20–40 years old, and an additional 18% are >40 years of age.

This rapidly growing number of childhood cancer survivors creates an obligation within the health care community to describe the health and well-being of this vulnerable population. Cancer and its treatment during childhood can result in a variety of long-term sequelae, such as impairment in growth and development, neurocognitive dysfunction, cardiopulmonary compromise, endocrine dysfunction, renal impairment, gastrointestinal dysfunction, musculoskeletal sequelae, and subsequent malignancies. It has been demonstrated quite conclusively that long-term survivors of childhood cancer carry a high burden of morbidity, with one third of survivors reporting severe or life-threatening complications 30 years after their primary diagnosis [3]. These sequelae are not only related to the specific therapy employed but may also be determined by individual host characteristics. Furthermore, these long-term sequelae can potentially have an adverse effect on the overall quality of life of the survivors.

BURDEN OF MORBIDITY

Several large studies of childhood cancer survivors have described the long-term sequelae associated with specific therapeutic exposures, as well as the late mortality experienced by survivors that is in excess of the age- and sex-matched general population. Several investigators have attempted to estimate the burden of morbidity by quantifying the chronic medical problems experienced by this population [4–6]. Chronic medical problems have been defined as health problems that cause physical, psychological, or social difficulty and therefore justify ongoing medical intervention. These reports suggest that approximately two thirds of survivors will experience at least one chronic medical problem and about one third will experience a late effect that is severe or life threatening. In a recent study, Oeffinger et al. [3] confirmed the findings reported in previous studies in a large cohort of 10,397 adult survivors of childhood cancer. Individuals identified to be at highest risk included those who were treated for Hodgkin's disease or brain tumors, as well as those who had received chest radiation and anthracyclines. Overall, the survivors were at an eightfold higher risk of reporting a severe chronic health condition, when compared with age- and sex-matched siblings.

These studies demonstrate quite conclusively that the implications of cure are not trivial, and that indeed the burden of morbidity carried by childhood cancer survivors is quite substantial. Furthermore, these data support a critical need for continuing follow-up of childhood cancer survi-

vors into adult life, and, more importantly, an imminent need to identify the resources necessary to provide such longitudinal care. There is also an urgent need for the survivors and their health care providers to be aware of the "at-risk" populations in order to develop appropriate surveillance strategies.

KNOWLEDGE ABOUT PAST DIAGNOSIS AND TREATMENT

An investigation of childhood cancer survivors' knowledge about their past cancer diagnosis and treatment demonstrated that only 72% of cancer survivors were able to accurately and precisely report their cancer diagnosis [7]. Furthermore, although 94% of the cancer survivors reported past exposure to chemotherapy, only 52% of those having received doxorubicin could report exposure to the drug, and only 30% of those exposed to daunomycin could report the exposure accurately. Similarly, while exposure to radiation therapy was reported by 89%, only 70% of childhood cancer survivors exposed to radiation could accurately describe the site of radiation. Most importantly, only 35% of survivors understood that serious health problems could result from past treatment.

STANDARDIZED RECOMMENDATION FOR FOLLOW-UP OF CHILDHOOD CANCER SURVIVORS

The Children's Oncology Group (COG) has developed risk-based, exposure-related guidelines [8] specifically designed to direct follow-up care for patients who have completed treatment for pediatric malignancies. These guidelines represent a set of comprehensive screening recommendations that can be used to standardize and direct the follow-up care for this group of cancer survivors. Ongoing monitoring facilitates early identification of and intervention for treatment-related complications in order to increase quality of life for these patients. Specially tailored patient education materials, known as "Health Links" accompany the guidelines, offering detailed information on guideline-specific topics in order to enhance health promotion in this population with specialized health care needs. The COG guidelines and Health Links can be downloaded from http://www.survivorshipguidelines.org.

Here, we review some of the known and emerging late effects in survivors of childhood cancer, and the relationship between these effects and individual therapeutic exposures, in order to suggest reasonable starting points for the evaluation of specific long-term problems using the screening recommendations from the COG guidelines. Detailed examples of specific screening strategies outlined within the COG guidelines are summarized in Table 1. We con-

Table 1. Selected exposure-based screening recommendations

Category	Therapeutic exposure	Potential late effect	Recommended screening
Neurocognitive	Radiation involving the brain (including total-body irradiation); intrathecal methotrexate; intermediate-/high-dose i.v. methotrexate or cytarabine	Neurocognitive deficit	Baseline neuropsychological assessment, repeated as clinically indicated and at key educational transition points; yearly assessment of vocational/educational progress
Cardiac	Anthracycline chemotherapy Chest radiation	Cardiomyopathy; subclinical left ventricular dysfunction Cardiomyopathy; subclinical left ventricular dysfunction; early-onset atherosclerotic heart disease; valvular disease; pericardial complications	Yearly history and physical exam; baseline electrocardiogram; periodic echocardiogram as indicated based on dose and age at exposure; fasting glucose and lipid profile every 2 yrs; cardiac consultation as indicated for symptomatic patients, for patients with subclinical abnormalities on screening evaluations, and for patients who are pregnant or considering pregnancy who have received cumulative anthracycline doses ≥300 mg/m² or <300 mg/m² if combined with radiation potentially impacting the heart
Pulmonary	Carmustine; lomustine; busulfan; bleomycin Bleomycin Radiation impacting the lungs	Pulmonary fibrosis Pulmonary fibrosis; interstitial pneumonitis; acute respiratory distress syndrome Pulmonary fibrosis; delayed interstitial pneumonitis; restrictive/obstructive lung disease	Yearly history and physical exam; baseline measure of pulmonary function, including DLCO and spirometry; baseline chest x-ray; consider repeat evaluations prior to general anesthesia and as clinically indicated
Endocrine	Radiation impacting the thyroid; radiation impacting the HP axis	Hypothyroidism (primary or central); hyperthyroidism; growth hormone deficiency; central adrenal insufficiency; hyperprolactinemia	Yearly history and physical exam; yearly thyroid function test (free T4, TSH); 8 a.m. serum cortisol if radiation to HP axis ≥40 Gy—test yearly for at least 15 yrs; prolactin level if positive history for galactorrhea, amenorrhea (females), or decreased libido (males)
Gonadal function	Alkylating chemotherapy; surgical removal of both gonads; radiation involving the gonads	Hypogonadism; gonadal failure; infertility; premature menopause (females)	Yearly history and physical exam including evaluation of secondary sexual characteristics and sexual function; baseline (females, age 13; males, age 14) assessment of gonadal function (LH, FSH, estradiol, or testosterone); repeat as clinically indicated in patients with delayed puberty or signs/symptoms of hormonal deficiency; additional evaluations as indicated (e.g., semen analysis)

(continued)

Table 1. (Continued)

Category	Therapeutic exposure	Potential late effect	Recommended screening
Second malignancies	Etoposide; teniposide; anthracyclines	Acute myeloid leukemia	CBC, platelet, differential yearly for 10 yrs following exposure
	Alkylating chemotherapy	Acute myeloid leukemia/myelodysplasia	
	Radiation (any field)	SMN in radiation field (skin, bone, soft tissue)	Yearly history and physical exam with inspection and palpation of tissues in radiation field
	Radiation impacting the thyroid	Thyroid cancer	Yearly thyroid exam
	Radiation impacting the breast	Breast cancer	Monthly breast self-exam; clinician breast exam yearly until age 25, then every 6 mos; mammogram with adjunct MRI yearly beginning 8 years after radiation or at age 25, whichever comes last
	Radiation impacting the colon	Colorectal cancer	Colonoscopy every 5 yrs beginning 10 yrs following radiation or at age 35, whichever comes last

Screening recommendations are adapted from the *Children's Oncology Group Long-Term Follow-Up Guidelines,* which are available in their entirety at http://www.survivorshipguidelines.org.
Abbreviations: DLCO, carbon monoxide diffusion capacity; FSH, follicle-stimulating hormone; HP, hypothalamic–pituitary; LH, luteinizing hormone; MRI, magnetic resonance imaging; SMN, subsequent malignant neoplasms; T4, thyroxine; TSH, thyroid-stimulating hormone.

clude this paper by describing some of the challenges faced in this arena.

SECOND MALIGNANT NEOPLASMS

Follow-up of a large cohort of childhood cancer survivors has demonstrated a sixfold higher risk of developing a second cancer, when compared with the general population, and this risk continues to increase as the cohort ages [9]. The incidence and the type of second malignancy differ with the primary diagnosis, type of therapy received, and presence of genetic predispositions. The more commonly reported second malignant neoplasms in childhood cancer survivors are breast, thyroid, and bone cancers, and therapy-related myelodysplasia and acute myeloid leukemia (t-MDS/AML). t-MDS/AML has been associated with specific chemotherapeutic agents, such as alkylating agents and topoisomerase II inhibitors [10]. A dose-dependent relationship is noted with alkylating agents, which typically cause t-MDS/AML after latencies of 5–10 years. Cytogenetic abnormalities in alkylating agent–associated t-MDS/AML characteristically involve chromosome 5 or 7. t-MDS/AML associated with exposure to topoisomerase II inhibitors classically has a shorter latency, no preceding dysplastic phase, and cytogenetic abnormalities involving

chromosome 11q23. While the risk for solid tumors continues to climb with increasing follow-up, the risk for t-MDS/AML plateaus after 10 years [11]. Ionizing radiation is associated with several types of cancer, with the risk being highest when the exposure occurs at a younger age [10, 12]. The risk increases with the total dose of radiation [13–16], and with increasing follow-up after radiation [17]. Examples of radiation-associated tumors include breast [11], lung, and thyroid [15] cancers, brain tumors [16], and osteosarcoma [13]. Female patients treated with mantle radiation before the age of 30 years are at a significantly higher risk of developing radiation-related breast cancer than those treated after age 30 [11, 18]. The large majority of these women are diagnosed at a relatively young age, often before 40 years of age. Because outcome is closely linked to stage at diagnosis, early diagnosis should confer a survival advantage [19]. Mammography in isolation may not be the ideal screening tool for radiation-related breast cancers occurring in relatively young women with dense breasts, hence the recommendations by the American Cancer Society to use adjunct screening with magnetic resonance imaging (MRI) [20]. An increased risk of developing thyroid cancer has been described after radiation therapy for several primary cancers, including Hodgkin's disease, acute lym-

phoblastic leukemia (ALL), and brain tumors, and after total-body irradiation for hematopoietic cell transplantation. Higher doses of radiation as well as exposure to radiation at a young age have been identified as risk factors, although a recent study demonstrated a threshold effect, with a decreasing risk at very high doses [15]. An increased risk for lung cancer (relative risk, of 2.6- to 7.0-fold) was observed following exposure to chest radiation, especially in patients treated for Hodgkin's lymphoma [21]. Cigarette smoking seems to multiply the risk associated with therapy-related lung cancer. It is therefore critical to make every effort to counsel survivors regarding the risks of smoking and to provide those who do smoke with information about smoking cessation programs.

Genetic predisposition may play a role in the development of second cancers, as evidenced by the higher risk for second cancers among patients with the genetic form of retinoblastoma. Radiation further increases the risk of a second cancer in hereditary patients. Compared with the general population, carriers of germline mutations in *RB1* who survive retinoblastoma (hereditary retinoblastoma survivors) are at an increased risk for sarcomas, melanoma, and cancers of the brain and nasal cavities. In addition, survivors of hereditary retinoblastoma who are not exposed to high-dose radiotherapy have a high lifetime risk of developing late-onset epithelial cancers, such as lung cancer, and bladder cancer [22]. The cumulative incidence for developing a new cancer 50 years after diagnosis of retinoblastoma approaches 36% for hereditary and 5.7% for nonhereditary patients [23]. Furthermore, members of families with Li-Fraumeni syndrome have been reported to be at a higher risk for multiple subsequent cancers, with the highest risk observed among survivors of childhood cancer [24]. It therefore appears that germline mutations in tumor suppressor genes, such as those occurring in Li-Fraumeni syndrome, might interact with therapeutic exposures, resulting in an increased risk for second cancers.

Screening

Because subsequent malignancies remain a significant threat to the health of survivors treated for cancer during childhood, vigilant screening is important for those at risk. Risk for t-MDS/AML usually manifests within 10 years following exposure. Recommendations include monitoring with an annual CBC for 10 years after exposure to alkylating agents or topoisomerase II inhibitors. Most other subsequent malignancies are associated with radiation exposure. Screening recommendations include a careful annual physical examination of the skin and soft tissues in the radiation field, with radiographic or other cancer screening evaluations as indicated. Specialized recommen-

dations for females who received radiation with potential impact to the breast (i.e., radiation doses ≥20 Gy to the mantle, mediastinal, whole lung, and axillary fields) include monthly breast self-examination beginning at puberty, annual clinical breast examinations beginning at puberty until age 25 years, and then a clinical breast examination every 6 months, with annual mammograms and MRIs beginning 8 years after radiation or at age 25 (whichever occurs later). Screening of those at risk for early-onset colorectal cancer (i.e., radiation doses ≥30 Gy to the abdomen, pelvis, or spine) should include colonoscopy every 5 years beginning at age 35 years or 10 years following radiation (whichever occurs last).

NEUROCOGNITIVE SEQUELAE

Neurocognitive sequelae of treatment for childhood cancer occur as a consequence of whole-brain radiation, high-dose systemic methotrexate and/or cytarabine, or intrathecal methotrexate. Risk factors include higher radiation dose, young age at the time of therapy, treatment with both cranial radiation and systemic or intrathecal chemotherapy, and female gender [25]. Furthermore, the impact of school absenteeism related to the acute effects of cancer or its treatment needs to be factored in for all cancer survivors, irrespective of treatment. Severe deficits are most frequently noted in children with brain tumors, especially those who were treated with radiation therapy, and in children who were <5 years of age at the time of treatment. Neurocognitive deficits usually become evident within 1–2 years following radiation, and are progressive in nature [26]. The decline over time is typically reflective of the child's failure to acquire new abilities or information at a rate similar to peers, rather than of a progressive loss of skills and knowledge. Affected children are particularly prone to problems with receptive and expressive language, attention span, and visual and perceptual motor skills, with irradiation- or chemotherapy-induced destruction in normal white matter partially explaining intellectual and academic achievement deficits [27]. They most often experience academic difficulties in the areas of reading, language, and mathematics. Children in younger age groups treated with cranial radiation and those treated for brain tumors, especially those with a higher IQ prior to radiation, may experience significant drops in IQ scores. The use of special education services has been shown to be significantly higher among childhood cancer survivors, in particular among leukemia and brain tumor survivors, when compared with age- and sex-matched siblings [28]. Risk factors include younger age at diagnosis and exposure to cranial radiation with or without intrathecal methotrexate, with the risk increasing at higher doses of radiation. Investigators have tested the hy-

pothesis that use of psychostimulants, such as methylphenidate (MPH), improves cognitive and social functioning among ALL and brain tumor survivors with attention and learning problems in school. There are data to support the idea that treatment with MPH can at least temporarily reduce attentional and social deficits among these survivors. However, long-term follow-up is needed to understand the sustainability of this benefit and the subpopulations that benefit the most [29].

Screening

Patients who received therapy that may potentially impact neurocognitive function should undergo a baseline neuropsychological evaluation, repeated as clinically indicated and at key transition points (e.g., when moving from grade school to middle/junior high school), as well as an annual assessment of their vocational or educational progress [30].

CARDIOVASCULAR FUNCTION

The anthracyclines (e.g., doxorubicin, daunomycin, and idarubicin) are well-known causes of cardiomyopathy [31, 32]. Chronic cardiotoxicity usually manifests itself as cardiomyopathy, pericarditis, and congestive heart failure. The incidence of cardiomyopathy is dose dependent, and may exceed 30% among adult patients who received a cumulative anthracycline dose $>600 \text{ mg/m}^2$. With a total dose of $500-600 \text{ mg/m}^2$, the incidence is 11%, falling to $<1\%$ for cumulative doses $<500 \text{ mg/m}^2$ [31].

However, a lower cumulative dose of anthracyclines may place children at greater risk for cardiac compromise. A cumulative dose $>250 \text{ mg/m}^2$ (in association with radiation to the heart) was associated with a higher risk for clinical heart failure (cumulative incidence, 20% at 25 years) than a cumulative dose $<250 \text{ mg/m}^2$ (5%) [33]. Cardiomyopathy can occur many years after completion of therapy, and the onset may be spontaneous or coincide with exertion or pregnancy, especially during the third trimester.

Radiation damages the myocardium by injuring capillary endothelial cells, which causes the obstruction of the capillary lumen and the formation of fibrin and platelet thrombi [34]. This leads to ischemia, myocardial cell death, and fibrosis, affecting the compliance of the heart and thus causing diastolic dysfunction. Coronary artery disease, as a result of premature fibrosis and probable acceleration of atherosclerosis, has been reported following radiation to the mediastinum, with a cumulative risk of 21% at 20 years after radiation [35]. Other known risk factors for cardiovascular disease, such as hypertension, dyslipidemia, and smoking, contribute to this risk. Chronic cardiac toxicity associated with radiation also presents as pericardial effu-

sions or constrictive pericarditis, usually with radiation doses >40 Gy [36].

Screening

Patients who received anthracycline chemotherapy need ongoing monitoring for late-onset cardiomyopathy, with the frequency of evaluation based on total cumulative dose and age at the time of initial therapy [37]. In addition to monitoring for cardiomyopathy, survivors who received radiation to fields impacting the heart also need monitoring for potential early-onset atherosclerotic heart disease, valvular disease, and pericardial complications. Heart-healthy lifestyles should be encouraged for all survivors, including implementation of a regular exercise program, dietary recommendations, as well as recommendations for screening for dyslipidemia. Specific recommendations for monitoring based on age and therapeutic exposure are delineated within the COG guidelines [8].

PULMONARY FUNCTION

Pulmonary radiation can lead to pulmonary fibrosis and pneumonitis. Clinically apparent pneumonitis with cough, fever, or dyspnea occurs in 5%–15% of patients who received >30 Gy in standard fractions to $>50\%$ of the lung. Obstructive changes have also been reported after conventional radiation therapy. Following hematopoietic cell transplantation, both restrictive and obstructive lung disease, including bronchiolitis obliterans, are well described [38].

Several chemotherapeutic agents are also responsible for pulmonary disease in long-term survivors. Interstitial pneumonitis and pulmonary fibrosis have been reported in children after exposure to bleomycin [39], with the chronic lung toxicity being dose dependent above a threshold cumulative dose of 400 units/m^2 and exacerbated by concurrent or previous radiation therapy. As with bleomycin, carmustine- and lomustine-related pulmonary toxicity is dose related. Cumulative carmustine doses $>600 \text{ mg/m}^2$ result in a 50% incidence of symptoms. Female patients are at a higher risk for this complication than their male counterparts.

Additional factors contributing to chronic pulmonary toxicity include superimposed infection, underlying pneumonopathy (e.g., asthma), cigarette smoking, respiratory toxicity, chronic graft versus host disease, and the effects of chronic pulmonary involvement by tumor or reaction to tumor. Increased oxygen concentrations associated with general anesthesia or SCUBA diving also have been found to exacerbate pulmonary fibrosis [40].

Screening

Monitoring for pulmonary dysfunction in childhood cancer survivors includes the assessment of symptoms such as chronic cough or dyspnea on annual follow-up. Risks of smoking and exposure to secondhand smoke should be discussed with all patients. Pulmonary function tests (including carbon monoxide diffusion capacity and spirometry) and chest x-ray are recommended as a baseline upon entry into long-term follow-up for patients at risk, repeated as clinically indicated in symptomatic patients and in those with subclinical abnormalities on screening evaluation. Repeat evaluation should also be considered for at-risk patients prior to general anesthesia. Patients with risk factors for lung complications are discouraged from SCUBA diving.

GROWTH

Severe growth retardation, defined as a standing height below the fifth percentile, has been observed in as many as 30%–35% of survivors of childhood brain tumors and in 10%–15% of patients treated with certain antileukemia regimens [41, 42]. The effects of cranial irradiation are age related, with children <8 years of age at the time of cranial irradiation at risk for adult height below the third percentile [41]. Treatment with growth hormone prior to closure of epiphyses in patients with documented growth hormone deficiency usually results in near normalization of final height, unless the spinal axis has also been irradiated.

Screening

Monitoring of long-term survivors for growth problems relies on the use of standardized curves, available online (http://www.cdc.gov/growthcharts). Because single values for heights and weights are unreliable for children, frequent serial measurements should be obtained to establish each child's pattern of growth. Endocrine consultation may be indicated for children whose height is less than the third percentile or crosses two or more percentiles, or whose growth velocity is <4–5 cm/year.

GONADAL FUNCTION

Male Gonadal Function

All therapeutic modalities (radiation, surgery, and alkylating chemotherapy) cause both germ cell depletion and abnormalities of gonadal endocrine function among male cancer survivors. Radiation to the testes is known to result in germinal loss with decreases in testicular volume and sperm production and increases in follicle-stimulating hormone (FSH). Effects are dose dependent, following fractionated exposures of 0.1–6 Gy. Radiation therapy may

also be toxic to Leydig cells, although at doses higher than those that are toxic to germ (Sertoli) cells. As summarized by Sklar [43], Leydig cell damage is dose dependent and inversely related to age at treatment. Boys treated prepubertally or peripubertally with ≥20 Gy for testicular leukemia, in addition to suffering germ cell depletion, are at a high risk for delayed sexual maturation associated with low testosterone levels, despite increased luteinizing hormone (LH) levels. Adolescent and young adult male testes are relatively radioresistant, and fractionated doses >30 Gy to the testes may induce Leydig cell failure in only about 50% of patients.

Bilateral orchiectomy will, of course, result in infertility, as well as testosterone deficiency requiring ongoing hormonal replacement therapy beginning during puberty. These patients should be managed in collaboration with an endocrinologist.

Alkylating agents decrease spermatogenesis in a dose-dependent manner. Gonadal damage following cumulative doses of cyclophosphamide <7.5 gm/m^2 (or 200 mg/kg, as used in hematopoietic cell transplantation) has been shown to be reversible in up to 70% of patients after therapy-free intervals of several years. In contrast to their prominent effects on germ cell epithelium, chemotherapy effects are less striking on slowly dividing Leydig cells, and may be age related. Following exposure to alkylating agents in prepubertal boys, normal pubertal progression and normal adult levels of testosterone are the rule; gynecomastia with low testosterone and increased LH have been reported in patients treated during adolescence, and compensated Leydig cell failure (increased LH with low normal testosterone levels or exaggerated FSH and LH responses to LH-releasing hormone) without gynecomastia is common in adults [44].

Screening

Screening for problems related to male gonadal function in survivors includes an annual age-appropriate history with specific attention to problems with libido, impotence, or fertility and examination for gynecomastia, Tanner staging of body hair, and assessment of penile and testicular size. Hormonal evaluation, including at least a single measurement of serum LH, FSH, and testosterone levels, is recommended as a baseline at age 14 years, and in boys in whom puberty appears to be delayed. Males at risk for infertility may benefit from semen analysis; honest and sensitive discussions of fertility should be part of their follow-up visit. When abnormalities in testicular function are detected, close cooperation with an endocrinologist is essential in planning hormonal replacement therapy or in monitoring patients for spontaneous recovery. When no abnormalities are noted on history and physical examination but sexual

maturity has not been completed, these studies should be repeated every 1–2 years. Conversely, in light of the potential for recovery of spermatogenesis and interpatient variations in gonadal toxicity, reminders about contraception should be given.

Female Gonadal Function

In contrast to the process in male survivors, germ cell failure and loss of ovarian endocrine function occur concomitantly in females. Radiation effects are both age and dose dependent. In women >40 years old at the time of treatment, irreversible ovarian failure is an almost universal result of 4–7 Gy of conventionally fractionated radiation delivered to both ovaries. Prepubertal ovaries are relatively radioresistant, and despite higher doses (12–50 Gy), primary amenorrhea and delayed puberty eventually occurred in only 68% of patients treated at a mean age of 6.9 years [45]. Secondary amenorrhea resulting from such modest doses appears to be reversible within several months to 4 years in 50%–60% of patients [46].

Total-body irradiation (10-Gy single fraction) has been associated with primary amenorrhea and absent secondary sexual characteristics in most patients treated prior to puberty and followed for as long as 10 years [47]. However, others have reported normal pubertal progression although with elevated FSH levels following total-body irradiation during early childhood [48]. As with standard radiation, greater age at the time of total-body irradiation has been found to predict ovarian failure [49]. Premature menopause has also been reported in the setting of hematopoietic cell transplantation [47].

Although chemotherapy-related gonadal toxicity is seen less frequently in females than in males, ovarian failure has been associated with chemotherapy, especially the alkylating agents, and the toxicity is dose and age dependent. Following myeloablative doses of alkylating agents, including busulfan and cyclophosphamide, permanent ovarian failure can be expected at all ages [50]. For survivors who retain normal ovarian function after cancer therapy, there is an increased risk for premature menopause [51]. The risk factors associated with an early menopause include exposure to high doses of alkylating agents and abdominopelvic radiation.

Screening

The diagnostic evaluation of ovarian dysfunction relies on history (primary or secondary amenorrhea, menstrual irregularity, and pregnancies or difficulty with conception) and Tanner staging of breast and genital development. Serum gonadotropin (FSH, LH) and estradiol levels should be obtained as a baseline at age 13 years and as clinically indicated, in the absence of clinical evidence of puberty (menarche, development of secondary sexual characteristics), in order to assess the need for hormone therapy to induce puberty. In addition, because young women who have progressed through puberty may experience early onset of menopause, they should also undergo assessment of gonadotropin and estradiol levels if there are clinical symptoms of estrogen deficiency (e.g., irregular menses, amenorrhea, hot flashes, and vaginal dryness). Survivors with concerns regarding fertility are urged to seek consultation with a reproductive endocrinologist.

HYPOTHYROIDISM

Childhood cancer survivors are at a higher risk for developing hypothyroidism, when compared with the general population [52]. While direct radiotherapy to the thyroid gland can result in hypothyroidism, a scatter from cranial and spinal radiation, as well as total-body irradiation used for conditioning for hematopoietic cell transplantation, are also known to be associated with the development of hypothyroidism. These radiation exposures lead to hypothyroidism as a result of a direct impact of radiation on the thyroid gland. Cranial radiation may also cause central hypothyroidism by impairing the function of the pituitary gland and/or the hypothalamus, if the dose exceeds 30 Gy.

Screening

The diagnostic evaluation of thyroid dysfunction relies on history and physical examination, as well as annual thyroid function tests (free thyroxine, thyroid-stimulating hormone). Survivors with abnormal exams or screening tests are referred to an endocrinologist for consideration for hormone replacement therapy.

METABOLIC SYNDROME

There is emerging evidence to indicate that cancer survivors are at a higher risk for metabolic syndrome [53, 54]. Metabolic syndrome is a cluster of disorders related to insulin resistance that includes central obesity, elevated plasma glucose, dyslipidemia, hypertension, and a prothrombotic and proinflammatory state [55]. Growth hormone deficiency has emerged as a contributor to central obesity and related metabolic disorders, including insulin resistance and dyslipidemia. Preliminary evidence indicates that long-term growth hormone deficiency may be associated with adverse cardiovascular and diabetes risk profiles as a consequence of cranial radiation [56].

HEALTH CARE USE BY YOUNG ADULT SURVIVORS OF CHILDHOOD CANCER

Health care use by a large cohort of long-term survivors of childhood cancer revealed that, whereas 87% of the survi-

Table 2. Components of a comprehensive treatment summary

Essential elements	Details
Demographics	Name, date of birth, treating institution, treatment team
Cancer diagnosis	Date, site(s), stage
Medical history	Hereditary/congenital history, major medical events (in addition to cancer diagnosis)
Relapse(s)	Date(s) and site(s), if applicable
Subsequent malignant neoplasms	Date(s), types, if applicable
Protocol(s)	Title(s)/number(s), dates initiated and completed
Completion of therapy	Date
Chemotherapy	Names and administration routes for all agents; cumulative dose (in mg per m^2) and age at first dose for anthracyclines; determination of intermediate/high dose ($\geq 1,000$ mg/m^2) versus standard dose ($<1,000$ mg/m^2) for cytarabine and methotrexate; cumulative doses, if known, should be recorded for all agents, particularly for alkylators and bleomycin
Radiation	Dates, type, fields, total dose, number of fractions/dose per fraction
Surgical procedures	Type(s), date(s), site(s), laterality (if applicable)
Hematopoietic cell transplant	Type(s), date(s), history of chronic graft versus host disease

vors reported general medical contact within the past 2 years, and 72% reported a general physical examination within the same time period, only 42% reported a cancer-related visit, and only 19% reported a visit to the cancer center [57]. Furthermore, cancer-related visits declined with time since diagnosis, placing the burden on the general practitioner for providing ongoing care of these survivors. Factors associated with no contact with the health care system by these survivors included a lack of health insurance, male gender, and a lack of concern about future health.

DELIVERING SURVIVORSHIP CARE

Childhood cancer survivors, an especially high-risk population, seek and receive care from a wide variety of health care professionals, including oncologists, medical and pediatric specialists, surgeons, primary care physicians, gynecologists, nurses, psychologists, and social workers. Providing appropriate health care for survivors of cancer is emerging as one of the major challenges in medicine. The challenge arises because of the heterogeneity of this patient population treated with numerous therapeutic modalities in an era of a rapidly advancing understanding of late effects. The Institute of Medicine has recognized the need for a systematic plan for lifelong surveillance that incorporates risks based on therapeutic exposures, genetic predisposition, health-related behaviors, and comorbid health conditions [2]. Optimal health care delivery to this unique population requires the establishment of necessary infrastructure including several key components [58]: (a) longitudinal care using a comprehensive multidisciplinary team approach; (b) continuity, with a single health care provider coordinat-

ing needed services; and (c) an emphasis on the whole person, with sensitivity to the cancer experience and its impact on the entire family.

Although the number of childhood cancer survivors is rapidly increasing, health care professionals outside academic centers are likely to see only a small number in their practice, and because of the heterogeneity of treatments received, there will likely be little similarity in their required follow-up care. It is increasingly apparent that primary care physicians are generally unfamiliar with the risks and health care problems of childhood cancer survivors. There is a veritable absence of information regarding this population in the primary care–based literature [58]. This is driven in part by the fact that adult survivors of childhood cancer represent a small fraction of a primary cancer physician's practice [59].

Ideally, a multidisciplinary team approach needs to be used in addressing the needs of this population, and academic settings allow for the establishment of such specialized teams. Most long-term follow-up centers have a core team consisting of a pediatric oncologist, advanced practice nurse, and psychosocial support, with additional optional subspecialist support in the form of endocrinology, cardiology, pulmonology, etc. Many of these long-term follow-up clinics are located within the pediatric unit. Although a pediatric environment may not be the most ideal venue for providing follow-up care to adolescent and young adult cancer survivors, it is often necessary because of logistic or financial constraints. Some pediatric oncology centers have implemented transition models, in which the care of adolescent and young
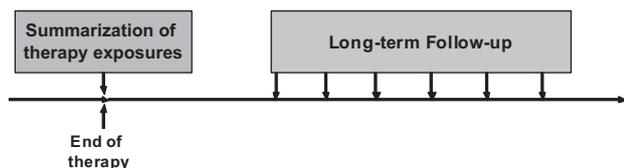
Figure 1. Comprehensive follow-up of cancer survivors.

Figure 2. Childhood cancer survivorship: future directions.

adult survivors is provided by a more age-appropriate provider, usually after a period of joint care. The aim of transition to adult health care is to enable every survivor to maintain the best possible physical health and achieve their full psychosocial, educational, and vocational potential [60]. This model is well established in the transitional care of adolescents or young adults with various chronic disorders [61]. The wide range of complications that might occur during long-term follow-up of childhood cancer survivors has resulted in the development of specialized oncology-led transition programs [62], although other long-term follow-up programs have relied on follow-up by nonspecialist primary care providers [63].

However, a paucity of such specialized long-term follow-up centers and their limited geographic access make these centers an option only for survivors who live nearby or who can afford the time and expenses in order to travel to a distant center. Therefore, finding ways to educate survivors and their local health care providers regarding needed follow-up is a priority. There is also a critical need to develop targeted education for primary care physicians and survivors.

The COG has developed a resource guide to assist institutions in establishing and enhancing long-term follow-up programs and services for childhood cancer survivors. The *Long-Term Follow-Up Program Resource Guide* offers a broad perspective from a variety of long-term follow-up programs within the Children's Oncology Group and can be downloaded from http://www.survivorshipguidelines.org.

Regardless of the setting for follow-up, the first step in any evaluation is to have at hand an outline of the patient's medical history and, most importantly, a treatment summary, with inclusion of the elements listed in Table 2. Once completed, the treatment summary allows the survivor or their health care provider to interface with the COG guidelines to determine recommended follow-up care. Before the long-term survivor of childhood cancer graduates from a pediatric oncologist's care, this treatment record and possible long-term problems should be reviewed with the family and, in the case of an adolescent or young adult, with the patient. Correspondence between the pediatric oncologist
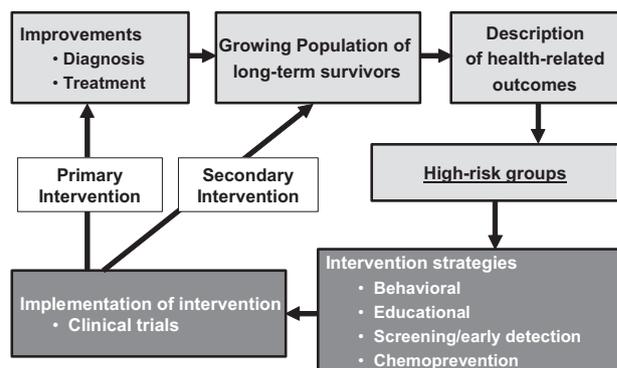
and subsequent caretakers should address these same issues.

CONCLUSIONS AND FUTURE DIRECTIONS

The growing population of childhood cancer survivors carries a significant burden of morbidity, necessitating comprehensive long-term follow-up of these survivors. This follow-up should ideally begin at the completion of active therapy, with a documented summarization of therapeutic exposures that dictates the use of recommendations within the long-term follow-up guidelines, thus ensuring standardization of care received by survivors (Fig. 1). However, many barriers prevent effective follow-up—the most fundamental barrier being the lack of knowledge of long-term survivors and the primary care physicians caring for them. Shortcomings of the health care system are also potential barriers to long-term follow-up, including logistical issues such as a lack of capacity within centers, training and educational deficiencies, and ineffective communication between pediatric oncologists and primary care physicians that subsequently provide the large bulk of the follow-up. Finally, a major obstacle faced by the long-term survivors of childhood cancer in the U.S. is associated with difficulties in obtaining affordable health insurance that may make it impossible for survivors to seek and obtain appropriate long-term care, even if they are aware and willing [64].

Improvement in childhood cancer diagnosis and treatment with the resultant growing population of survivors has also resulted in increasing emphasis on research focusing on adverse health-related outcomes and identification of high-risk groups (Fig. 2). Appropriate surveillance will facilitate timely identification and appropriate management of incipient or established late effects, and reduce the morbidity and mortality associated with these complications. However, the long-term costs and benefits of surveillance,

early detection, and management need further investigation.

Attention also needs to focus on the development of intervention strategies, such as behavior modification, educational interventions, screening for early detection of late effects, and chemoprevention. Execution of these intervention strategies in the setting of clinical trials would allow us to understand the impact of the specific interventions in terms of early detection, with an overall reduction in morbidity and mortality and an ultimate improvement in the overall quality of life of childhood cancer survivors.

AUTHOR CONTRIBUTIONS
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Cancer Survivorship: A Pediatric Perspective

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