Late Morbidity After Successful Treatment of Children with Cancer

Smita Bhatia, MD, MPH, and Louis S. Constine, MD†*

Abstract: Over the last 4 decades, there has been a tremendous improvement in survival of children diagnosed with cancer, with 5-year survival rates now averaging 80%. The rapidly growing population of childhood cancer survivors creates an obligation to understand the health and well being of these individuals. Use of cancer therapy at an early age can produce a large burden of morbidity, as demonstrated quite conclusively by the fact that approximately two thirds of these survivors will experience at least one late effect, and approximately 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, cardiopulmonary compromise, endocrine dysfunction, renal impairment, gastrointestinal dysfunction, musculoskeletal sequelae, and second cancers, are related not only to the specific therapy used, but may also be determined by individual host characteristics. This review provides an update of the known late effects observed in childhood cancer survivors to provide the rationale for evaluation of specific long-term problems in this growing population of individuals at risk for chronic health conditions.

Key Words: childhood cancer, survivorship, long-term sequelae, chronic health conditions, screening recommendations

(*Cancer J* 2009;15: 174–180)

Effective risk-based therapy for childhood cancer has been the cornerstone of the tremendous progress in survival over the last 4 decades, with 5-year survival rates now at 80%.[1] This has resulted in a growing population of childhood cancer survivors—an estimated 300,000 survivors in the United States[2]—creating an obligation to increase the awareness within the healthcare community of the health of this vulnerable population. Treatment of childhood cancer can potentially be associated with a spectrum of long-term sequelae, such as impairment in growth and development, cognitive dysfunction, cardiopulmonary compromise, endocrine dysfunction, musculoskeletal sequelae, and second cancers. It has been conclusively demonstrated that long-term survivors of childhood cancer carry a high burden of morbidity; in fact, one-third of the survivors report severe or life-threatening complications 30 years after diagnosis of their primary cancer.[3] A recent study has demonstrated that long-term survivors of childhood cancer are at an 8.4-fold increased risk of premature death when compared with an age-matched and sex-matched general population, with increases in cause-specific mortality seen for deaths due to second cancers, cardiac, and pulmonary causes.[4] The following sections will provide an update on late effects occurring in childhood cancer survivors, and the relationship between these effects and individual therapeutic exposures to suggest reasonable starting points for surveillance of specific long-term problems, and the challenges faced in that arena (Table 1). Specific recommendations for monitoring based on therapeutic exposure are delineated within the *Children's Oncology Group (COG) Long-Term Follow-Up Guidelines* (www.survivorshipguidelines.org)[5] and are summarized for each late effect in the following sections.

From the *Department of Population Sciences, City of Hope National Medical Center, Duarte, CA; and †Departments of Radiation Oncology and Pediatrics, University of Rochester Medical Center, Rochester, NY.

Reprints: Smita Bhatia, MD, MPH, Department of Population Sciences, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010. E-mail: sbhatia@coh.org.

ISSN: 1528-9117/09/1503-0174

SECOND CANCERS

Data from large studies have demonstrated that childhood cancer survivors are at a 6-fold increased risk of developing a second cancer, when compared with the general population, and this risk continues to increase as the survivors age.[6] The magnitude of risk and the type of second cancers substantially differ according to type and dose of therapeutic exposures, and the presence of genetic predisposition. The more commonly reported second cancers 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.[7] A dose-dependent relationship is noted with alkylating agents, which typically cause t-MDS/AML after latencies of 5 to 10 years. Cytogenetic abnormalities in the alkylating agent-associated t-MDS/AML characteristically involve chromosomes 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. Although the risk of solid tumors continues to climb with increasing follow-up, the risk for t-MDS/AML plateaus after 10 years.[8]

Ionizing radiation is associated with several types of cancer, with the risk being highest when the exposure occurs at a younger age.[7,9] The risk increases with the total dose of radiation,[10–13] and with increasing follow-up after radiation.[14] Examples of radiation-associated tumors include breast,[8] lung, and thyroid cancer,[12] brain tumors,[13] and osteosarcoma.[10,15,16] Female patients treated with mantle radiation for Hodgkin lymphoma before the age of 30 years are at a significantly higher risk of developing radiation-related breast cancer, in comparison with those treated in their adult years.[8,17] An increased risk of developing thyroid cancer has been described after radiation therapy for several primary cancers, including Hodgkin lymphoma, acute lymphoblastic leukemia, brain tumors, and after total body irradiation for hematopoietic cell transplantation. Increasing dose of radiation and exposures to radiation at a young age have been identified as risk factors, although a recent study demonstrates a threshold effect, with a decreasing risk at very high doses.[12]

Genetic predisposition may play a role in the development of second cancers, as evidenced by an increased risk among patients with the genetic form of retinoblastoma, further enhanced by radiation therapy. After 40 years, the cumulative incidence of second cancers (including sarcomas, and lung, breast, and bladder cancers) approaches 30%.[18] Furthermore, members of families with Li-Fraumeni syndrome have been reported to be at an increased risk of multiple subsequent cancers, with the highest risk observed among

TABLE 1. Selected Exposure-Based Screening Recommendations*

Therapeutic Exposure	Potential Late Effect	Recommended Screening
Neurocognitive dysfunction		
Radiation involving brain (including total body irradiation) Intrathecal methotrexate Intermediate/high dose IV 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 compromise		
Anthracycline chemotherapy	Cardiomyopathy Subclinical left ventricular dysfunction	Yearly history and physical exam Baseline electrocardiogram Periodic echocardiogram as indicated based on dose and age at exposure
Chest radiation	Cardiomyopathy Left ventricular dysfunction Early-onset atherosclerotic heart disease Valvular disease Pericarditis	Fasting glucose and lipid profile every 2 yr 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 of >300 mg/m^2 or <300 mg/m^2 if combined with radiation potentially impacting the heart
Pulmonary dysfunction		
Carmustine Lomustine Busulfan Bleomycin	Pulmonary fibrosis	Yearly history and physical exam Baseline measure of pulmonary function, including DLCO and spirometry Baseline chest x-ray
Bleomycin	Pulmonary fibrosis Interstitial pneumonitis Acute respiratory distress syndrome	Consider repeat evaluations prior to general anesthesia and as clinically indicated
Radiation impacting the lungs	Pulmonary fibrosis Delayed interstitial pneumonitis Restrictive/obstructive lung disease	
Endocrine dysfunction		
Radiation impacting thyroid	Hypothyroidism (primary or central)	Yearly history and physical exam
Radiation impacting hypothalamic-pituitary axis	Hyperthyroidism Growth hormone deficiency Central adrenal insufficiency Hyperprolactinemia	Yearly thyroid function test (free T4, TSH) 8 am serum cortisol if radiation to HP axis >40 Gy—test yearly for at least 15 yr Prolactin level if positive history for galactorrhea, amenorrhea (females) or decreased libido (males)
Gonadal function		
Alkylating chemotherapy Surgical removal of both gonads Radiation involving 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 (eg semen analysis)
Second cancers		
Etoposide Teniposide Anthracyclines	Acute myeloid leukemia	CBC, platelet, differential yearly for 10 yr after 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 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 mo Mammogram with adjunct MRI yearly beginning 8 yr after radiation or at age 25, whichever comes last
Radiation impacting the colon	Colorectal cancer	Colonoscopy every 5 yr beginning 10 yr following radiation or at age 35, whichever comes last

*Screening recommendations adapted from the *Children's Oncology Group Long-Term Follow-Up Guidelines;* available at www.survivorshipguidelines.org.

survivors of childhood cancer.[19] It, therefore, seems that germline mutations in tumor suppressor genes, such as those occurring in the Li-Fraumeni syndrome, might interact with therapeutic exposures, resulting in an increased risk of second cancers. Similarly, polymorphisms in genes responsible for drug metabolism or transport or those involved in DNA repair may play a critical role in determining susceptibility to the development of second cancers. These questions are currently being addressed systematically by researchers.

Screening

Because second cancers remain a significant threat to the health of childhood cancer survivors, vigilant screening is important for those at risk. Risk for t-MDS/AML usually manifests within 10 years after exposure. Recommendations include monitoring with annual complete blood count for 10 years after exposure to alkylating agents or topoisomerase II inhibitors. Most other second cancers are associated with radiation exposure. Screening recommendations include careful annual physical examination of the skin and soft tissues in the radiation field with radiographic or other cancer screening evaluations as indicated. Because outcome after breast cancer is closely linked to stage at diagnosis, close surveillance resulting in early diagnosis should confer survival advantage.[20] Mammography, the most widely accepted screening tool for breast cancer in the general population, may not be the ideal screening tool in isolation for radiation-related breast cancers occurring in relatively young women with dense breasts; hence, the recommendations by the American Cancer Society include the use of adjunct screening with magnetic resonance imaging.[21] Thus, specialized recommendations for females who received radiation with potential impact to the breast (ie, radiation doses of 20 Gy or higher 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 magnetic resonance imagings beginning 8 years after radiation or at age 25 (whichever occurs later). Screening of those at risk for early-onset colorectal cancer (ie, radiation doses of 30 Gy or higher to the abdomen, pelvis, or spine) should include colonoscopy every 5 years beginning at age 35 years or 10 years after radiation (whichever occurs last).

NEUROCOGNITIVE SEQUELAE

Neurocognitive sequelae occur as a consequence of whole brain radiation, high-dose systemic methotrexate and/or cytarabine, or intrathecal methotrexate. Risk factors include increasing radiation dose, young age at the time of therapy, treatment with both cranial radiation and systemic or intrathecal chemotherapy, and female gender.[22] Severe deficits are most frequently noted in children with brain tumors, especially those who were treated with radiation therapy, and in children who were younger than 5 years of age at the time of treatment. Neurocognitive deficits usually become evident within 1 to 2 years after radiation and are progressive in nature.[23] 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-induced or chemotherapy-induced destruction in normal white matter partially explaining intellectual and academic achievement deficits.[24] Children in the younger age groups treated with cranial radiation may experience significant drops in IQ scores. Aside from local irradiation of central structures, local tumor effects and initial surgical intervention also play a role in neurocognitive impairment.[25] Utilization 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-matched and sex-matched siblings.[26] Management of acute lymphoblastic leukemia (ALL) with chemotherapy alone has become the standard of care. There is evidence of subtle long-term neurocognitive deficits in survivors of childhood ALL after treatment with chemotherapy alone. These deficits are restricted to attention, executive function, and complex fine-motor functioning, whereas global intellectual function is relatively preserved. Younger patients and females are at higher risk for these deficits.[27,28]

Screening

A baseline neuropsychological evaluation is recommended for patients who received therapy that may potentially impact neurocognitive function. This should be repeated as clinically indicated and at key transition points (transitioning from grade school to middle/junior high school), as well as annual assessment of their vocational or educational progress.[29]

CARDIOVASCULAR FUNCTION

Chronic cardiotoxicity usually manifests itself as cardiomyopathy, pericarditis, and congestive heart failure. Anthracyclines (eg, doxorubicin, daunomycin, and idarubicin) are well-known causes of cardiomyopathy.[30,31] The incidence of cardiomyopathy is dose dependent and may exceed 30% among adult patients who received a cumulative anthracycline dose in excess of 600 mg/m^2. With a total dose of 500 to 600 mg/m^2, the incidence is 11%, falling to less than 1% for cumulative doses less than 500 mg/m^2.[30] However, a lower cumulative dose of anthracyclines may place children at increased risk for cardiac compromise. A cumulative dose of greater than 250 mg/m^2 (along with radiation to the heart) was associated with a higher risk of clinical heart failure (cumulative incidence, 20% at 25 years) compared with a cumulative dose lower than 250 mg/m^2 (5%).[32] Chronic cardiac toxicity associated with radiation alone presents as pericardial effusions or constrictive pericarditis, usually with radiation doses exceeding 40 Gy.[33] Restrictive cardiomyopathy, characterized by diastolic dysfunction, predominates in childhood cancer survivors who were treated with radiation alone, whereas systolic dysfunction dominates in survivors who also received anthracyclines. Coronary artery disease has been reported after radiation to the mediastinum, with a cumulative risk of 21% at 20 years after radiation.[34]

Screening

Patients exposed to anthracyclines 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.[35] In fact, asymptomatic cardiotoxicity can be demonstrated in patients who have normal clinical assessments, and abnormalities can be linked to lower self-reported health and New York Heart Association cardiac function scores.[36] Survivors who received radiation to fields impacting the heart also need monitoring for potential early-onset atherosclerotic heart disease, valvular disease, and pericardial complications.

PULMONARY FUNCTION

Pulmonary radiation can result in pulmonary fibrosis and pneumonitis. Clinically apparent pneumonitis with cough, fever, or dyspnea occurs in 5% to 15% of patients who received 10 to 20 Gy in standard fractions to more than 30% of the lung. Risks of similar magnitude are observed for subjective evidence of pulmonary compromise, such as a perceived reduction in exercise capacity.[37] After hematopoietic cell transplantation, both restrictive and obstructive

lung disease, including bronchiolitis obliterans are well described.[38] Obstructive changes have also been reported after conventional radiation therapy. Very young children who are treated with radiation to their thorax can manifest restrictive changes due to impaired growth of the rib cage.

Interstitial pneumonitis and pulmonary fibrosis have been reported in children after exposure to bleomycin[39] in a dose-dependent fashion above a threshold cumulative dose of 400 units/m^2, and exacerbated by concurrent or previous radiation therapy. Carmustine-related and lomustine-related pulmonary toxicity is also dose related. Cumulative carmustine doses >600 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 (eg, asthma), cigarette smoking, chronic graft versus host disease, the effects of chronic pulmonary involvement by tumor or reaction to tumor, and increased oxygen concentrations associated with general anesthesia.[40]

Screening

Monitoring includes assessment of symptoms such as chronic cough or dyspnea on annual follow-up. Risks of smoking and exposure to second hand smoke should be discussed. Pulmonary function tests (including DLCO and spirometry) and chest x-ray are recommended as a baseline on entry into long-term follow-up for patients at risk, repeated as clinically indicated in symptomatic patients. Repeat evaluation should also be considered before general anesthesia for those at risk.

GROWTH

Severe growth retardation (standing height $<$5th percentile) has been observed in one third of childhood brain tumor survivors and in 10% to 15% of patients treated on certain antileukemia regimens.[41,42] This is primarily because of hypothalamic damage with impaired secretion of growth hormone releasing factor. The effects of cranial irradiation are age related, with children less than 8 years of age at the time of cranial irradiation at risk for adult height below the third percentile.[41] Treatment with growth hormone before 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. Existing data suggest that treatment with growth hormone is not associated with an increased risk of central nervous system tumor progression or recurrence, or of leukemia (either new or recurrent).[43]

Survivors of childhood ALL are also at increased risk for adult short stature, including those treated with chemotherapy alone. However, the risk is highest for those treated with cranial and craniospinal radiotherapy at a young age.[44]

Screening

Monitoring of long-term survivors for growth problems relies on the use of standardized curves available online (www.cdc.gov/growthcharts), with endocrine consultation for children whose height is less than third percentile, crosses 2 or more percentiles, or whose growth velocity is $<$4 to 5 cm/year.

GONADAL FUNCTION

Male Gonadal Function

All 3 therapeutic modalities [radiation, surgery, and chemotherapy (alkylating agents)] 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 after fractionated exposures of 0.1 to 6 Gy. Patients treated with less than 3 or 4 Gy can recover spermatogenesis. Radiation therapy may also be toxic to Leydig cells, although at doses higher than those which are toxic to germ (Sertoli) cells. As summarized by Sklar,[45] Leydig cell damage is dose dependent and inversely related to age at treatment. Boys treated prepubertally or peripubertally with $\geq$20 Gy for testicular leukemia, in addition to suffering germ cell depletion, are at high risk of delayed sexual maturation associated with decreased testosterone levels, despite increased luteinizing hormone (LH) levels. Hormonal function in adolescent and young adult male testes is relatively radioresistant, and fractionated doses greater than 30 Gy to the testes may induce Leydig cell failure in only about 50%.

Of course, bilateral orchiectomy results in infertility, as well as testosterone deficiency requiring ongoing hormonal replacement therapy beginning in puberty, in collaboration with an endocrinologist.

Alkylating agents decrease spermatogenesis in a dose-dependent manner. Gonadal damage after cumulative doses of cyclophosphamide lower than 7.5 g/m^2 (or 200mg/kg, as used in hematopoietic cell transplantation) have been shown to be reversible in up to 70% of patients. Chemotherapy effects are less striking on slowly dividing Leydig cells, and may be age related. After exposure to alkylating agents in prepubertal boys, normal pubertal progression and normal adult levels of testosterone can be expected; 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.[46]

Screening

Screening for problems related to male gonadal function include 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 seems to be delayed. Semen analysis should be offered to survivors at risk for infertility. 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 to 2 years.

Female Gonadal Function

Germ cell failure and loss of ovarian endocrine function occur concomitantly in females. Radiation effects are both age and dose dependent. In women older than 40 years at the time of treatment, irreversible ovarian failure is an almost universal result when 4 to 7 Gy of conventionally fractionated radiation is delivered to both ovaries. Prepubertal ovaries are relatively radioresistant, and despite higher doses (12–20 Gy), primary amenorrhea and delayed puberty eventually occurred in only 68% of patients treated at a mean age of 6.9 years.[47] Secondary amenorrhea resulting from such modest doses seems to be reversible within several months to 4 years in 50% to 60% of patients.[48]

Total body irradiation (10 Gy single fraction) has been associated with primary amenorrhea and secondary sexual characteristics absent in most patients treated before puberty and followed

up for as long as 10 years.[49] However, others have reported normal pubertal progression, although with elevated FSH levels, after total body irradiation during early childhood.[50] As with standard radiation, increasing age at the time of total body irradiation has been found to predict ovarian failure.[51] Premature menopause has also been reported in the setting of hematopoietic cell transplantation.[49]

Ovarian failure has been associated with alkylating agents and the toxicity is dependent on dose and age at exposure. After myeloablative doses of alkylating agents, including busulfan and cyclophosphamide, permanent ovarian failure can be expected at all ages.[52] For survivors who retain normal ovarian function after cancer therapy, there is an increased risk of premature menopause, especially among those who received high doses of alkylating agents and abdomino-pelvic radiation.[53]

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 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), 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 (eg, irregular menses, amenorrhea, hot flashes, and vaginal dryness).

CHRONIC HEALTH DISEASE IN CHILDHOOD CANCER SURVIVORS—BURDEN OF MORBIDITY

Several investigators have described the burden of morbidity by quantifying the chronic medical problems experienced by this population.[54–56] These reports suggest that approximately two thirds of the 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 these findings reported in the previous studies in a large cohort of 10,397 adult survivors of childhood cancer. Overall, the survivors were at an 8-fold higher risk of reporting a severe chronic health condition, when compared with age-matched and sex-matched siblings. Individuals identified to be at highest risk included those treated for Hodgkin disease or brain tumors, and those exposed to chest radiation and anthracyclines.

These studies demonstrate quite conclusively that the implications of cure are not trivial, and that 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 survivors into adult life. There is also an urgent need for the survivors and their healthcare providers to be aware of the "at risk" populations to develop appropriate surveillance strategies.

KNOWLEDGE ABOUT PAST DIAGNOSIS AND TREATMENT

An investigation of the childhood cancer survivors' knowledge about past cancer diagnosis and treatment demonstrated that only 72% of the cancer survivors were able to accurately and precisely report their cancer diagnosis.[57] Furthermore, only 70% of the childhood cancer survivors exposed to radiation could accurately describe the site of radiation. Most importantly, only 35% of the survivors understood that serious health problems could result from past treatment.

HEALTHCARE UTILIZATION BY YOUNG ADULT SURVIVORS OF CHILDHOOD CANCER

Healthcare utilization by a large cohort of long-term survivors of childhood cancer revealed that although 87% of the survivors 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.[58] 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 healthcare system by these survivors included lack of health insurance, male gender, and lack of concern about future health.

DELIVERING SURVIVORSHIP CARE

Childhood cancer survivors seek and receive care from a wide variety of healthcare professionals, including oncologists, specialists, surgeons, primary care physicians, gynecologists, nurses, psychologists and social workers. Providing appropriate healthcare for survivors of cancer is emerging as one of the major challenges in medicine. The challenge arises due to the heterogeneity of this patient population treated with numerous therapeutic modalities in an era of 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 healthcare delivery to this unique population requires the establishment of necessary infrastructure including several key components:[59] (1) longitudinal care utilizing a comprehensive multidisciplinary team approach, (2) continuity, with a single healthcare provider coordinating needed services, and (3) 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, healthcare 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 healthcare problems of childhood cancer survivors. There is a veritable absence of information regarding this population in the primary care-based literature.[59] 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.[60] A recent survey of 8522 long-term cancer survivors demonstrated that although 88.8% of survivors reported receiving some form of medical care, only 31.5% reported care that focused on their prior cancer, which the authors described as "survivor-focused" care. Furthermore, only 17.8% reported survivor-focused care that included advice about risk reduction or discussion or ordering of specific exposure-based screening tests. For example, among patients at increased risk for cardiomyopathy or breast cancer, only 28% and 41% had undergone a recommended echocardiogram or mammogram, respectively.[61] However, paucity of 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 to travel to a distant center. Therefore, finding ways to educate survivors and their local healthcare providers regarding needed follow-up is a priority.

The COG has developed risk based, exposure-related guidelines (*Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*)[5] 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 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 to enhance health promotion in this population with specialized healthcare needs. Examples of specific screening strategies outlined within the COG *Long-Term Follow-Up Guidelines* are summarized in Table 1. The *Guidelines* and the *Health Links* can be downloaded from www.survivorshipguidelines.org.

In addition, 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 COG and can be downloaded from www.survivorshpguidelines.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 healthcare provider to interface with the COG *Long-Term Follow-Up 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 the survivors. 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 healthcare 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 follow-up. Finally, a major obstacle faced by survivors of childhood cancer in the United States is the difficulty in obtaining affordable health insurance making it impossible for survivors to seek and obtain appropriate long-term care, even if they are aware and willing.[62]

Improvement in childhood cancer 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. 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 benefit of surveillance, early detection, and management need further investigation.

Attention also needs to focus on 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 early detection, with an overall reduction in morbidity and mortality and an ultimate improvement in the overall quality of life of childhood cancer survivors.

TABLE 2. Components of a Treatment Summary

Elements	Details
Demographics	Name, date of birth, treating institution
Cancer diagnosis	Date, site(s), stage
Protocol(s)	Title(s)/number(s), dates initiated and completed
Relapse(s)	Date(s) and site(s), if applicable
Second cancers	Date(s), types, if applicable
Completion of therapy	Date
Chemotherapy	Names and administration routes for all agents cumulative dose (in mg per m^2)
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

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