Long-Term Survivors of Childhood Cancer: The Late Effects of Therapy

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Additional information is available at the end of the chapter

Abstract

The overall cure rate for pediatric malignancies is significantly improved to over 75% with an estimated 270,000 survivors of childhood cancer in the United States currently. The achievement of high cure rates for most pediatric malignancies has been accompanied by a growing population of childhood cancer survivors who are at an increased risk for a myriad of health problems resulting from their cancer or its treatment. Some cancer-related complications do not become apparent until several years following cancer treatment. As the survivors of childhood cancers age, the effects of therapy may be exacerbated by effects of aging on organ function. Late effects encompass a variety of detrimental conditions including organ dysfunction, psychosocial complications, and subsequent malignancies that may negatively impact quality of life and may predispose them to early mortality. In contrast to the multitude of publications describing treatment-related sequelae in childhood cancer survivors, relatively few provide specific recommendations for health screening and risk-reduction counseling to guide healthcare providers in monitoring this vulnerable population. In this chapter, we will summarize the evaluation and management of childhood cancer survivors who may be encountered across a wide variety of healthcare settings, salient issues influencing healthcare for childhood cancer survivors, of which guidelines currently available and limitations in current practice.

Keywords: late effects, pediatric oncology, cancer survivors, long-term follow-up

1. Introduction

Over 12,400 children and adolescents younger than 20 years of age are diagnosed with cancer in the United States every year [1]. Survival for many pediatric cancers has improved significantly in the past three decades with improvement in therapies. The surveillance,

epidemiology, and end results data estimate that the overall five-year survival rate among children for all cancer sites combined improved from 58% for patients diagnosed in 1975–1977 to 80% for those diagnosed in 1996–2003 [1].

There were an estimated 388,501 survivors of childhood cancer in the United States as of January 1, 2011, of whom 83.5% are ≥5 years after diagnosis [2]. Frequently, long-term survivors of childhood cancer report late cancer-related effects that diminish quality of life and persisting after cancer treatment may result in premature onset of common diseases associated with aging such as obesity, diabetes mellitus, cardiovascular disease, hypertension, and second cancers [3–5].

Risk-based health care that involves a personalized plan for surveillance, screening, and prevention is recommended to reduce cancer-related morbidity in childhood cancer survivors. However, there are few consensus recommendations and very few specialized centers providing this care. Moreover, to implement this model, the survivor and healthcare provider must have accurate information about cancer diagnosis, treatment modalities, and potential cancer-related health risks to guide screening and risk-reducing interventions. Childhood Cancer Survivor Study (CCSS) data show that approximately half of the approximately 14,000 responding long-term survivors of childhood cancer had not been seen by a physician during the previous 2 years for evaluation of cancer-related problems. A recent survey of Pediatric Oncology Group and Children's Cancer Group member sites reported that 44% of the sites have a mechanism for following adult survivors, but only 15% of the programs have a formal database for these patients [6].

In this chapter, we describe the common late effects based on therapy received for cancer and provide the current evidence regarding guidelines available for long-term follow-up of pediatric cancer survivors. We also address the lacunas in patient and physician education and current evidence regarding interventions to address this to improve the quality of life for pediatric cancer survivors.

2. Late effects of cancer therapy

Late effects are those toxicities related to therapy for cancer that are absent or subclinical at the end of therapy but manifest later. Compensatory mechanisms that initially maintain the function of injured organs may fail with growth, development, and aging. We discuss below the common late effects of cancer chemotherapy in children. **Table 1** summarizes the most common late effects in survivors of childhood cancer. **Tables 2** and **3** summarize some of the common late effects and screening methodology used to monitor and manage them.

2.1. Mortality

Type and intensity of therapy as well as the patient's age at therapy determine not only the overall survival but also the frequency of late effects of cancer therapy [7]. Some studies have shown excessive mortality rates in five-year survivors of childhood cancer [8–12]. The Childhood Cancer Survivor Study (CCSS), a retrospective cohort study initiated in 1994, was

Adverse event category
Alopecia
Ear, nose, and throat
Fatigue
Pain
Pulmonary
Tissue hypoplasia
Urology
Miscellaneous
Ophthalmology
Gastroenterology
Cardiovascular
Angina pectoris/Myocardial infarction
Cardiomyopathy
Nephrologic
Hypertension
Tubular dysfunction
Orthopedic
Amputation/Prothesis/Rotationplasty
Scoliosis/Low back pain
Psychosocial/Cognitive problems
Cognitive problems
Emotional problems
Fertility
Oligospermia/Azoospermia
Metabolic
Obesity
Second tumors
Malignant
Endocrine
Growth hormone deficiency
Thyroid disorders
Panhypopituitarism
Neurologic
Seizures
Motor dysfunction/Hemiparesis
Sensory loss

Table 1. Common adverse events in a cohort of childhood cancer survivors.

Organ	Therapy	Screening test
Musculoskeletal	Radiotherapy(RT)	Physical exam scoliosis exam (annually if growing), X-ray pm
Breast	Mediastinal RT	Breast exam. mammography beginning age 25–30
CNS	Cranial RT	Neurocognitive testing (baseline, q 3-5 yrs pm). MRI (baseline)
Neuroendocrine	Hypothala/mic-pituitary RT	Growm curve q yr. bone age (age 9)
		GH stimulation test
		TSH, Free T4.T3 (baseline q 3-5 yr pm)
		LH FSH. test/est. prolactin (baseline, pm)
		8 am cortisol (baseline, pm)
Cardiac	Anthracyclines mediastinal T-spine RT	ECHO'EKG (baseline for all; q 3-5 yr after anthracycline) Holter q 5 yrs pm (high-dose anthracycline) Stress test/ dobutamine stress echo pm (after RT)
Pulmonary	RT	PFT baseline, q 3-5 yrs pm
	Bleomycin, CCNU/BCNU	
Ovary	Alkylating agents	Menstrual 'Hx annually
	RT	LH FSH estradiol baseline (age>12) and pm
Testes	Alkylating agents	LH FSH. testos baseline (age >12) and pm
	RT	Spermatoanalysis pm
Renal	Cisplatin (carboplatin),	Creatinine, Mg, q 1-2 yrs
	Ifosfamide,	Ceatinine clearance baseline and q 3-5 yrs pm
	RT	Urinalysis (RT. ifosfamide)
		Ifosfamide: serum phosphate. urine glucose, protein
Bladder	Cyclophosphamide,	Urinalysis annually for heme
	Ifosfamide. RT	
Thyroid	RT to neck, mediastinum	TSH, FreeT4,T3q yr X 10
		Scans (U/S) pm
Liner	6-MP$_7$MTX,Act-d, RT	Liver function tests every 1–3 years
GI	Intestinal RT	Stool guiac q yr, colonoscopy (ACS)

Table 2. Example of screening methodology for late effects specific to treatment received.

designed to study late effects among long-term survivors of childhood cancer. It showed a 10.8-fold excess in overall mortality. Risk of death was significantly higher in females, those with an initial diagnosis of leukemia or brain tumor and those diagnosed with cancer before they turned 5 years old. Sixty percent of deaths were from recurrence of the original cancer that was the leading cause of death. Statistically significant excess mortality rates were seen due to various causes shown in **Table 4**. Treatment-related associations were reported for cancer mortality (radiation, epipodophyllotoxins, alkylating agents), cardiac mortality (chest irradiation), and other deaths (radiation, anthracyclines). No excess mortality was seen for external causes [13].

Chemotherapy

If patient received:

Actinomycin or antimetabolite	ALT	Periodically
	Bone densitometry	Optional
Aminogtycoside, high dose	Audiology	Optional
Anthracycline	Echocardiogram	Every 3 years
($\geq$300 mg/m^2, or anthracycline administered prior to age 1 year	EKG	Optional
or $\geq$200 mg/m^2 with radiation involving the chest)		
BCNU, CCNll, bleoraycin	CXR	Baseline
	Pulmonary function tests	Baseline and as needed
Cisplatin	BUN, creatinine, magnesium	Annually
	Audiology	Optional
Corticosteroids	Bone deisitometry	Optional
Cyclophosphamide	FSH, LH, estradiol	Optional
	Semen analysis	Optional
	Urinalysis	Annually
	Urine cytology	Optional
Cyclosporine	Bone densitometry	Optional
Etoposide	CBC with platelets and differential	Annually
Nitrogen mustard, procarbazine	CBC with platelets and differential	Annually
	FSH, LH, estradiol	Optional
	Testosterone	Optional
	Semen analysis	Optional
Vinciistine	ALT	Periodically

Radiation therapy

If patient received;

Cranial or craniospinal radiation	Cataract screening	Periodically
	Audiology	Optional
	Dental screening	Annually
	TSH, Free T$_4$	Annually
	Lipid profile	Annually
	Bone densitometry	Optional
Mande radiation	TSH	Annually
	Lipid profile	Annually

	Mammogram (females)	Start 8 years after radiation, then annually
	Plain radiographs of irradiated site	Optional
Abdominal radiation	Hernoccult screening	Annually
	Urinalysis	Annually
Pehic radiation	FSH.LH	Optional
	Semen analysis	Optional
High-dose radiation of the Hunk or extremities	Plain radiographs of the irradiated sites	Optional
Surgery		
If patient received:		
Nephrectomy	BUN, creatinine, urinalysis	Annually
Splenectomy	Verify immunizations	Annually
	Antibiotic prophvlaxis	Optional

Table 3. Organ-specific late effects of cancer therapy and screening methodology.

-Recurrence

-Treatment-related consequences

Subsequent neoplasm

Lip, oral cavity, pharynx, lung

Digestive organs and peritoneum

Bone and articular cartilage

Connective and other soft tissue

Melanoma and other skin

Breast

Genitourinary organs

Brain and other parts of nervous system

Lymphatic and hematopoietic

Other subsequent cancer

Cardiac

Ischemic heart disease

Cardiomyopathy

Congestive heart failure

Other cardiac

Pulmonary

Pulmonary fibrosis

Other pulmonary

Other sequelae

Infectious disease

Other sequelae

-Nontreatment-related causes of death

External causes

Motor vehicle accident

Other accident

Suicide

Homicide

Medical conditions

Human immunodeficiency virus

Pneumonia

Other bacterial/viral infection

Heart disease

Cerebrovascular disease

Other medical condition

Table 4. Specific causes of mortality in Childhood Cancer Survivor Study cohort.

2.2. Growth and development

The effects on growth and development are dependent on dose and the developmental process of the organ in question. Therapy for the treatment of malignancy may interfere with development in terms of physical growth, neurocognitive growth, musculoskeletal growth (hypoplasia), and, ultimately, pubertal development.

2.3. Physical growth

Growth is often impaired in children with active cancer and those undergoing intense therapies due to hypermetabolic states, the effects of chronic disease, and poor nutrition. After the completion of therapy, many children experience a growth spurt and normalization of growth but specific therapies may interfere with this [14].

2.3.1. Hypoplasia

Localized radiotherapy affects skin and musculoskeletal growth causing cosmetic concern in radiation-treated survivors. Asymmetric radiation fields result in differential growth of the radiated versus nonirradiated tissue. Functional effects, such as muscle or back pain due to

radiation-induced scoliosis, can occur. Hypoplasia is not apparent at the end of therapy but becomes manifest with growth, particularly during the pubertal spurt. Particular sensitivity of adipose tissue to radiation may lead to asymmetric fat distribution with weight gain any time in life. Breast asymmetry occurs after unilateral chest radiotherapy prior to maturity. Doses of 20 Gy may stop breast development completely, whereas 10 Gy to the breast bud may cause hypoplasia [15, 16]. Lactation may not be possible for women [17].

2.3.2. Linear growth effects

Cranial irradiation affects linear growth by its effect on the hypothalamic-pituitary axis. The effect is dependent on dose and age. Patients treated with large doses of whole brain radiotherapy are likely to have growth hormone deficiency requiring hormone replacement. Growth velocity after lower doses of radiotherapy may proceed normally until puberty, at which time the classic "growth spurt" may be impaired [18]. Early onset of puberty is common after cranial radiation, reducing final height [18] and this effect is more pronounced if the child is younger at the time of radiation [19]. Childhood cancer survivors treated with cranial radiation may have a higher body mass index [20], which is inversely related to the age of puberty [21, 22]. After spinal radiotherapy, the effect of aberrant growth hormone release and early puberty may be worsened by vertebral stature loss after spinal irradiation [23]. These effects can be mitigated prior to closure of the epiphyses. Close monitoring of growth is needed but may not be sufficient. The role of growth hormone stimulation beginning shortly after completion of therapy and inhibition of the pubertal spurt to prolong the potential growth phase is being assessed [19].

2.3.3. Intellectual development

Intellectual outcome after the completion of therapy is important for integration successfully into society after completion of therapy. Central nervous system (CNS) radiotherapy or high-dose chemotherapy that achieves sufficient CNS levels for the prevention of meningeal leukemia may result in cognitive deficits [24]. Impairment of memory, attention, and visual perceptual motor skills result in problems with language, reading, and arithmetic and poor academic achievement [24, 25]. Brain injury may become more apparent years after the completion of therapy and intellectual growth suffers over time [26]. The severity of the effect is determined by both dose of therapy and the time at which it was given. Higher doses [>36 Gy] have significant deficits that virtually always require special educational efforts [27]. Cognitive effects of radiation on infant development are profound and hence high doses may be deferred until after age two [27]. Preschool children receiving doses in the range of 18–24 Gy of cranial radiotherapy often require special educational resources, and older children may have difficulties with complex systems such as a new language or high-level mathematics [27]. At lower doses of radiation, children are likely to remain within the mainstream education efforts but may need help to achieve maximal success. Significant doses of intrathecal chemotherapy may have similar effects [27]. Most survivors enter college at the same rates as siblings, except for those receiving 24 Gy or treated as preschoolers; however, an overall need for special education exists and occupational success may not be equal to that of siblings [28].

2.4. Organ specific effects

2.4.1. Gonadal toxicity and pubertal development

It is tough to clinically assess the extent of treatment-induced gonadal damage suffered during childhood. Anticipatory guidance can be given based upon reported experience. Close monitoring throughout puberty is vital as initial pubertal development may proceed even with severe gonadal injury as a result of adrenal corticoid hormones. Long delays in assessment may have severe social consequences.

Alkylating agents are known for inducing infertility; little gonadal toxicity is noted after the antimetabolites, vinca alkaloids, anthracyclines, bleomycin, or platinum derivatives. Sertoli cells are more sensitive than Leydig cells to radiation and alkylating agents [29, 30]. Young boys may proceed with normal masculinization, potency, and libido even with azoospermia due to preservation of Leydig cells. Testosterone levels as well as pubertal development should be assessed for recipients of high-dose chemotherapy. By late puberty, testosterone deficiency should be treated to normalize masculinization. Even though ovaries are less sensitive than testes to gonadotoxic agents [30, 31], an affected female child may experience pubertal delay and amenorrhea. Hormone replacement to preserve feminization and periods may be needed. Another reason for treating estradiol deficiency is the prevention of osteoporosis and early coronary artery disease. Cranial radiation at higher doses can also result in secondary gonadal insufficiency by impairment in LH/FSH production and secretion. In those brain tumor patients receiving hypothalamic-pituitary axis radiation as well as alkylating agents (e.g., BCNU, CCNU), direct gonadal effects as well as secondary gonadal insufficiency are seen [31].

Reversibility is dependent on dose of gonadal radiation or alkylating agents. Ovarian function is unlikely to recover long after the immediate therapy due to loss of ova. The testis is more sensitive to cytotoxic therapies than the ovary, but late recovery (2–12 years after radiotherapy) has been reported [32]. Prediction of fertility in an adult woman may be indicated by evaluation of her menstrual cycle. The same dose of drug is more likely to affect an older woman than a younger one [33]. Although young women may not become amenorrheic after cytotoxic therapy, the risk of early menopause exists. Direct radiotherapy to the ovaries also causes infertility. Oophoropexy is commonly offered to prevent infertility in women whose ovaries would otherwise remain in the radiation field. Lower doses or even scatter of radiation within the small body of an infant or toddler may have profound effects. Oophoropexy is not an option in this population since the small torso does not offer a sanctuary for the ovaries. Flank radiotherapy such as for Wilms' tumor does not affect the ovaries but may result in reduced fetal size by effects on the uterine muscle and vasculature [34, 35].

Male sterility is usual after approximately 10 g/m^2 of cyclophosphamide. The prepubertal state offers, at best, only limited protection to testes treated with cyclophosphamide [36]. Ten percent of men will become sterile after one to two cycles of MOPP chemotherapy commonly used in Hodgkin's disease in the past, while 80–100% are sterile after six courses [36]. Low doses (2–3 Gy) of radiotherapy result in azoospermia in all males, with late recovery noted occasionally after a period of years.

New reproductive technologies have improved outcomes for infertile cancer survivors. Sperm banking, the ability to inseminate ova with only small numbers of spermatozoa, and artificial insemination are the most frequently used approaches for sterile male survivors. Female survivors have more limited options. Storage of ova is being researched actively [37].

Hyperprolactinemia is another easily treatable and fairly common but often missed effect of hypothalamic-pituitary irradiation that may impair fertility as well as growth and libido [38]. Appropriate endocrinologic interventions with dopamine agonists can be helpful.

2.4.2. Cardiac

Anthracyclines are important in the treatment of most childhood cancers. Unfortunately, cardiac damage is most pronounced after treatment with anthracyclines, with additive effects of cyclophosphamide and radiation therapy. Anthracyclines cause decrease in myocyte number by causing myocardial cell death. Residual myocytes hypertrophy in a compensatory manner [39]. Cardiac injury during or shortly after the completion of chemotherapy may progress, stabilize, or improve after the first year [40]. Patients with reduced cardiac function within 6 months of completing chemotherapy are at increased risk for the development of late cardiac failure [41].

Myocardial injury can be detected with sensitive screening tests, even after a cumulative dose of 45 mg/m^2 [42, 43]. Unfortunately, these tests are not routinely available. Initial improvement in cardiac function from compensatory changes may diminish with later stressors in life. For example, myocardial depressants such as alcohol or increased afterload brought on by exercise, growth spurts, or pregnancy may induce late cardiac failure. Isometric exercise may increase the risk for late cardiac failure, particularly in after neck or mantle radiotherapy [44]. There is evidence to suggest that there is a continuum of injury that will manifest itself throughout the lives of these patients [45]. Many pediatric cardiologists may advise patients to avoid excessive alcohol intake and isometric exercises such as weight-lifting. Those who have received the higher doses of anthracyclines need the closest monitoring and counseling.

Pregnancy, a time of increased cardiac demand, is a dangerous period for anthracycline-treated women. These women need to be evaluated by a cardiologist. Obstetricians should be made aware that these women may have limited ability to compensate for the increased cardiac output of pregnancy. Careful monitoring during pregnancy and the postpartum period is essential. Women with significantly limited cardiac reserve may be advised that pregnancy may carry unacceptable risk [44].

Severe cardiac effects of radiation may be noted including valvular damage, pericardial thickening, and ischemic heart disease [46]. Patients have an increased risk of both angina and myocardial infarction years after radiotherapy for Hodgkin's disease [47], with a relative risk of 3.1 for cardiac death with Hodgkin's disease [48]. This risk was noted in those receiving >30 Gy of mantle irradiation and was greatest for those treated before 20 years of age [49]. The use of anteriorly weighted ports, reduction in total tumor and daily fraction dose, and cardiac shielding are some of the techniques being used to reduce the effects of radiation [49].

2.4.3. Pulmonary

The effects of chemotherapy on the lungs may be lethal or may improve gradually. However, pulmonary function tests may not return to normal, and there may be slow clinical decline. Long-term outcome depends on severity of the acute injury, the extent of compensation, and the likelihood of decompensation. It is reported that 35% of children treated for brain tumors with nitrosourea and radiotherapy died of pulmonary fibrosis, 12% within 3 years and 24% after a symptom-free period of 7–12 years [50]. Therefore, the recommended dose limit of nitrosourea's in children has been lowered from 1500 to 750 mg/m^2 but the late effects of this lower dose need to be assessed [50]. Some chemotherapy drugs like cyclophosphamide when used orally may cause restrictive lung disease by inhibition of chest wall growth. This effect may become apparent as late as 7 years after the completion of therapy [51]. It has not been reported after modern intravenous cyclophosphamide regimens. Patients treated with bleomycin may experience pulmonary insufficiency from interstitial pneumonitis characterized by a reticulo-nodular pattern [52, 53]. Even after the completion of therapy, the risk for overt decompensation remains for at least 1 year. A recent study by Kung et al. has noted that 22% of Hodgkin's disease patients with normal pulmonary function tests at the end of therapy developed abnormalities with follow-up of 1–7 years [54, 55]. In long-term follow-up, pulmonary dysfunction is usually subclinical. Subconscious avoidance of exercise is rarely attributed to therapy or recognized by the patient himself. Patients who have been treated with pulmonary radiation and cytotoxic agents such as BCNU, CCNU, and bleomycin should undergo pulmonary function testing every 5–8 years [56]. Such patients should avoid exposure to pulmonary toxins, most notably cigarettes. Radiation itself (>9 Gy) raised the risk of lung cancer after Hodgkin's disease.

2.4.4. Genitourinary tract

The most commonly noted renal problems after radiation therapy, especially with doses greater than 20 Gy are tubular damage and hypertension associated with renal artery stenosis [57, 58]. Children may be susceptible to these complications at lower doses. In addition, chemotherapy may exacerbate these effects [59]. Chemotherapy alone, particularly platinum compounds are notorious for glomerular and tubular injury [60, 61]. Glomerular injury may recover over time, while tubular injury persists. The nitrosourea may affect glomerular function. Ifosfamide results in renal Fanconi's syndrome with glycosuria, phosphaturia, and aminoaciduria [62]. Hypophosphatemia may result in slow growth and bone disease. Glomerular filtration may also be affected by ifosfamide. In children, there is a risk of renal decompensation with growth with any of these injuries. The bladder is susceptible to cytotoxic agents such as cyclophosphamide and ifosfamide that have acrolein as a by-product. Acrolein may result hemorrhage cystitis, fibrosis, diminished bladder volume, and rarely bladder cancer [63–65]. Patients who have received one of these agents should have an annual urinalysis, with further evaluation if hematuria is noted. Radiation may induce bladder fibrosis, decreasing contractibility and decreased volume depending on dose and area exposed [66]. Scarring may also diminish function of the urethra and ureter.

2.4.5. Thyroid gland

Damage to thyroid is common after radiotherapy to the neck and chest. Patients treated for Hodgkin's disease in whom the thyroid was irradiated had a 47% risk of overt or compensated hypothyroidism at 26 years [67]. Although compensatory increase in thyroid-stimulating hormone (TSH) initially maintains the euthyroid clinical state, further deterioration of thyroid function often results in clinical symptomatology. Treatment with thyroid hormone is recommended with persistent evidence of compensated hypothyroidism. Chronically elevated TSH levels in the presence of irradiated thyroid tissue can enhance tumor development [68, 69]. Benign nodules, Graves' disease, thyroid cancer, and Hashimoto's thyroiditis are some of the other disorders seen after radiation to the gland [67].

2.4.6. Gastrointestinal/hepatic

There is not much literature describing long-term effects to this system. This may be due to long latency of the late effects or under detection. Many chemotherapeutic agents as well as radiotherapy may be damaging to the liver; therefore, it may be difficult to attribute the harm to specific therapy. Transfusions increase the risk of viral hepatitis. Hepatitis C has been identified in increasing numbers of survivors [70]. Fibrosis and adhesions of bowel are known to occur after radiotherapy.

2.4.7. Second malignancies

About 4% of survivors develop a secondary malignancy within 25 years of diagnosis of the primary cancer [71]. This is an excess risk of six times among survivors compared to healthy individuals and is contributed to by the carcinogenic effects of treatments for the original childhood cancer as well as to genetic predisposition [71]. Bone cancers, mostly osteosarcomas, are the most common solid second cancers observed after all types of childhood cancer other than retinoblastoma [72, 73]. There is probably some element of genetic predisposition, which would include, for example, constitutional mutations of the p53 gene that contributes to secondary cancers after childhood cancers [74, 75]. Second primary leukemia is diagnosed in about 0.2% of survivors of childhood cancer within 6 years of diagnosis of the original cancer—about eight times the expected number of leukemia [76].

2.4.8. Education, psychosocial, and quality of life issues

Evidence suggests that survivors of childhood cancer experienced a range of educational, behavioral, and social problems. The extent of problems experienced varies by the disease and its treatment, as well as by demographic and family variables [77, 78]. Children miss substantial amounts of schooling during treatment, and this affects both academic achievement and social relationships. Fairly consistent evidence shows that intrathecal chemotherapy and radiotherapy to the CNS impacts academic achievement and learning. Children under 5 years at diagnosis are particularly vulnerable. A general decline in intellectual function or deficits in specific skills, including attention, concentration, and mathematical reasoning may be seen [79, 80]. Measurement of social function is more complex than measurement of academic

function, and perhaps for this reason there is limited literature describing social functioning among survivors. Among children of school age, there is some evidence that survivors of a central nervous system tumor are less popular with other children [81]. Many survivors need appropriate and sensitive counseling to enable them to choose and succeed in appropriate employment [82]. There is a considerable variation in quality of life among survivors [82]. Several studies report compromises in mental health among survivors [82].

3. Prevention of late effects

Several agents designed to protect normal tissues from the toxic effects of specific therapeutic agents are being evaluated. Examples of these agents include amifostine (cisplatinum-induced ototoxicity) [83] and dexrazoxane (anthracycline-induced cardiomyopathy) [84]. Long-term follow-up will be required to assess the efficacy of all these strategies. Research related to determination of whether agents used to protect normal tissues will or slow down the progression of an adverse late effect, is less well developed. Specific research initiatives include the use of afterload reducing agents for prevention of further progression of myocardial dysfunction [85], use of chemoprevention for prevention of secondary malignancies, lifestyle and behavior modification, and education to increase awareness of the need for screening for early detection.

3.1. Guidelines for follow-up of pediatric cancer survivors

Awareness of the potential health problems as a result of treatment for cancer in childhood is less than optimal among practitioners and survivors themselves. In contrast to the multitude of publications describing treatment-related sequelae in childhood cancer survivors, relatively few provide specific recommendations for health screening and risk-reduction counseling to guide healthcare providers in monitoring this vulnerable population [5, 86–90]. To reach this goal, several barriers need to be surpassed, notably education of survivors and healthcare providers regarding the late effects of cancer treatment; availability of standardized guidelines for follow-up of the survivors in a feasible and practical setting and ongoing communication between the cancer center that provided acute care for the patient and the facility providing follow-up care. Among the hurdles to guideline development are ongoing changes in pediatric cancer therapy, long latency periods required to evaluate many late effects, the unknown effects of aging, and the multiple factors known to influence cancer-related health risks in patients who received cancer therapy during childhood [86, 91]. Despite these challenges, two sets of clinical follow-up guidelines designed to guide care for pediatric cancer survivors have recently been published and are described below.

3.1.1. Children's Oncology Group (COG) Long-Term Follow-up (LTFU) Guidelines

The COG is a 242-member National Cancer Institute-supported cooperative clinical trials group whose goals include minimizing the risk of long-term effects that may impact duration and/or quality of life in pediatric cancer survivors. COG recently developed risk-based, exposure-related guidelines (Long-Term Follow-up Guidelines for Survivors of Childhood,

Adolescent, and Young Adult Cancers] for use in directing follow-up care for survivors of pediatric malignancies [86].

The COG-LTFU Guidelines are risk-based, exposure-related clinical practice guidelines for screening and management of late effects resulting from therapeutic exposures used during the treatment of pediatric malignancies. The guidelines are both evidence-based and based on the collective clinical experience of experts (matching the magnitude of the risk with the intensity of the screening recommendations). The screening recommendations are provided in these guidelines area consensus statement from a panel of experts in the late effects of pediatric cancer treatment. A therapy-based design was chosen to permit formatting of the guidelines by therapeutic exposure since the therapeutic interventions for a specific pediatric malignancy may differ considerably based on the patient's age, presenting features, and treatment era [86]. The guidelines are therefore organized according to therapeutic agent, and cross-referenced to other topics with related toxicities. The guidelines are designed to standardize and direct follow-up care that facilitates early identification of and intervention for treatment-related complications. Limitations include the potential for false-positive screening evaluations and increased patient anxiety related to an increased awareness of possible complications. Costs of long-term follow-up care may also be prohibitive for some patients.

Goal of implementation of these guidelines is to increase quality of life and decrease complication-related healthcare costs for pediatric cancer survivors by providing standardized and enhanced follow-up care throughout the life span. The guidelines are intended for use beginning 2 or more years following the completion of cancer therapy to [1] promote healthy lifestyles [2], provide ongoing monitoring of health status [3], facilitate early identification of late effects, and [4] provide timely intervention for late effects. The information within these guidelines is important for clinicians (e.g., physicians, nurse practitioners, physician assistants, nurses) in the fields of pediatrics, oncology, internal medicine, family practice, and gynecology, as well as subspecialists in many fields (e.g., endocrinology, cardiology, pulmonology) [86]. **Figure 1** presents an example model of how these guidelines were developed.

3.1.2. SIGN guidelines

The goal of Scottish Intercollegiate Guidelines Network (SIGN) is to develop evidence-based clinical guidelines aimed at reducing variations in clinical practice and outcomes for patients [91]. SIGN is composed of members from all medical specialties, nursing, pharmacy, dentistry, allied health professionals, patients, health service managers, social services, and researchers [91]. SIGN recently developed national guidelines for pediatric cancer survivors (SIGN guidelines) [91].The SIGN guideline provides a detailed review of the following topics with evidence for each and grading for each recommendation and its rationale: (1) assessment and achievement of normal growth; (2) achievement of normal progression through puberty and factors affecting fertility; (3) early identification, assessment and treatment of cardiac abnormalities; (4) assessment of thyroid function; and 5] assessment and achievement of optimum neurodevelopment and psychological
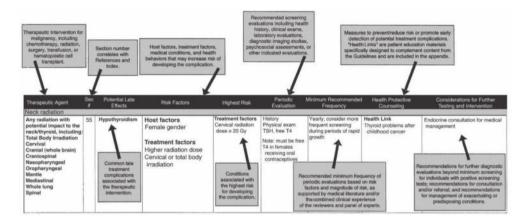
Figure 1. Sample excerpt from the Children's Oncology Group Long-Term Follow-Up Guidelines for survivors of childhood, adolescent, and young adult cancers. TSH, thyroid-stimulating hormone.

health [92, 93]. Limitations of the SIGN guideline include lack of specific follow-up recommendations for areas such as renal, pulmonary, gastrointestinal, ocular, auditory, and musculoskeletal systems as well as second malignancies. In addition to clinical recommendations, the SIGN guideline contains recommendations for the delivery of follow-up care for pediatric cancer survivors, based on the intensity of treatment received. The degree of long-term risk is determined by site of the underlying malignancy, type and intensity of treatment, and age of patient at treatment. Three levels of follow-up are described: "Level 1" follow-up is suggested for those survivors for whom the benefit of clinical follow-up is not clearly established. Annual or even every two-year postal or telephone contact is recommended. "Level 2" follow-up is suggested for the majority of patients on current protocols. Nurse or primary care follow-up on an annual basis may suffice. "Level 3" follow-up is for patients who have received radiotherapy, bone marrow transplantation, or megatherapy, and who have a significant risk of long-term morbidity [92, 93]. Recommendations for these patients include follow-up in a medically supervised long-term follow-up clinic three to four times per year [92, 93].

3.1.3. Application of guidelines to clinical practice

The main challenge of providing quality care to a pediatric cancer survivor is combining routine age-appropriate health maintenance with exposure-related screening for potential late-onset complications related to pediatric cancer therapy. Ideally, evaluations should be individualized based on the survivor's treatment history. A balance between over-screening, which might induce anxiety related to unlikely complications, and under-screening for potentially life-threatening complications that if missed at an early phase may require more aggressive intervention later needs to be achieved. Screening guidelines that can be individualized based on the patient's risk for developing a particular complication are therefore ideal. As

the COG and SIGN guidelines become more widely implemented over time, refinements will undoubtedly be made that will make them even more clinically relevant and practical for survivors who are followed in future years.

The importance of educating both survivor and healthcare professionals about potential late effects cannot be over-emphasized since a wide range of providers are involved in the follow-up of these patients including nurses, psychologists, social workers, adult and pediatric primary care providers, and specialists in many fields. Ultimately, as with all clinical practice guidelines, decisions regarding implementation of specific screening modalities and ongoing clinical management should be tailored to individual patients, taking into consideration all relevant factors, including medical and psychosocial history, therapeutic exposures, risk factors, and co-morbidities [93].

3.1.4. Limitations in providing long-term follow-up care

3.1.4.1. Patient factors

Misperceptions about their cancer diagnosis, treatment, and cancer-related health risks exist among cancer survivors [94–96]. Byrne et al. [90] surveyed 1928 adult survivors of childhood cancer diagnosed between 1945 and 1974 to assess knowledge of their cancer diagnosis. Overall, 14% of survivors were not aware that they had cancer. Lesser knowledge of their diagnosis was associated with younger age at treatment, nonwhite race, less intensive treatment, and lower parental education status. It is possible that racial, socioeconomic, and cultural factors that were prevalent during the period when the patient was diagnosed may influence the interaction amongst the oncologist and patient [90]. Historically, some healthcare professionals and families prefer giving limited information about cancer-related health risk to survivors due to concerns about inducing anxiety. In a similar study from 1970 to 1986, Childhood Cancer Survivor Study (CCSS) investigators evaluated the accuracy of self-reported information acquired from a cross-sectional survey of 635 adult survivors of childhood cancer. Knowledge about cancer history and its associated health risks is improved in more recently treated survivors compared to the Byrne study [94]. More than 90% of participants were aware of their cancer diagnosis but not all elements of their history in a recent study. The knowledge deficits about cancer-related health risks in older survivors may limit their participation in screening and risk-reducing programs [97].

3.1.4.2. Provider factors

Healthcare providers encountering childhood cancer survivors must be knowledgeable about potential cancer-related adverse effects in order to prescribe appropriate monitoring and interventions should health problems arise. Because of the rarity and complexity of numerous histologic subtypes with unique epidemiology, biology, and treatment regimens managing long-term childhood cancer survivors is an intimidating task for primary care physicians. Healthcare providers are unlikely to care for more than a handful of survivors, usually each with different cancers, treatment exposures, and health risks making it difficult to attain proficiency. Consequently, primary healthcare providers in the community are often uncomfortable with supervising the care of childhood cancer survivors.

The knowledge, attitudes, and beliefs of physicians providing care for survivors of childhood cancer have not been well studied. Several investigators coordinating late effects surveyed a convenience sample of 236 physicians from around the United States, in private or academic practices using a 36-item questionnaire that asked about knowledge, attitudes, and beliefs in providing health care for adult survivors of childhood cancer [98]. In comparison with pediatric oncologists, primary care physicians (general internists and family physicians) reported a lower level of knowledge regarding both common childhood cancers and the late effects with treatment exposures. A recent study in the UK reported a crosssectional postal survey as well as a cross-sectional postal survey of general practitioners of 10,979 adult survivors of childhood cancer in Britain. This study has shown that there are wide variations in the extent to which survivors of childhood cancer are discharged from hospital follow-up [99]. Adult oncologists generally reported a higher level of knowledge of these factors than primary care physicians, but considerably less than pediatric oncologists. Notably, primary care physicians expressed a lower level of comfort in managing survivors. These data point to a need for resources and interventions that specifically address the unique needs and medical management of childhood cancer survivors that primary care providers might benefit from.

3.1.5. Solutions for coordinated care for childhood cancer survivors

3.1.5.1. Specialized long-term follow-up clinics

Multidisciplinary long-term follow-up teams at some pediatric oncology treatment centers have established long-term follow-up clinics. Follow-up in this model is limited to an annual comprehensive multidisciplinary health evaluation, and survivors are encouraged to establish an ongoing relationship with a primary healthcare provider in the community for routine health maintenance. Benefits of this approach are that the patient remains in contact with a team that is knowledgeable and has a standardized program of long-term follow-up care, contact with the original treatment center is maintained, and multidisciplinary referrals available within the healthcare system. Disadvantages include the lack of familiarity of the pediatric treatment team with age related health-care issues that might arise, reluctance of the older patient to return to a pediatric facility, reimbursement for specialized services not covered by insurance companies, and problems of access due to long distances between the medical center and the survivor's residence [100].

3.1.5.2. Transition models

In some instances, institutions have established formalized transition programs with specialized long-term follow-up programs for adult survivors of childhood cancer because of reluctance of pediatric oncology centers to take care of adult cancer survivors. Transition programs may utilize both oncology and primary care providers in a collaborative framework, and maintain many of the benefits of the specialized long-term follow-up clinics, with the benefit of care providers with expertise in adult medicine. One limitation is that since the focus is on survivorship care, and ongoing primary care is often not accessible through these specialized programs, and distance to the center may remain a barrier [100].

3.1.5.3. Transition to adult oncology

In this model, when the survivor reaches adulthood, the pediatric provider makes a referral to an adult oncologist for ongoing follow-up. Advantages of this system include ongoing monitoring for disease recurrence in an adult medical care system, and accessibility to care in the local community. Disadvantages include the limited familiarity of most adult oncologists with the potential late complications of chemotherapy and radiotherapy in children and the appropriate follow-up evaluations indicated for childhood cancer survivors [100].

3.1.5.4. Community-based care

Follow-up care may be provided by an adult primary care provider (e.g., internist, family practitioner), who maintains communication with the original pediatric oncology treatment team. Advantages of this model include ability to maintain a relationship with a provider in the community who is familiar with their specialized healthcare needs and disadvantages include the primary care provider's lack of familiarity with potential late effects. There may also be limited access to multidisciplinary specialty care providers that many survivors require [100].

4. Conclusions

As pediatric oncologists, our work is not done when the cancer is cured. We must try to recognize, monitor and decrease the late effects of cancer therapy when possible and, if not possible, to understand the effects so that future treatment regimens can be designed with less risks of late effects. Remarkable improvement in cure rates has been achieved by persistent stress on designing effective therapy. Only by continued, systematic follow-up of large cohorts of survivors will we know the full spectrum of damage caused by cytotoxic therapy and possible interventions that may mitigate the effects. Ongoing methods for educating both the patient and the primary caretakers must be devised. We must set up programs to evaluate the survivors to assess and care for chronic organ damage, providing the necessary support for the primary physician. As part of a collaborative effort, the primary care provider and the specialist must work toward the goal of best possible quality of life for the pediatric cancer survivor.

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