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Late Effects in Adult Survivors of Childhood Cancer: Considerations for the General Practitioner

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ABSTRACT

Childhood cancer survivorship is a national public health priority, with an increasing number of survivors who face late effects from both disease and treatment. As childhood cancer survivors are living into adulthood, care of the late effects associated with their diagnosis and treatment can become complex. Often these patients no longer have follow-up with the treating pediatric hospital and seek medical care from an adult primary care professional. Combining the results of current survivorship research with clinical experience, we describe common late effects that general internists and primary care professionals may encounter during routine visits with adult survivors of childhood cancer. Recommendations and resources are provided for identifying and managing late effects.

INTRODUCTION

During the past 60 years, significant advances have been made in childhood cancer therapy. Today children diagnosed with a cancer are expected to be cured—almost 80% will survive into adulthood. In 1997, there were an estimated 270,000 childhood cancer survivors in the United States, of whom approximately 1 in 640 were between the ages of 20 and 39 years.[1] These numbers have continued to grow; by 2010, there are projected to be 1 in 250 young adult survivors between 20 and 29 years of age.[2]

Survivors of childhood cancer and bone marrow transplant (BMT) comprise a large and heterogeneous group, with a variety of diagnoses and a plethora of treatments, each with their own set of potential late effects. As survivors age, nearly two-thirds will develop a chronic health condition. In a quarter of survivors, these conditions will be moderate, severe, or life threatening.[2] Late effects from cancer treatment can occur soon after treatment is completed or may not appear until many years later. The potential incidence of late effects is influenced by the underlying disease process, types, and dose of treatment received, and age at time of treatment. Host factors such as gender, ethnicity, genetics, and health behaviors (including tobacco, alcohol, diet, exercise, etc)—as well as underlying medical conditions—can also influence the occurrence and/or severity of any late effects. Differences in treatment regimens over time may also affect the types and risks of side effects. Any organ system can potentially be affected.

For many years, pediatric oncologists have provided oncology care as well as primary care to childhood cancer survivors. However, as the numbers of adult survivors of childhood cancer grow, like adult survivors of congenital cardiac disease and cystic fibrosis, adult care professionals will become health care professionals for survivors of childhood cancer, and they need to be aware of the unique issues and problems these survivors may face.

As a primary care professional caring for these patients, it is important to recognize that their prior cancer treatment may have lifelong effects. These may present as typical medical issues but may also require additional screening and intervention based on the patient's past medical history and treatment. Table 1 provides a summary of potential late effects a childhood cancer survivor may experience. The late effects listed are arranged by organ system. The organ systems affected and the potential late effects are influenced by the survivor's treatment. Not all survivors are at risk for all late effects. A brief overview of potential late effects related to commonly used chemotherapy agents and radiation (Table 2) and commonly encountered childhood cancers (Table 3) is provided for general refer-

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Table 1. Organ System and Potential Late Effects Related to Cancer Therapy

Organ System	Potential Late Effect
Brain	Seizures; learning disabilities; memory problems and/or speed of processing; neurological problems; brain tumors
Endocrine	Hypo/Hyperthyroidism; growth hormone deficiency; cortisol deficiency; SIADH; prolactin deficiency; precocious puberty
Eyes	Cataracts; dry eyes
Ears	Hearing loss; Eustachian tube dysfunction; balance problems
Dental	Cavities; malformed or missing teeth; short roots; gum disease
Sinus	Recurrent sinusitis
Heart and Vascular System	Cardiomyopathy; conduction abnormalities; valve damage; pericarditis; peripheral vascular disease
Lungs	Restrictive lung disease; pneumonitis; bronchiolitis obliterans
Breast	Asymmetry; underdeveloped; breast cancer
Liver	Fibrosis; hepatitis; gall bladder dysfunction
Gastrointestinal	Fibrosis; polyps; bowel obstruction; chronic GVHD; asplenia (actual or functional); GERD
Kidney	Renal dysfunction and/or failure; hypertension
Bladder	Fibrosis; dysfunction; malignancy
Gynecology	Abnormal menstruation; premature menopause; pregnancy complications; vaginal dryness; infertility
Testes	Gonadal failure; impotence; infertility
Skeletal	Amputation; chronic pain; arthritis; avascular necrosis; fracture; osteochrondroma; osteopenia; functional deficits
Skin	Scars; striae; dyspigmentation; secondary cancers; dystrophic nails; alopecia
Psychosocial	Altered peer and family relationships; school, work, and insurance issues; anxiety; depression; survivor's guilt
Peripheral Nervous System	Neuropathies; weakness; phantom pain
Global	Fatigue

Abbreviations: SIADH, syndrome of inappropriate antidiuretic hormone hypersecretion; GVHD, graft-versus-host disease; GERD, gastroesophageal reflux disease

ence. The focus of this article is to provide an overview of late effects by organ systems as well as risk factors and screening guidelines for the potential late effects, recommendations for patient follow-up, and referral.

Cardiovascular Effects

Symptom Presentation and Risk Factors: Cardiovascular disease is a significant medical problem for many Americans. Childhood cancer survivors may be at additional or increased risk for cardiovascular disease secondary to their treatment with chemotherapy and/or radiation. For some survivors of pediatric cancer, treatment-related late effects may not arise until growth and pubertal development have completed. Cardiotoxicity may not appear until many years after the end of treatment. In particular, cardiotoxicity related to the use of anthracycline (eg, daunomycin, doxorubicin, and mitoxantrone) has been the subject of many studies. As a consequence, treatment regimens have changed over the years.[3] Specific late effects include cardiomyopathy, arrhythmias, and left ventricular dysfunction. Pericardial and atherosclerotic disease have also been reported. The increase in blood volume that occurs as a result of pregnancy may adversely affect cardiac function.[4] Clinical symptoms including shortness of breath, chest pain, palpitations, and abdominal symptoms (eg, nausea or vomiting) may predominate in younger patients (<25).

Factors associated with highest risk for cardiotoxicity include those who were <5 years at time of treatment , female, and African American ethnicity. Radiation therapy to the chest or upper left abdomen (involves the left ventricle) also increases risk; higher total dosage is associated with higher risk. The risk for developing late cardiac complications increases with time from anthracycline exposure. Medical conditions such as obesity, congenital heart disease, and pregnancy can contribute to the risk.

Recommendations and Resources: Patients who have received cardiotoxic cancer treatment should have medical follow-up that includes regular cardiac monitoring to detect heart problems early. This is particularly important since these patients are often asymptomatic. An echocardiogram is recommended at entry to long-term follow-up and then subsequently at intervals based on age at the time of treatment, radiation dose, and cumulative anthracycline dose received. A fasting lipid panel profile is recommended every 2 years for survivors who received radiation to the chest. Discussions

Table 2. Frequently Used Chemotherapy Agents and Potential Late Effects

Chemotherapy Class and Drug(s)	Often Used In	Potential Late Effect
Anthracyclines Daunomycin Doxorubicin Mitoxantrone	Leukemias (AML, higher risk ALL) Lymphoma Neuroblastoma Wilms tumor (if higher risk/stage) Osteosarcoma Some soft tissue sarcomas Some liver tumors	Cardiac dysfunction Can be acute More often chronic, may be progressive Related to total dose (mg/m^2 – not mg) Second cancers Usually, but not always, leukemia Enhances radiation effects
Alkylating agents Mechlorethane Cyclophosphamide Ifosfamide Melphalan Cisplatin Carboplatin Nitrosoureas (BCNU[a], CCNU[b]) Dacarbazine and Procarbazine Busulfan	Leukemias (if higher risk ALL) Lymphomas Brain tumors Neuroblastoma Wilms Tumor (if higher risk) Osteosarcoma Soft tissue sarcomas Some liver tumors Retinoblastoma	Marrow suppression Scarring, bleeding of bladder (especially cyclophosphamide and ifosfamide) Infertility, gonadal dysfunction, early menopause Secondary cancer Usually, but not always, leukemia Damage, scarring of lung tissue Hearing loss (especially cisplatin, carboplatin) Kidney dysfunction
Topoisomerase II inhibitors Etoposide Teniposide	Leukemias (AML, higher risk ALL) Some lymphomas Neuroblastoma Wilms Tumor (if higher risk/stage) Some Osteosarcoma Soft tissue sarcomas Some liver tumors Germ Cell tumors	Secondary leukemia or other cancer Infertility or gonadal dysfunction
Bleomycin	Lymphoma	Scarring of lungs, pulmonary fibrosis
Anti-metabolites Methotrexate 5-fluoruracil Cytarabine 6-mercaptopurine 6-thioguanine	Leukemias Lymphoma Brain tumors Osteosarcoma Some liver tumors	Hepatic fibrosis Especially mercaptopurine and thioguanine Neurocognitive changes Mainly with methotrexate when given intrathecally or in high doses
Vinca alkyloids Vincristine Vinblastine	Leukemia (ALL) Lymphomas Neuroblastoma Wilms Tumor Soft tissue sarcomas Liver tumors	Rare weakness, sensation loss Worse if underlying Charcot-Marie-Tooth disease
Steroids Prednisone Dexamethasone	Leukemia (ALL) Lymphomas	Avascular necrosis Weight gain May increase risk for metabolic syndrome
Radiation	Leukemia (high risk CNS) Lymphomas (stage dependent) Brain tumors (type dependent) Neuroblastoma (stage dependent) Wilms tumor (stage dependent) Soft tissue tumors (type, stage & surgery dependent)	Tissue changes Secondary cancers, more often solid tumors Thyroid Breast Sarcoma Neuro-cognitive changes Infertility, or other endocrine dysfunction Pre-term delivery

[a]Carmustine
[b]lomustine
Abbreviations: AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; CNS, central nervous system

with patients regarding the safety of aerobic exercise and discouraging heavy weightlifting and wrestling are imperative. Smoking should be strongly discouraged, while healthy eating and exercise should be encouraged.[5] Although childhood cancer survivors may have additional risk factors for cardiovascular disease compared to the general population, it may be possible to modify the risk for cardiovascular disease through lifestyle modification and close medical follow-up.

More frequent cardiac monitoring during pregnancy may be indicated. The Children's Oncology Group (COG) Long-Term Follow-Up Guidelines (2008) recommend additional cardiology evaluation for those women who are pregnant or plan to become pregnant and have received >300mg/m^2 of anthracycline therapy or <300mg/m^2 plus chest radiation.[5] Recommendations include echocardiograms before and periodically during pregnancy (especially in the third trimester) and cardiac function monitoring during labor and delivery.

Pulmonary Effects

Symptom Presentation and Risk Factors: Chemotherapy and radiation therapy can put patients at potential risk for pulmonary late effects. Although changes may be subtle, they may greatly impact a survivor's quality of life. Lung volumes can be reduced, thus limiting the ability to participate in more strenuous activities. Clinical symptoms may include shortness of breath, wheezing, chest pain, and frequent lung infections, such as bronchitis or pneumonia.

Recommendations and Resources: For patients at risk for pulmonary toxicity due to their cancer treatment, a yearly medical check-up is recommended. A chest x-ray and pulmonary function tests may identify lung problems that are not evident on physical exam. The recommendations for frequency of testing are based on the previous treatment the patient received. The COG guidelines include consideration for the administration of pneumococcal (pneumonia) and yearly influenza (flu) vaccinations. Smoking is discouraged, and it is recommended that the survivor avoid second-hand smoke. The importance of regular physical activity and exercise should be encouraged. A complete check-up by a pulmonologist is advised prior to participating in scuba diving.

Musculoskeletal and Bone Health

Symptom Presentation and Risk Factors: Surgery, chemotherapy, and radiation therapy have been instrumental in decreasing mortality rates for patients with muscle and bone tumors. However, chemotherapy can limit soft tissue growth, and treatment regimens with steroid administration can impair bone mineralization, bone growth, or cause avascular necrosis. Radiation and therapy can also hinder growth of bone and tissue. Depending on the area irradiated, this can result in asymmetrical growth with potential risk for scoliosis and increased risk for fractures.

Recommendations and Resources: For patients at risk for musculoskeletal complications, early intervention is imperative to maximize bone health and to decrease the risk for osteoporosis. It is important to encourage patients to have adequate calcium intake or supplementation, to incorporate regular exercise, and to avoid smoking. Follow-up with orthopedics may be needed for survivors of bone or soft tissue tumors who have had limb-sparing procedures or those who have prosthetic devices.

Endocrine and Fertility Issues

Symptom Presentation and Risk Factors: Childhood cancer survivors who received chemotherapy, radiation, and/or surgical treatment during a time of growth and development may be at risk for endocrine and fertility complications. Patients who are treated at a young age or who received radiation treatment to their head, neck, and/or spine are at highest risk for developing endocrine abnormalities. Obesity may be a major problem—particularly for acute lymphocytic leukemia (ALL) survivors who are female, are treated at a young age, and have received cranial radiation. Childhood cancer and BMT survivors also may be at risk for infertility or premature menopause. Patients at highest risk are those who have received radiation therapy to their abdomen, high doses of alkylating agents, and/or bone marrow transplant conditioning regimens. Sexual dysfunction, such as erectile dysfunction and vaginal dryness, can also occur.

Recommendations and Resources: Survivors, particularly those treated at a young age, should have close monitoring of their growth and pubertal development. Patients at the highest risk for endocrinopathies are those who have received radiation to the head, neck, or spine and/or BMT. Close monitoring of growth charts, Tanner staging, thyroid function, gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]), and other hormones (estradiol, testosterone) should be monitored for patients who are at risk. Prompt evaluation by a pediatric endocrinologist is recommended if any abnormalities are identified.

Patients with obesity, particularly abdominal obesity, should be counseled regarding weight control. Counseling regarding regular exercise and healthy eating

habits is important for survivors to decrease other health concerns that may arise secondary to their obesity.

For patients at risk for early menopause, counseling regarding family planning issues is important as these women may have a shortened timeframe for fertility. For men and women at risk for infertility, referral to a reproductive medicine specialist for further evaluation of fertility (ie, semen analysis, hormone levels) may be necessary. Referral to a center familiar with cancer and BMT survivors may also be beneficial.

Fertile Hope and the Lance Armstrong Foundation (Appendix A) are excellent resources for childhood cancer and BMT survivors dealing with fertility issues. They can be an excellent resource both prior to therapy, as well as after therapy has been completed. Information available to patients includes referral centers and fertility options.

Other Organ Systems

Symptom Presentation and Risk Factors: Chemotherapy, surgery, and radiation can affect many other body organs as well. Radiation therapy can contribute to vision loss or cataract development. Extensive steroid use can predispose survivors to cataract development. Chemotherapy agents, radiation therapy, and some antibiotics can result in hearing loss. Routine dental follow-up every 6 months is highly recommended to assess for dry mouth, dental caries, malformed dentition, enamel breakdown, and tooth decay.

A history of multiple blood product transfusions while undergoing treatment increases the risk for hepatitis and liver disease. Patients transfused prior to 1992 have the highest risk.

Gastrointestinal late effects can include liver and bowel symptoms. Patients with a history of surgery, radiation, or BMT are at risk for the development of fibrosis, bowel obstruction, polyps, or other concerns. Liver fibrosis can occur as a result of chemotherapy, radiation, and multiple transfusions. Some patients experience altered immune function. Patients who have had a splenectomy or who have a nonfunctional spleen are at risk for severe encapsulated bacterial infection.

Cancer treatment and exposure to certain antimicrobials can contribute to long-term kidney and bladder dysfunction. Patients with a single kidney require special attention to their kidney function and may need special precautions, including the use of a flank guard, when playing contact sports.

Recommendations and Resources: Regardless of the late effect, it is imperative that a detailed history be documented and a comprehensive exam performed. Survivors who are at risk for other organ late effects should be identified and screening measures initiated. Specific follow-up recommendations are outlined in the COG guidelines based on the survivors' risk factors.[5]

Secondary Cancers

Symptom Presentation and Risk Factors: Secondary cancers are a known complication after childhood cancer treatment and BMT. The risk for occurrence of secondary cancers is estimated to be at least 2-8 times higher than risk for the general population to develop a primary cancer.[6-8] The incidence of secondary cancers is 3%-12% in the first 20 years after diagnosis and increases over time. Potential risk factors for developing a secondary malignancy after childhood cancer include exposure to radiation, exposure to specific chemotherapeutic agents (alkylating agents and topoisomerase II inhibitors), genetic predisposition, and BMT patients with a history of chronic graft-versus-host disease.

Recommendations and Resources: Patients with a history of cancer or BMT may need additional screening for secondary cancers depending on the type of cancer and the treatment they received. It is important for the primary care professional to be aware of any previous treatment and its implications for the development of a secondary cancer.

Patients who have a history of radiation as part of their cancer treatment or BMT preparative regimen should have inspection and palpation of the skin and soft tissues in the radiated fields.[5] Female patients should have mammography and breast magnetic resonance imaging (MRI) at an earlier age if they have received radiation to their chest.[5]

Patients exposed to certain chemotherapeutic agents, specifically alkylating agents and topoisomerase II inhibitors, have been shown to have an increased risk for myelodysplasia and acute myelogenous leukemia (AML). The incidence of developing a secondary AML peaks 4-6 years after exposure and typically does not occur later than 15 years from exposure. Patients who have been exposed to these agents should have a complete blood count checked annually for at least 10 years after the completion of chemotherapy.[5]

Neurocognitive and Psychosocial Late Effects

Symptom Presentation and Risk Factors: Adult survivors of pediatric cancer are at risk for development of cognitive late effects. At increased risk are those who have had central nervous system (CNS) disease and/or treatment, such as brain tumor and ALL survivors. Research has consistently shown that contributing factors to the development of cognitive late effects include

systemic and in particular, intrathecal chemotherapy and/or cranial irradiation,[9] which have a primary effect on the white matter of the brain. The effect is age and dose dependent, such that younger children and those who receive higher doses of intrathecal chemotherapy and/or radiation are at greater risk.[9]

Cognitive late effects differ from acute cognitive problems commonly reported by patients during chemotherapy and/or radiation ("chemo brain") that resolve once treatment is completed. Cognitive late effects may be subtle to severe and may include problems with or decreases in intellectual functioning, attention, memory, executive functioning, and processing speed.

Although the majority of studies have found that, overall, cancer survivors adjust adequately to life after treatment,[10-12] some survivors experience psychosocial difficulties, such as symptoms of depression and anxiety, and social problems. Risk factors associated with poor psychosocial outcome include diagnosis, type and length of treatment, severity of disease, age at diagnosis, medical late effects of disease and treatment, length of remission, and time since diagnosis.[11]

Recommendations and Resources: When survivors present with neurocognitive difficulties, it is important to consider leukoencephalopathy, which may occur after CNS treatment for ALL or other disorders. A referral for imaging studies may be warranted. In general, if neurocognitive problems exist, the primary physician should provide a referral to a psychologist or neuropsychologist for neurocognitive testing (referrals may be obtained from local cancer centers); preferably testing will be completed by those who have experience in assessment of this population. Stimulant medications, such as methylphenidate, have been prescribed by clinicians to treat attention/concentration, processing speed, and or executive functioning problems in cancer survivors, given its efficacy in patients with attention-deficit/hyperactivity disorder (ADHD). Preliminary results of ongoing randomized clinical trials of stimulant medication use in childhood cancer survivors are promising.[13]

With psychosocial problems such as adjustment or health-related quality-of-life difficulties, cognitive behavioral therapy, provided by a mental health professional with experience working with individuals with medical conditions, is an empirically supported treatment for these issues (eg, anxiety, depression). Sometimes a combination of therapy and psychotropic medication may be warranted. Long-term survivorship clinics have mental health professionals who specialize in the psychosocial treatment of cancer survivors.

If cognitive problems are detected, the psychologist will make specific recommendations for assistance in school. For an adult, a referral to Wisconsin's Department of Vocational Rehabilitation and other vocational resources is recommended. Colleges and universities have disability programs that may assist cancer survivors with disability accommodations if needed. Cancer survivors who will be attending college may be eligible to apply for scholarships based upon their cancer history, such as scholarships offered through the American Cancer Society. Organizations such as The Sam Fund and Care. Commit. Change. (CCC) provide financial assistance, college scholarships, and scholarship information and resources for young adult survivors of cancer. There are a number of psychosocial support programs and resources available in the community that may be helpful to survivors. See Appendix A for a comprehensive list of websites.

DISCUSSION

Childhood cancer follow-up care has taken place in a variety of settings: primary care clinics (pediatrics, internal medicine, family practice, ob/gyn), oncology clinics (pediatric and adult), and specialized long-term follow-up clinics. The health care professional may be less familiar with the magnitude of cancer-related health risks and screening these survivors face, and—in the setting of a busy practice—may lack the time to gain expertise in survivor care. Although follow-up may occur at the tertiary care center, the majority of after-cancer care occurs in the primary care arena. For this reason, ready and easy access to resources to facilitate care is of paramount importance. Fortunately, there are many resources available (see Appendix A).

In Wisconsin there are 2 centers that provide care and recommendations for childhood cancer survivors. The Next Steps Clinic of the Midwest Athletes Against Childhood Cancer (MACC) Fund Center for Cancer and Blood Disorders provides care to oncology and BMT survivors. Survivors are provided with a treatment summary of their cancer care as well as recommendations for follow-up of current late effects, screening for potential late effects, referrals to other specialists, and assistance with nutritional, school, and psychosocial aspects of care. Educating survivors regarding their disease, treatment, and potential late effects is critical. Survivors are given a variety of written resources regarding survivorship issues. Depending on the specific needs of the survivor, these patients may continue to be seen annually in the survivorship clinic or may be transferred to their primary care professional for continued care. The Caring for Life Clinic at the American

Table 3. Common Childhood Cancers and Some Potential Late Effects

Frequently Used Chemotherapy Drugs	Important to Know	Potential Late Effect
	Acute Lymphocytic Leukemia	
Steroids Anti-metabolites (methotrexate, mercaptopurine, cytarabine) Vincristine Asparaginase Daunomycin or Doxorubicin Less often: Cyclophosphamide etoposide	Type of disease • Low, intermediate, high or very high risk Era of treatment Type(s) of treatment • Anthracyclines • Topoisomerase inhibitors • Alkylating agents • Radiation • Bone marrow transplant Age at time of treatment	Overall, few effects Most common • Avascular necrosis (older age, use of) dexamethasone • Neuro-cognitive problems (younger age) Metabolic syndrome
	Acute Myelogenous Leukemia	
Daunomycin, Mitoxantrone Etoposide Cytarabine Asparaginase (May include high dose therapy and stem cell rescue [BMT])	Age at diagnosis Was stem cell rescue (BMT) part of therapy Was radiation therapy used	Cardiac problems Infertility and/or other endocrine dysfunction Secondary malignancies Chronic GVHD (if allogeneic BMT) Immune dysfunction (if allogeneic BMT)
	Lymphomas	
Cyclophosphamide, ifosfamide Doxorubicin Vincristine Prednisone, Dexamethasone Etoposide Bleomycin	Kind of lymphoma • Hodgkin • Non-Hodgkin eg, Burkitt, other B-cell or T-cell Radiation? Which chemotherapy drugs	Cardiac problems Infertility Avascular necrosis Neuro-cognitive changes Secondary cancer (mostly leukemia unless also received radiation) Immune dysfunction
	Brain Tumors	
Nitrosoureas Cyclophosphamide Cisplatin, carboplatin Temozolomide Vincristine Thiotepa Methotrexate	Type Location Treatment • Chemotherapy • Radiation Surgery	Focal neurologic deficits related to tumor location or surgery Endocrine problems Neuro-cognitive problems Infertility Secondary cancers Pulmonary fibrosis
	Neuroblastoma	
Cisplatin, carboplatin Vincristine Doxorubicin Cyclophosphamide Etoposide; Topotecan, Irinotecan Temozolomide	Age and stage of disease at diagnosis What therapies • Chemotherapy • Radiation (How much? Where?) Stem cell rescue (BMT)	Cardiac dysfunction Hearing loss Infertility of other endocrine problem Secondary cancers

Abbreviations: GVHD, graft-versus-host disease; BMT, bone marrow transplant; CNS, central nervous system

Table 3. Common Childhood Cancers and Some Potential Late Effects (CONTINUED)

Frequently Used Chemotherapy Drugs	Important to Know	Potential Late Effect
	Wilms Tumor (Fortunately, Few)	
Vincristine Dactinomycin If higher risk/stage: Doxorubicin Cyclophosphamide Etoposide	Location (side), stage of tumor at diagnosis Therapy • Chemotherapy agents used anthracycline alkylator topoisomerase inhibitor Radiation (where and how much)	Cardiac dysfunction Pulmonary fibrosis Liver dysfunction Pre-term births Secondary cancers Renal dysfunction rare (unless predisposed to Wilms Tumor)
	Osteosarcoma	
Doxorubicin Cisplatin Methotrexate Less often: Etoposide Ifosfamide	Therapy	Musculoskeletal problems relating to tumor and/or surgery Cardiac dysfunction Hearing loss Renal dysfunction Second cancers
	Rhabdomyosarcoma, Ewing sarcoma, other soft tissue sarcomas	
Vincristine Dactinomycin Cyclophosphamide, Ifosfamide Doxorubicin Recent additions: Etoposide Irinotecan Topotecan	Age at diagnosis Location of primary tumor and any metastatic site Type(s) of therapy • Chemotherapy • Radiation • Surgery • Both radiation and surgery	Musculoskeletal problems relating to tumor location Cardiac dysfunction Secondary cancers Infertility or other endocrine problems Bladder scarring Pulmonary fibrosis
	Liver tumors	
Cisplatin 5-fluorouracil Vincristine Doxorubicin	Which tumor • Hepatoblastoma • Hepatocellular carcinoma • Other Chemotherapy agents used	Cardiac dysfunction Hearing loss Renal dysfunction
	Germ Cell tumors	
Bleomycin Cisplatin Etoposide	Age at diagnosis Type, stage of tumor Location of tumor • Extragonadal • Gonadal • CNS Chemotherapy agents used	Hearing loss Renal dysfunction Secondary cancers Endocrine problems mainly if CNS tumor
	Retinoblastoma	
Cyclophosphamide Carboplatin, cisplatin Vincristine Etoposide	Family history Unilateral or bilateral Therapy • Surgery • Chemotherapy • Cryotherapy Radiation	Vision loss Hearing loss Renal dysfunction Secondary cancers Pituitary dysfunction if tumor located there also

Abbreviations: GVHD, graft-versus-host disease; BMT, bone marrow transplant; CNS, central nervous system

Family Children's Hospital—University of Wisconsin Hospital and Clinics also provides survivorship care for the survivors of childhood cancer and BMT. Further information regarding the above 2 programs is available in Appendix A.

The patient's treating cancer/BMT institution can be a resource to the primary care professional in providing a complete treatment summary and recommendations for the individual survivor. If the survivor does not have access to the original treating facility, there are multiple survivorship clinics around the country that may be able to identify for a specific patient, his or her risks and screening recommendations. The COG website, www.childrensoncologygroup.org, provides information about and locations of survivorship clinics around the country.

The COG has developed, and continues to revise, a set of evidence-based guidelines for the follow-up and screening for chronic health conditions or late effects associated with therapy (www.survivorshipguidelines.org). Health links are also available for patients and their families, of which 5 have been translated into Spanish. These guidelines are intended to standardize the follow-up care of survivors throughout their lifetime, with an emphasis on evidenced-based screening for late effects of therapy rather than for recurrence of malignant disease, in order to facilitate early identification of late effects, promote a healthy lifestyle, and provide ongoing monitoring of health and timely intervention for late effects.

Adult caregivers will be seeing an ever-growing population of adult survivors of childhood cancer in their practices. It is vitally important that these health care professionals are aware that late effects of treatment can occur years after treatment. Because of this, adult survivors of childhood cancer and BMT need specialized screening for potential late effects based on their prior treatment. Resources are available to provide guidance to the general internist seeing these patients, and cancer survivorship clinics in Wisconsin are available as resources for adult childhood cancer survivors as well as the practitioners caring for them. There are multiple models for the care of the childhood cancer survivor (eg, life-long care at the pediatric treating institution, primary care model) each with their own unique advantages and disadvantages. However, a model of collaboration and communication between the specialized survivorship clinic and the primary care professional may be the most advantageous for the survivor in meeting his or her medical and psychosocial needs. A full discussion of this topic is needed,but is beyond the scope of this article. Continued efforts for ongoing surveillance need to be made between the primary care professional and survivorship clinic in order to provide comprehensive and holistic care to these survivors of childhood cancer.

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Appendix A. Childhood Cancer Survivor Resources for the Primary Care Provider

American Cancer Society: Health organization and largest non-governmental funder of cancer research and discovery.	*www.cancer.org*
Cancer Care: Provides free support services to anyone affected by cancer.	*www.cancercare.org*
Candlelighters Childhood Cancer Foundation: Provides information, awareness, advocacy, and research for childhood cancer patients and families.	*www.candlelighters.org*
A local chapter can be found in Madison, Wis (Capital Candlelighters).	*www.capcan.org*
The Caring for Life Clinic at the American Family Children's Hospital (University of Wisconsin): Comprehensive survivorship clinic in Madison, Wis	*www.uwhealth.org/pediatriccancer/caringforlifeclinic/11136*
CCC: An annual college scholarship program that recognizes survivors who demonstrate leadership, commitment to education, and betterment of their community.	*www.cccscholarships.org*
Children's Hospital of Wisconsin's Young Adult Oncology Group in Milwaukee: Young adult cancer survivors who meet monthly to provide one another with support, education, and resources in a fun and relaxed atmosphere.	*www.chw.org/yaog*
Children's Oncology Group: Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers.	*www.survivorshipguidelines.org*
Cure Search: Unites the Children's Oncology Group and the National Childhood Cancer Foundation to fund research.	*www.curesearch.org*
Fertile Hope: Nonprofit organization dedicated to providing reproductive information, support, and hope to cancer patients and survivors whose medical treatments present the risk for infertility.	*www.fertilehope.org*
Gilda's Club: Emotional and social support community.	*www.gildasclub.org/*
There are local chapters located in Milwaukee and Madison, Wis.	*www.gildasclubsewi.org* *www.gildasclubmadison.org*
Lance Armstrong Foundation: Unites people to fight cancer and pursue an agenda focused on prevention, access to screening and care, and improvement of the quality of life for cancer survivors.	*www.livestrong.org*
Leukemia & Lymphoma Society: Health organization dedicated to funding blood cancer research, education, and patient services.	*www.lls.org*
There are local chapters located in Brookfield, Madison, and Menasha.	*www.leukemia-lymphoma.org/all_page?item_id=5101*
National Cancer Institute: Conducts and supports research, training, health information dissemination, and other programs related to cancer diagnosis and treatment.	*www.cancer.gov*
National Children's Cancer Society: Provides support, information, and education to those impacted by childhood cancer.	*www.nationalchildrenscancersociety.com*
National Osteoporosis Foundation: Provides information regarding the importance of bone health.	*www.NOF.org*
Next Steps Clinic (Children's Hospital of Wisconsin): Comprehensive survivorship clinic in the Milwaukee, Wis area.	*www.chw.org/NextSteps*
Planet Cancer: An online community of young adults with cancer.	*www.planetcancer.org*
Sam Fund: Assists young adult survivors of cancer by providing financial support through the distribution of grants and scholarships.	*www.thesamfund.org*
U.S. Preventive Services Task Force: Provides recommendations for cancer screening.	*www.ahrq.gov/clinic/uspstfix.htm*

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