Seminars in Pediatric Surgery 24 (2015) 93–99

Contents lists available at ScienceDirect

Seminars in Pediatric Surgery

journal homepage: www.elsevier.com/locate/sempedsurg

Childhood cancer survivors: Considerations for surgeons in the transition from pediatric to adult care

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ARTICLE INFO

Keywords:
Cancer survivors
Late effects
Second malignant neoplasms
Surveillance
Survivorship care plans

ABSTRACT

There are over 380,000 childhood cancer survivors (CCS) alive in the US, and the population is growing. CCS face significant long-term morbidity and mortality as a consequence of their cancer treatment and thus require lifelong, risk-based health care focused on surveillance and early intervention to minimize the impact of late effects and second malignant neoplasms (SMN). Surgeons play a critical role in the treatment of childhood cancer and the subsequent management of long-term health complications. In this review, we provide an overview of late effects associated with cancer surgeries, potential late effects that may require surgery as an adult, and cancer therapies that may impact future safe surgery and anesthesia. We also describe the barriers to successful transition from pediatric to adult health care for CCS and the importance of treatment summaries, surveillance guidelines, and survivorship care plans for surgeons caring for CCS.

Introduction

One of the great successes in medicine is the treatment of childhood cancer. In the US, annually, there are approximately 11,000 new cases of cancer in people aged 21 years and younger. Due to advances in surgery, chemotherapy, radiation therapy (RT), and supportive care, over 80% of these patients will become long-term survivors.[1] As a consequence, there are more than 380,000 childhood cancer survivors (CCS) alive in the US,[2] and the population is expanding. This population faces significant health consequences of their cancer and its therapy, including end-organ dysfunction, second malignant neoplasms (SMN), and cognitive impairment. Of those children and adolescents treated for cancer in the 1970s through the 1990s, about 75% will develop a chronic health condition by 40 years of age; in more than 40% of survivors, the condition will be severe or life-threatening.[3] The Institute of Medicine (IOM) has recognized the serious health risks faced by CCS and has recommended lifelong, risk-based health care to mitigate the impact of these late effects. Such care includes a systematic plan for periodic surveillance and prevention that is adapted to the specific risks arising from the individual patient's previous cancer, therapy, genetic predisposition, health behaviors, and co-morbid conditions.[4,5] In response, various international groups have created and disseminated guidelines for the risk-based care of CCS.[6–10] In 2003, the Children's Oncology Group (COG) published the *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer* (available at: www.survivorshipguidelines.org), which provide surveillance guidelines based on survivors' exposures to cancer therapies.[6,10]

Pediatric surgeons play a critical role in both the treatment and the long-term follow-up of children with cancer. Surgeons who treat children with cancer and those who care for CCS need to be particularly aware of the late complications associated with cancer and its treatment. They should be familiar with those late effects associated with cancer surgeries, potential late effects that may require surgery as an adult, and lastly, cancer surgeries that may impact future safe surgery and anesthesia. Surgeons should be aware of published guidelines for survivor care, and survivorship care planning should include the surgical subspecialists to ensure that CCS receive focused, appropriate care aimed at minimizing morbidity and mortality.

Cancer surgeries associated with late complications

Please refer to www.survivorshipguidelines.org to review the COG Long-Term Follow-Up Guidelines for surveillance of patients who have undergone surgery as part of their primary cancer treatment.[10]

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http://dx.doi.org/10.1053/j.sempedsurg.2015.01.007
1055-8586/

Abdominal and pelvic surgery including laparotomy

Abdominal or pelvic surgery (for example, for resection of Wilms tumor, neuroblastoma, or rhabdomyosarcoma) places survivors at risk for adhesions and consequent bowel obstruction. In a study of 76 patients who underwent a laparotomy as part of a staging work-up for paratesticular rhabdomyosarcoma, 9 (11.8%) developed a subsequent bowel obstruction.[11] This was generally an early complication, occurring between 8 and 22 months after diagnosis. A study of survivors of bladder and prostate sarcomas similarly demonstrated that when adhesions did occur, they tended to be early complications.[12] Bowel obstructions are also well documented after staging laparotomy or splenectomy for Hodgkin lymphoma (HL), although these surgeries are no longer routine elements of HL care.[13,14] Bowel obstruction risk is further increased in patients who receive abdominal RT, which has been associated with chronic enterocolitis[15] and strictures. Radiation tolerance is influenced by both the dose and the volume of bowel in the radiation field.[16]

Nephrectomy

Nephrectomy is a common pediatric cancer surgery used for Wilms tumor (and other renal tumors such as clear cell sarcoma, congenital mesoblastic nephroma, and renal cell carcinoma). Nephrectomy may also be necessary for adrenal neuroblastoma in which the adrenal gland cannot be resected off of the underlying kidney. Nephrectomy may affect future renal function, although this relationship is confounded by the impact of nephrotoxic chemotherapy (e.g., ifosfamide) and RT on renal function.[17] Genetic predisposition to both Wilms tumor and renal dysfunction (e.g., WT1 gene mutations) may also modify this relationship. A Dutch study of 1442 CCS demonstrated that survivors who had undergone nephrectomy had an almost 9-fold increase in their risk for diminished renal function [as measured by glomerular filtration rate (GFR)].[18] A second study of 763 adult CCS demonstrated that nephrectomy increased the risk for decreased glomerular function, although most survivors maintained their GFR within the normal range.[19] There was also a higher risk for hypertension among those survivors treated with nephrectomy—almost a third had elevated blood pressure. COG guidelines suggest that survivors with a single kidney have their blood pressure checked annually and measurement of renal function and electrolytes at entry in a long-term follow-up program (and repeated as clinically indicated). Care should be taken to avoid nephrotoxic drugs (such as aminoglycoside antibiotics) and to use NSAIDs cautiously.

Splenectomy

Splenectomy as part of a staging laparotomy is no longer a standard practice in children with HL. However, adult HL survivors treated in prior eras may be rendered surgically asplenic and thus at risk for serious infections due to encapsulated organisms (*H. influenzae*, *S. pneumonia*, and *N. meningitidis*).[13] Asplenic patients require appropriate vaccination against these organisms —guidelines for the types and timing of vaccination have been published in the US,[20–22] UK,[23] and elsewhere. Antibiotic prophylaxis with penicillin is recommended in asplenic patients younger than 5 years old and for 1–2 years after splenectomy in older patients.[24] However, there is controversy as to when prophylaxis should be discontinued, with some bodies suggesting lifelong antibiotic prophylaxis. Sepsis is considered a medical emergency in asplenic patients—febrile patients require prompt medical attention, blood culture, and treatment with parenteral antibiotics with efficacy against encapsulated organisms (e.g., ceftriaxone or clindamycin).

Pulmonary surgery

There are several malignancies that can primarily involve the lung in children, including pleuropulmonary blastoma, inflammatory myofibroblastic tumors, and carcinoid tumors. Metastatic lesions are the most common cancers that involve the lung, with many tumors common in childhood having a tendency for pulmonary metastases (e.g., osteosarcoma, Wilms tumor, rhabdomyosarcoma, and hepatoblastoma). Children may undergo lung surgery for diagnosis or therapy (for example, in primary lung tumors and metastatic osteosarcoma). Such resections can range from small wedge resections, partial or complete lobectomies, to pneumonectomies. Lung resection has been associated with a long-term risk for decreased pulmonary function, particularly in patients who are also treated with chemotherapy agents that are toxic to the lung (e.g., bleomycin) or pulmonary RT.[25,26] There is a paucity of data on the impact of pulmonary resection as part of childhood cancer therapy—much of the published literature focuses on adults, many of whom have underlying deficits in lung function at the time of surgery. Children tend to tolerate and adapt to pulmonary surgeries better than adults do,[27] with hyperplasia and hyperinflation of the remaining lung tissue compensating for the loss of lung tissue, even in children who have had a pneumonectomy.[28] Current recommendations include yearly pulmonary exam and suggest pulmonary function testing (PFT) (including DLCO and spirometry) at entrance into a long-term follow-up clinic. Further testing should occur as clinically indicated. Survivors with abnormal PFTs should be considered for repeat testing prior to anesthesia.

Scoliosis

Spinal surgery (laminectomy and laminoplasty) or RT to a field that involves the spinal column can lead to scoliosis and kyphosis in survivors. Both intraspinal tumors and tumors that develop adjacent to the spine (e.g., neuroblastoma) can be indications for spinal surgery if they compress the spinal cord, or if resection is needed for local control. In a study that included 33 children treated with spinal surgery but not radiation, 24 survivors developed a spinal deformity.[29] Among 22 patients in the same study treated with laminectomy and RT, all 22 developed a deformity. The COG guidelines recommend that survivors treated with hemithoracic, abdominal, or spinal surgery, particularly if they also received RT to the spine, undergo at least yearly spine exam to assess for scoliosis and kyphosis until growth is completed.

Limb salvage or amputation

Bone sarcomas (particularly Ewing sarcoma and osteosarcoma) increase in incidence during adolescence, accounting for approximately 6% of cancers in 15–19 year olds. Surgical approaches to limb sarcoma therapy vary according to location, involvement of vital structures, likelihood of complete tumor excision, and surgeon preference. Amputation (which includes rotationplasty) and limb-sparing procedures (e.g., endoprosthesis, arthrodesis, allogeneic, or autogenous bone grafts) both play a role in the local control of extremity tumors. Although limb sparing is often the preferred option when feasible, there are concerns about the durability, risk for complications, and level of function after these procedures.[30] A review by Nagarajan et al.[31] listed the more common late complications of limb salvage procedures as nonunion, pathologic fractures, aseptic loosening, leg-length discrepancies, implant breakage, and poor joint movement. Late complications of amputation include stump-prostheses problems, stump and phantom limb pain, and bone overgrowth.[31] Studies comparing functional and quality-of-life outcomes after limb

salvage vs. amputation have shown inconsistent results, with some suggesting superior functional and quality-of-life outcomes after limb salvage, while others have demonstrated no differences between groups. A study of 57 survivors of lower limb osteosarcoma during childhood or young adulthood revealed that quality of life was dependent on lower limb function, but the type of surgery (amputation vs. limb salvage) did not impact the relationship.[32] Given the risk for complications of limb salvage, and the need to ensure good prosthetic fit, annual assessment is recommended. Further, antibiotics should be considered for patients with endoprostheses undergoing dental surgery—guidelines have been published by the American Dental Association.[33]

Oophorectomy and orchiectomy

Ovaries and testes may require removal if involved with a germ cell tumor. In addition, orchiectomy is indicated in the case of paratesticular rhabdomyosarcoma. Among female survivors who have had a single ovary removed, the possibility for future fertility remains if the contralateral ovary has not been exposed to gonadotoxic doses of radiation or alkylating agent chemotherapy. A study of 64 survivors of malignant germ cell tumors of the ovary treated with fertility-preserving surgery (i.e., removal of the affected ovary with preservation of the contralateral ovary and uterus) observed that of the 38 women who subsequently attempted conception, 29 (76%) were successful.[34] Similar rates of success have been reported in other series.[35,36]

Knowledge about fertility and other outcomes in males with a single testicle has been generated from studies of survivors of germ cell tumors[37] as well as men with a history of unilateral cryptorchidism.[38,39] Among a cohort of 680 men treated for a testicular germ cell tumor, 207 reported attempting conception after therapy.[37] Of those patients treated with surgery alone, 85% of those that attempted to conceive were successful. In contrast, 71% of those patients who received chemotherapy in addition to orchiectomy conceived. Studies of males with unilateral cryptorchidism have shown no decrease in successful paternity in men with a single testicle.[38] Males treated with bilateral orchiectomy will require endocrine follow-up for hormone replacement.

Examples of late effects requiring surgical care

SMN

After recurrence, SMN result in the highest risk of mortality in long-term CCS.[40,41] SMN have been reported in 5–15% of long-term CCS, with a 30-year cumulative incidence approaching 10% in a large North American cohort of CCS.[42,43] Surgeons should be aware of the risk and risk factors for solid tumor development, as well as the surveillance recommendations for their detection, since for many of these tumors, early detection and treatment often improve outcomes.

Among CCS treated in the 1970s and 1980s, breast cancer is the most frequent SMN, after non-melanoma skin cancers.[43–47] Breast cancer occurs in a relatively young age in this population, and the cumulative incidence increases with age, ranging from 10% to 30%.[44,48] Exposure to chest RT for HL treatment during this era accounts for the majority of breast cancers in CCS.[44,45,48,49] Recently, Moskowitz et al.[47] showed that in a cohort of 1230 women exposed to chest RT, the cumulative incidence of breast cancers among HL survivors was 30% by 50 years of age (95% CI: 20.7–34). Given these high rates of breast cancer at a young age, both the COG and the American Cancer Society (ACS) recommend initiating early breast cancer surveillance in these women with both breast magnetic resonance imaging (MRI) and mammography in women exposed to chest RT.[48,50,51] Of importance for surgeons who may diagnose and treat breast cancer in CCS, previous exposure to chest RT may impede healing after biopsy and surgeries and may prevent lumpectomy as an option, as further radiation exposure may not be possible in many cases.

Radiation exposure also results in an increased risk for secondary sarcomas and gastrointestinal malignancies.[52–54] Clinicians should counsel survivors to report lumps, bumps, or pain in the radiation field in order to detect second tumors as early as possible. For sarcomas in particular, resectable tumors have significantly improved outcomes.[55] Likewise, for survivors who received over 35-Gy radiation exposure to the abdomen, the COG recommends early colorectal cancer surveillance with colonoscopy starting at 35 years of age.[54]

Approximately 10% of SMN among CCS are cancers of the thyroid gland.[56] This risk is primarily attributable to RT. This risk does not plateau throughout adulthood and is highest for those survivors who received a thyroid dose of 15–30 Gy.[57,58] Current COG recommendations include yearly thyroid-stimulating hormone and T4 (to assess for hypothyroidism) as well as a clinical thyroid examination to detect thyroid masses/nodules. Surveillance with imaging is not recommended as there has been no evidence to date that detection with radiologic surveillance improves outcomes for thyroid carcinomas.

Osteonecrosis

Osteonecrosis is the result of bone death due to inadequate blood supply and bone marrow ischemia. It can lead to an array of symptoms ranging from mild discomfort to debilitating pain and immobility, joint swelling, and articular collapse. Osteonecrosis is most commonly observed in acute lymphoblastic leukemia (ALL) survivors, with an incidence ranging from 1.6% to 9.3%.[59,60] Higher incidence is associated with older age at cancer treatment (>10 years).[59] Treatment-related risk factors include prolonged exposure to corticosteroids, asparaginase, and RT.[59,61] Symptoms usually develop within 2–3 years of treatment.[59,60] In over 90% of cases, weight-bearing joints are affected, with hips and knees being most common. Frequently, multiple joints are affected.[59,60] The preferred modality for evaluating osteonecrosis is MRI.[62] However, the utility of MRI for surveillance has not been established, since not all patients with radiographic evidence of osteonecrosis will develop progressive joint destruction.[63] Depending on the joint location, severity, patient age, and status of cancer treatment, survivors can be treated with physical therapy, limitation of weight-bearing, analgesia, and/or surgery. Of 31 children who developed osteonecrosis in a cohort of 1951 patients treated on a single ALL trial, 13 patients required a total of 22 surgical procedures.[64] Surgical interventions for osteonecrosis include core decompression, rotational osteotomy, vascularized bone graft, and joint replacement.

Late effects that impact-safe surgery

Beyond the morbidities that may result after surgery for a childhood cancer, surgeons need to consider long-term morbidities resulting from other components of cancer therapy (i.e., RT and chemotherapy) that may impact the feasibility and safety of future surgeries. For example, radiation may impact options for surgeries that involve structures in the radiation field. Treatment of SMN or other late effects of radiation in the irradiated field may be hampered by poor wound healing, which can lead to chronic ulceration, infection, poor cosmetic outcome, and psychological distress.[65]

Chronic medical conditions that arise from chemotherapy or radiation can impact-safe surgery. Cardiac and lung disease are the most common causes of non-cancer-related premature mortality in survivors. Clinical or sub-clinical organ dysfunction may impact the safety of anesthesia and surgery. Consequently, knowledge of a cancer survivor's prior therapy and their specific risks for late effects is vital for informing a surgeon's decisions around surgical interventions and the need for investigations prior to surgery. As discussed below, a treatment summary and a survivor care plan are critical documents for informing physicians (including surgeons) about prior exposures, current morbidities, and future risks.

Cardiovascular late effects

Survivors treated with anthracycline chemotherapy agents (e.g., doxorubicin and daunorubicin) are at an increased risk for cardiomyopathy as a consequence of cardiac myocyte damage. Anthracyclines are a commonly used class of chemotherapy agents and are received by approximately 50% of children with cancer. Risk factors for anthracycline-induced cardiomyopathy include higher cumulative doses, younger age at therapy, and concomitant receipt of radiation to a field that involves the heart. Cardiac dysfunction can develop acutely or shortly after completing therapy, but most cases do not manifest until years or even decades after exposure. The COG recommends screening echocardiography every 1, 2, or 5 years, depending on dose, age, and receipt of radiation. The safety of surgery in patients who have developed cardiomyopathy should be assessed in consultation with a cardiologist. However, for patients with a history of anthracycline exposure but no manifestations of cardiac disease, there is limited literature to guide care. Among pregnant women who have been treated with anthracyclines, the outcomes of pregnancy are good, unless clinical or sub-clinical cardiac dysfunction has been identified prior to pregnancy.[66,67] These women are at an increased risk for cardiac compromise and thus assessment of cardiac status with current echocardiogram is recommended. Similarly, for cancer survivors undergoing major surgeries, it would appear reasonable to confirm normal cardiac function prior to anesthesia, although guidelines for who require such an assessment have not been published. RT to a field that includes the heart can also lead to long-term cardiac disease. The impact of radiation extends beyond the myocardium to include all cardiac structures (i.e., pericardium, conducting system, valves, and coronary arteries). Knowledge of prior RT (including dose and field) as well as any clinical or sub-clinical manifestations of cardiac sequelae is needed to guide pre-surgical planning.

Pulmonary late effects

Radiation to a field that involves the lungs and certain chemotherapy agents (e.g., bleomycin, busulfan, and nitrosoureas) can cause pulmonary damage. Interstitial lung disease is the most frequent manifestation of cancer therapy, but airways disease and pulmonary vascular disease can also occur.[17] Knowledge of prior therapy with pulmonary toxins, and of current clinical symptoms or pulmonary function abnormalities, is essential for making informed decisions about the safety of surgery and anesthesia. Concerns have been raised regarding the risk for progressive pulmonary toxicity in patients who receive high concentrations of oxygen after prior therapy with bleomycin therapy.[68,69] This has led to a recommendation that supplemental oxygen (e.g., during anesthesia) should be limited to the lowest concentration possible to minimize the risk. However, some studies have failed to demonstrate a relationship between fractional inspired oxygen and risk for pulmonary toxicity.[70,71] In fact, fluid balance and a history of smoking appear to be more important risk factors for post-operative pulmonary morbidity.

Transitions of care for childhood cancer survivors

The issues involved in transition from care in a pediatric cancer center to long-term follow-up as an adult differ from those observed in children with other chronic childhood diseases. At the time of transition, the malignant disease is seldom of concern; instead, survivors' health is impacted by delayed effects of treatment, often not evident for years or decades after the cancer therapy. Studies indicate that most adult survivors do not receive risk-based care as recommended by the IOM.[72,73] For example, Nathan et al.[74] examined over 8000 adult CCS and found that among women at a high risk for breast cancer and survivors at a high risk for colorectal cancer, only 46% and 12% had received appropriate surveillance with mammography and colonoscopy, respectively. Many factors contribute to suboptimal transitions and resultant lack of risk-based care including survivor, provider, and system-based factors. First, survivors are often treated at a young age and as a result, often have limited knowledge of the therapies they received and their potential consequences.[75] For example, in a study of 635 adult CCS, only a minority could accurately report exposure to anthracyclines and chest radiation.[75] Some survivors also have cognitive and psychological challenges that can impede their ability to appropriately transition to adult care. In North America, the majority of adult survivors of childhood cancer receive their health care from a primary care provider (PCP) in the community. Less than 20% are followed up in a cancer center-based long-term follow-up program.[73] Studies indicate that PCPs are largely unaware of the health conditions CCS face and do not know about the available surveillance guidelines for long-term follow-up.[76,77] Moreover, pediatric oncologists often report suboptimal knowledge of late effects and surveillance guidelines, which impedes successful transitions to adult providers.[78] No studies have examined surgeons' knowledge, but given the paucity of CCS in individual surgical practices, it is likely limited. It is critical that surgeons who see survivors, many of whom are at a high risk of morbidity and early mortality, have a clear understanding of their cancer history, including the details of treatment.

Lastly, barriers inherent to the health care system impact survivors transitioning from pediatric to adult long-term follow-up care. In the recent past, insurability was a barrier to receiving long-term follow-up care for many young adult survivors of childhood cancer.[79] Until the enactment of the Affordable Health Care Act (ACA), employers largely provided health benefits for young adults as they aged out of parental or public insurance plans; this was often costly or inadequate.[80] With the ACA, young adults may remain on parental plans longer and can obtain insurance through the exchanges.[81] Pre-existing conditions no longer prevent survivors from obtaining appropriate insurance. However, given the high cost of many of the tests recommended for risk-based surveillance, many of the tests are not covered or only partially covered by insurance policies, and knowledge of insurance coverage among childhood cancer survivors is incomplete.[82] For example, given significantly elevated rates of breast cancer at an early age, both the COG and the ACS recommend that women who were exposed to chest radiotherapy for their childhood cancer initiate breast cancer surveillance with breast MRI and mammography at an early age.[48,51] Some insurance policies will not provide reimbursement for the cost of these specialized tests or will reimburse a small portion tests, placing a high financial burden on those survivors who comply with these recommendations.[83] Lastly, some policies often have limited numbers of covered physicians, and finding a physician with

willingness and expertise to follow-up this high-risk population may be difficult.[84,85] As was the case prior to the ACA, access and coverage may disproportionately affect racial and ethnic minorities and those in lower socio-economic strata.

To date, no studies have examined the overall health care costs of the childhood cancer survivor population. Given the magnitude of the chronic morbidity in the adult childhood cancer survivor population,[3] it can be assumed the financial burden to the health care system is high. Several studies have examined the yield of the COG Long-Term Follow Guidelines and cost-effectiveness of some of the specific recommendations within the guidelines. Landier et al. reported on the yield of the COG guidelines for 370 childhood cancer survivors who underwent nearly 5000 screening tests during the course of 1188 clinic visits. While some tests, such as thyroid function testing, audiometry, DXA scanning, serum ferritin, and pulmonary function testing resulted in clinical relevant findings, many tests including screening CBC (for therapy-related leukemia) and EKG were of low yield.[86] Analyses using mathematical modeling by Yeh et al.[87] as well as Wong et al.[88] have examined the cost-effectiveness of the COG recommendations for surveillance echocardiograms for survivors exposed to chest radiation and anthracyclines. These studies suggest that performing echocardiographic surveillance less often than currently recommended by the COG guidelines may be nearly as effective in reducing risk of congestive heart failure, at significantly reduced cost. These yield and cost-effectiveness studies have been used to inform the most recent version of the COG guidelines, but the bulk of the published guidelines have not been subject to a cost-effectiveness analysis.

In 2006, the IOM published a seminal report, "Cancer Survivors: Lost in Transition," which called for survivorship care plans for all cancer survivors. This was echoed in the recent American College of Surgeons Commission on Cancer (COC) mandate that all cancer survivors must receive a survivorship care plan by 2015.[89] A survivorship care plan includes a detailed treatment summary, an overview of potential late effects, recommendations for follow-up, and contact information for the treating cancer center. In recent nationally representative surveys, physicians reported that treatment summaries and survivorship care plans are of the most important tools they would need in caring for adult CCS.[77,90] Yet, less than 30% of physicians caring for CCS reported ever receiving a care plan. Research has indicated that receipt of a survivorship care plan improves rates of risk-based health care.[91] Thus, as more adult providers (including PCPs, surgeons, and obstetrician–gynecologists) care for CCS in their practices, efforts must be made to improve dissemination of these documents. Likewise, concerted efforts to educate physicians across specialties must be implemented so that this vulnerable population receives appropriate care. It has been suggested that these efforts should begin in medical school and extend through post-graduate training and continuing medical education for all physicians.

Summary

Surgeons play a critical role in childhood cancer treatment and can provide significant expertise in caring for survivors. They must be empowered to recognize the complications of cancer surgeries, to intervene surgically in the treatment of certain late effects and SMN, and to consider late effects that may impact-safe surgery and anesthesia. It is imperative that when surgeons provide care to a CCS, they have a good understanding of the survivor's individual cancer history, its therapies, and associated risk of late effects and SMN and available surveillance guidelines.

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