Fertility, Cardiac, and Orthopedic Challenges in Survivors of Adult and Childhood Sarcoma

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OVERVIEW

The combination of cisplatin, doxorubicin, and methotrexate was established as the standard backbone of contemporary osteosarcoma therapy in 1986. Since then, however, further improving the survival of patients with osteosarcoma has been challenging—30% to 40% of patients with osteosarcoma still die of this disease. In addition, these patients often experience loss of fertility at a young age, short- and long-term treatment-related cardiotoxicity, and adverse orthopedic effects from surgical resection of the tumor or endoprosthetic reconstructions. Cancer treatment often markedly increases the risk of infertility later in life, causing many patients substantial distress and regret. Sperm banking and oocyte cryopreservation are standard of care and should be available to all at-risk patients. Newer techniques, such as autologous gonadal tissue transplant for prepubertal children, are being developed, and newer systemic agents have infertility risk profiles that remain undefined and warrant further study. Cost and access remain barriers to these options. The late effects of anthracycline-induced cardiotoxicity are also increasingly a problem for these patients. These effects are often progressive and can be disabling. Adding dexrazoxane to doxorubicin therapy significantly reduces the risk for most adverse cardiac outcomes without compromising the efficacy of induction chemotherapy. Limb salvage surgery remains the standard of care for treatment in the majority of patients with extremity sarcomas. Modular metal prostheses and allograft reconstructions comprised the majority of surgical procedures for limb salvage surgery. The most common mechanism of failure of these implants is infection and mechanical failure of the implant.

Currently, more than 640,000 adolescent and young adult (age 15 to 39) cancer survivors live in the United States. This number is expected to rise sharply during the next decade.[1] Survival depends greatly on the type and stage of cancer, but with a combination of local and systemic treatment, cure rates range from 85% among patients with stage I disease to 10% to 20% for patients with stage IV disease.[2] However, the cure has a cost: the same life-saving surgery, radiation, and anthracycline chemotherapy used to treat cancer often comes with the loss of fertility, early and late cardiotoxicity, and orthopedic problems. These outcomes include loss of spermatogenesis and premature ovarian failure; acute cardiomyopathy during chemotherapy and late cardiomyopathy in subsequent decades; infections and complications of limb-salvage surgery; and death.[3,4]

PRESERVING FERTILITY IN PATIENTS WITH SARCOMA

Oncofertility is a term coined in 2006 to describe the specific care patients with cancer require to preserve their present or future reproductive capacity.[5] The field is at the intersection of reproductive specialists and oncologists, and is designed to bring more and better reproductive options to cancer survivors.

Infertility can be distressing for adolescents and young adults, particularly those who have not started their own families. The effects of cancer-related infertility are long-standing, with increased grief and decreased quality of life reported even 10 years after diagnosis.[6,7] Up to 75% of nulliparous patients report wanting to have children.[8] Soft tissue sarcoma comprises 7% of the total number of cancer cases, and disproportionately affects children: it is the third most common childhood cancer,[9] accounting for 20% of cancers in children and 10% in adolescents and young adults.[10] It can present in a wide variety of locations and histologic types, with rhabdomyosarcoma accounting for almost one-half of cases.[9] As a result of the wide prevalence of soft tissue sarcomas among adolescents, and because treatment can typically result in infertility, efforts to preserve fertility before therapy can be beneficial in young patients with sarcoma.

As tumors of muscle and bone, sarcomas can arise anywhere in the body, especially in the thigh, pelvis, and

retroperitoneum. Therefore, reproductive organs can potentially be in the radiation field or within the scatter region for radiation therapy. Increasingly complex treatment techniques, such as intensity-modulated radiation therapy, may improve clinical outcomes, although a larger area can be exposed to radiation, albeit at lower doses.[11] For males, even cumulative doses as low as 2 Gy to the gonads can affect fertility. For females, the damaging dose is age dependent; lower radiation doses can affect fertility more as age increases,[12] probably because of the natural decrease in the number of follicles with aging. Thus, the radiation dose most likely to cause ovarian failure decreases from 15 Gy in girls to 6 Gy in women.[13,14]

Systemic multiagent therapy, which includes alkylating agents, for patients with high-grade sarcoma is individualized, yet a concern for later fertility issues. Systemic therapy is considered a principle backbone of therapy for certain sarcomas, including Ewing sarcoma and rhabdomyosarcoma. It is well known that alkylating agents as part of systematic therapy can decrease fertility in both male and female cancer survivors.[15] In males, it inhibits spermatogenesis and can cause prolonged azoospermia. Although this effect is dose-dependent,[16,17] and though efforts are always made to avoid a toxic dose, the effects in combination regimens are additive and not fully understood.[18] Dacarbazine and taxanes usually cause only temporary sterility, but they can also have an additive effect when combined with alkylating agents.[19]

In females with sarcoma, abdominal or pelvic irradiation decreases ovarian reserves. Any radiation exposure to the uterus or ovaries increases the risk of infertility, and higher doses of radiation further increase this risk.[15] Additionally, alkylating agents commonly used for sarcoma, such as ifosfamide, carry a high risk of amenorrhea and subsequent infertility.[20]

All patients with sarcoma should be informed of the increased risk of infertility from treatment. If they are interested, or even undecided, they should be offered a fertility consult and a referral to a specialist as soon as possible, ideally before treatment is initiated.[21]

Options for preserving fertility continue to evolve. For males, sperm banking before treatment is the best way to preserve fertility. Before chemotherapy, viable sperm may be collected by masturbation, penile vibrostimulation, electroejaculation, or, in rare cases, testicular sperm extraction. Semen samples must be analyzed to ensure the presence of sperm. If sperm are absent or in sexually immature patients, sperm can be extracted by testicular biopsy.[22]

Both testicular sperm and cryopreserved ejaculated sperm require assisted reproduction with intracytoplasmic sperm injection for conception. After chemotherapy, non-obstructive azoospermia can also be treated with testicular sperm extraction, but success rates are limited, reaching 20% after exposure to alkylating agents.[23] Unfortunately, spermatogenesis is not always recovered, and a pregnancy can only be achieved through a sperm donor.

In females, age is critically important because follicular reserve decreases with time and decreases further with cancer treatment.[24] Given the potential impact of cancer treatment on female fertility, the risk of infertility and fertility preservation options should be discussed before cancer therapy is initiated. After cancer therapy is complete, fertility treatments may be less successful and many patients will often require donor eggs or surrogates.[21]

Oncofertility options for women most commonly include embryo and oocyte cryopreservation. Despite a high success rate and being a validated method for preserving fertility, embryo cryopreservation presents a unique problem: it requires sperm from the patient's partner or a donor, which is an unrealistic option for minors.[21] Oocyte cryopreservation is a practical alternative and should be recommended to all female patients at risk for infertility, with appropriate counseling. The process requires injecting follicle-stimulating hormone for egg retrieval, and it is only possible in post-pubertal females.[25] Delay in starting cancer therapy is a strong concern because a complete ovulation-and-egg retrieval cycle can take up to 4 weeks. However, with options such as natural cycle stimulation, egg retrieval can be done in less than 2 weeks.[26]

Other options for preserving fertility in prepubertal patients remain experimental. These options include in vitro maturation of immature eggs, autologous transplantation of cryopreserved ovarian tissue, and cryopreservation of testicular tissue.[21]

Oncofertility is a developing field for which the future still holds several challenges, from educating providers to determining the effects of new therapeutic agents on fertility. Newer agents that have improved survival in patients with sarcoma include trabectedin, a new DNA-binding molecule,[27] and several molecular-targeted agents including pazopanib and sunitinib, which are multikinase angiogenesis inhibitors,[28,29] and crizotinib and imatinib, which inhibit tyrosine kinases.[30,31] Animal studies show that targeted molecules are generally safer for fertility than conventional chemotherapy,[32] but long-term studies in humans are still required.

The biggest challenge of oncofertility is providing access to care to all patients. Costs can be prohibitive and are currently not covered by most insurance companies.[33]

KEY POINTS

- **Preserving fertility, treating cardiotoxicity, and minimizing orthopedic interventions and complications are integral aspects of caring for patients with sarcoma.**
- **Sperm banking and oocyte cryopreservation should be considered for all patients at risk of losing fertility.**
- **Adding the cardioprotectant dexrazoxane to cancer treatment can reduce anthracycline-related cardiotoxicity without compromising efficacy.**
- **Tumor resection and failed limb-preserving surgeries can result in serious infections and complications.**
- **The increasing number of survivors of sarcoma makes studying the late effects of treatment more important.**

TABLE 1. Cardiotoxic Effects of Selected Cytotoxic Agents

Treatment	Cardiotoxic Effect
Anthracyclines Daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone	Arrhythmias, pericarditis, myocarditis, HF, LV dysfunction
Liposomal anthracyclines Pegylated liposomal doxorubicin hydrochloride (DOXIL, CAELYX)	HF, LV dysfunction, arrhythmias
Antimetabolites Capecitabine, carmustine, clofarabine, cytarabine, 5-fluorouracil, methotrexate	Ischemia, chest pain, MI, HF, arrhythmias, pericardial effusions, pericarditis, hemodynamic abnormalities
Antimicrotubule agents Paclitaxel, vinca alkaloids	Hypotension or hypertension, ischemia, angina, MI, bradycardia, arrhythmias, conduction abnormalities, HF
Alkylating agents Busulfan, chlormethine, cisplatin, cyclophosphamide, ifosfamide, mitomycin	Endomyocardial fibrosis, pericarditis, tamponade, ischemia, MI, hypertension, myocarditis, HF, arrhythmias
Small-molecule tyrosine kinase inhibitors Dasatinib, gefitinib, imatinib mesylate, lapatinib, erlotinib, sorafenib, sunitinib	HF, edema, pericardial effusion, pericarditis, hypertension, arrhythmias, prolonged QT interval, ischemia, chest pain
Monoclonal antibodies Alemtuzumab, bevacizumab, cetuximab, rituximab, trastuzumab	Hemodynamic abnormalities, LV dysfunction, HF, thromboembolism, angioedema, arrhythmias
Interleukins Denileukin, IL-2	Hypotension, capillary leak syndrome, arrhythmias, coronary artery thrombosis, ischemia, LV dysfunction
Miscellaneous agents All-retinoic acid, arsenic trioxide, asparaginase, etoposide, IFN-α, lenalidomide, 6-mercaptopurine, pentostatin, teniposide, thalidomide	Electrocardiographic changes, QT prolongation, torsades de pointes, other arrhythmias, ischemia, angina, MI, HF, edema, hypotension, bradycardia, thromboembolism, and retinoid acid syndrome that includes fever, hypotension, respiratory distress, weight gain, peripheral edema, pleural-pericardial effusions

Abbreviations: HF, heart failure; LV, left ventricular; MI, myocardial infarction.
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CARDIO-ONCOLOGY IN SARCOMA SURVIVORSHIP

Table 1 summarizes cardiotoxic effects of select cytotoxic therapies. Doxorubicin is a major agent for treating osteosarcoma. Event-free survival is lower in regimens with lower cumulative doses or dose-intensity, but higher doses increase the risk of cardiotoxicity.[34,35] The cumulative doxorubicin dose (up to 450 mg/m²) currently used in the United States to treat osteosarcoma is associated with acute cardiomyopathy during chemotherapy, late cardiomyopathy in subsequent decades, and death (Table 2). The hazard ratio of adverse cardiac outcomes in survivors who receive more than 250 mg/m² of anthracycline is two to five times as high as it is in those receiving doses less than 250 mg/m².[36] After 300 to 450 mg/m² of doxorubicin, the incidence of cardiomyopathy is readily apparent, with more than 25% of patients experiencing left ventricular systolic dysfunction beyond 15 years of follow-up.[37] Many long-term survivors are now between age 40 and 50, and they remain at risk for cardiac deterioration for the rest of their lives.

Trials using doxorubicin for osteosarcoma have reported a substantial incidence of acute cardiotoxicity. In one trial of 31 children and adults, cardiotoxicity required stopping doxorubicin administration in four patients.[39] In another, six of 164 patients experienced severe cardiotoxicity; five patients experienced events within 12 weeks of completing therapy.[40]

In 120 children and adults treated with bolus doses of doxorubicin in childhood (87 for acute lymphoblastic leukemia and 33 for nonmetastatic osteogenic sarcoma), 12 had transient early heart failure during or within 1 year after completing doxorubicin treatment.[41] Heart failure occurred later in 12 patients, seven of whom had also had early heart failure 3 to 16 years before. In three of the 12 patients with late heart failure, medical treatment failed; one underwent heart transplantation, one underwent heart-lung transplantation, and one died of documented ventricular fibrillation. Another five had initial episodes of heart failure at a mean of 10 years after completing doxorubicin treatment, including two women during the peripartum period and one during nonanthracycline chemotherapy for a relapse of cancer. When patients with clinical evidence of cardiotoxicity were excluded, the results were similar.[41]

Risk factors for cardiotoxicity with anthracycline therapy are described in Table 3. Multivariate analysis in this trial revealed that female sex and higher cumulative doxorubicin doses were associated with depressed left ventricular contractility (p < .001) and that these two variables interacted.[41] Independent and significant associations were found between a higher rate of administration of doxorubicin and increased left ventricular afterload (p < .001), left ventricular dilation, and depressed left ventricular function; between a higher cumulative doxorubicin dose and depressed left ventricular function (p < .001); between younger age at diagnosis and reduced left ventricular wall

TABLE 2. Characteristics of Different Types of Anthracycline Cardiotoxicity

Characteristic	Acute Cardiotoxicity	Early-Onset Progressive Cardiotoxicity	Late-Onset Progressive Cardiotoxicity
Onset	Within the first week of anthracycline treatment	< 1 year after completion of anthracycline treatment	≥ 1 year after completion of anthracycline treatment
Risk factor dependence	Unknown	Yes[a]	Yes[a]
Clinical features in adults	Transient depression of myocardial contractility	Dilated cardiomyopathy	Dilated cardiomyopathy
Clinical features in children	Transient depression of myocardial contractility	Restrictive cardiomyopathy and/or dilated cardiomyopathy	Restrictive cardiomyopathy and/or dilated cardiomyopathy
Course	Usually reversible after discontinuation of anthracycline	Can be progressive	Can be progressive

[a]See Table 3 for risk factors.
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thickness and mass and increased afterload; and between a longer time since completing doxorubicin therapy and reduced left ventricular wall thickness and increased afterload (p < .001).[41]

Late cardiotoxic effects of doxorubicin are increasingly a problem for survivors of childhood cancer. This cardiotoxicity is often progressive and can be disabling. However, given the efficacy of doxorubicin in treating childhood cancers, including osteosarcoma, many treatment initiatives have focused on preventing doxorubicin-related cardiotoxicity.

Dexrazoxane is a topoisomerase II inhibitor that protects against anthracycline-related cardiotoxicity, probably by scavenging free radicals and chelating heavy metals or by preventing the topoisomerase IIB–mediated DNA and mitochondrial damage induced by doxorubicin.[43,44] Used initially for cardioprotection in clinical trials of women with breast cancer receiving doxorubicin, dexrazoxane decreased the expected cardiotoxicity.[43] A recent meta-analysis of dexrazoxane use in children found that it substantially reduced the risk for most adverse cardiac outcomes.[45,46] In a study of 101 children with newly diagnosed metastatic osteosarcoma treated with trastuzumab, a humanized monoclonal antibody targeting HER2, in combination with cytotoxic chemotherapy and dexrazoxane, no patient developed clinical evidence of congestive heart failure after an average of 41.6 months of follow-up time.[47]

Dexrazoxane protects against cardiotoxicity without adverse outcomes in a wide range of cancers.[48] Its use has been endorsed by the American Heart Association and the American Academy of Pediatrics as a cardioprotectant in children and adolescents undergoing anthracycline-containing treatment protocols.[48] Doxorubicin has been used as the standard of good clinical care for all Dana-Farber Cancer Institute high-risk childhood acute lymphoblastic leukemia protocols involving anthracycline therapy since 2000 and on all Children's Oncology Group protocols involving treatment with at least 150 mg/m^2 doxorubicin or anthracycline administration at any dose with planned radiation treatment portals that may impact the heart since 2015.[49]

In a trial of children with osteosarcoma randomly assigned to receive doxorubicin with or without dexrazoxane, the dexrazoxane-treated children maintained higher mean left ventricular fractional shortening and were able to receive more doxorubicin.[50] In another trial, dexrazoxane reduced acute cardiotoxicity in young patients with sarcoma, but sample size limited the assessment of oncologic efficacy.[51] In a preliminary analysis of Children's Oncology Group protocols with random dexrazoxane assignments, long-term survivors of childhood cancer treated with doxorubicin and dexrazoxane appeared to have more preserved systolic function and reduced myocardial wall stress compared with

TABLE 3. Risk Factors for Anthracycline-Induced Cardiotoxicity

Risk Factors	Features
Total cumulative dose	Most important predictor of abnormal cardiac function
Age	For similar cumulative doses, younger age predisposes to greater cardiotoxicity (especially < 5 years)
Length of follow-up	Longer follow-up reveals higher prevalence of myocardial impairment
Sex	Females more vulnerable than males for similar doses
Concomitant mantle irradiation	Evidence of enhanced cardiotoxicity; not clear whether additive or synergistic
Others	Concomitant exposure to cyclophosphamide, bleomycin, vincristine, amsacrine, or mitoxantrone may predispose to cardiotoxicity; trisomy 21 and black race have been associated with a higher risk of early clinical cardiotoxicity
Rate of anthracycline administration	Higher rate was thought to predispose to greater toxicity, but current trials in children do not support this finding

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survivors treated with doxorubicin alone.[52] Schwartz et al showed that dexrazoxane did not interfere with the tumor cytotoxicity of preoperative induction chemotherapy in 242 children with leukemia enrolled in Children's Oncology Group protocol P9754.[53] Dexrazoxane was also not associated with acute cardiotoxicity in patients receiving either standard (450 mg/m^{2}) or intensified (600 mg/m^{2}) doses of doxorubicin.[53] Thus, dexrazoxane does not compromise response to induction chemotherapy.

In the study by Schwartz et al,[53] dexrazoxane was safely administered. It did not impair tumor response or interfere with cancer treatment efficacy. It also did not significantly increase the risk of secondary malignancy, and it allowed the cumulative doxorubicin dose to be increased in standard responders to induction chemotherapy. As well, in a randomized study of dexrazoxane administration with more than 12 years of follow-up, overall mortality did not differ by dexrazoxane status in three childhood cancer trials (1,008 patients).[54] These findings support the use of dexrazoxane in children and adolescents with osteosarcoma as it permits anthracycline dose-density increases without compromising overall long-term survival.

Cardiotoxicity secondary to anthracycline chemotherapy can be a devastating late effect of osteosarcoma treatment. Not only may it cause death and increase health care costs, but cardiac death was the second most common cause of late mortality in childhood cancer survivors reported by the Children's Cancer Survivor Study.[55] Heart failure, myocardial infarction, pericardial disease, and valvar abnormalities were substantially more prevalent in these patients than they were in siblings of cancer survivors.[36,56]

LONG-TERM OUTCOMES OF PATIENTS WITH SARCOMA AFTER ORTHOPEDIC SURGERY

Limb-salvage surgery remains the standard of care for treating patients with sarcomas of the long bones and is successful in about 90% of cases.[57] Innovations in implant design have increased the longevity of modular metal prostheses. Progress in allograft donation and processing has increased availability and survivability of allograft reconstructions. Despite advances in infection management and antibiotic development, the most common mechanism of failure in orthopedic interventions after treatment of sarcoma is infection. The second most common mechanism is failure of the construct from mechanical failure of the implant, whether from loosening of the implant away from the host or the fracture of the implant itself.[57-63] Amputation remains an option for these patients, and advances in prosthetic limbs allow a more active lifestyle, making this option more acceptable to patients.[64]

Bone Sarcomas

In bone sarcomas, after the primary lesion is removed, bones can be treated with what are termed the Five As: allograft, arthrodesis, arthroplasty (implanting metal modular oncologic endoprostheses), autograft, and amputation. The most common methods are arthroplasty and allograft. The method of reconstruction depends on the type of surgical resection (intercalary or intra-articular), the degree of residual bone loss, and the age of the patient. Adults more commonly receive modular endoprostheses, which allow immediate stability, immediate weight bearing, and do not rely on osseous integration as heavily as do allografts. The small bones and joints of younger and skeletally immature patients, as well as their potential growth, pose additional challenges.[59,61] Allografts often allow unique surgical approaches that can spare growth plates and thus are more commonly used in children.

Overall implant survival at 15 years for all endoprosthetic reconstructions is 80%.[57-63] Success is generally better in the upper arm than in the lower arm or the leg. Most limb-salvage procedures involve the proximal femur, the knee, and the distal femur or proximal tibia. Survival for proximal femur replacement is 93% at 5 years and 85% at 15 years.[62] Modular oncologic prostheses about the knee have about a 22% failure rate at 10 years. Infection is the most common mechanism of failure and has been up to 10% in large series.[62] The mechanism is aseptic loosening in about 5% of cases and implant fracture or failure in about 2%.[62] Functional outcome scores average 91%. Causes of prosthetic failure include soft-tissue failure, aseptic loosening, structural failure of the implant, infection, and local tumor recurrence.[57-63]

Overall allograft survival at 15 years is 70%.[65] As with modular prostheses, most reconstructions occur about the knee. Allograft reconstructions about the knee have about a 32% risk of failure at 10 years.[58,65] The primary mechanism of failure is infection. The 10-year risk of amputation is 11%. Functional outcome scores average 88%.[58] The most common mechanisms of failure are infection and failure of the reconstruction secondary to septic loosening and failure of the implant from infection, wear, or mechanical stresses at the host-bone interface that precludes long-term healing and osseous integration.

Infection is the most common method of failure for any long-bone reconstruction after sarcoma surgery.[57-65] Patients with a bone sarcoma typically undergo resection and reconstruction in combination after chemotherapy and are accordingly at risk for infection while immunosuppressed. Large surgical wounds are at particular risk for wound-healing complications. Breaching the skin can increase the risk of wound breakdown and infection, both of which endanger the reconstruction. The large bone defect left after resecting implants or allografts often precludes limb-salvage surgery and thus results in amputation.[58,59,64]

All methods of reconstruction are subject to failure-of-construct. In the setting of allograft, autograft and arthrodesis, failure of the allograft to heal to the host bone will allow the hardware to fail over time. The resulting hardware failure, pain, and subsequent revision surgeries may lead to amputation. Arthroplasty, especially to place a modular oncologic prosthesis or mega prosthesis, is uniquely susceptible to aseptic loosening. The large volume of bone loss places substantial stress on the bond between the implant

and the host site. This bond is often fixed with cement, and rotation forces incurred at this site are particularly likely to loosen it. Implant fixation techniques that foster osseous integration may improve long-term outcomes, but the weight bearing surfaces of these implants are still subject to wear at the bearing surfaces, especially in the young population who have more cycles on an implant.

Unique surgical procedures for children include vascularized bone grafting, rotationplasty, and growing prostheses.[59,61] The unique nature and small number of these procedures limits the amount of data about them. However, outcomes, such as retaining the limb with the use of an allograft, arthroplasty, or vascularized autograft, are better for both physical functioning and emotional acceptance than they are for amputation, which includes ablative surgery and rotationplasty.[59]

Pelvic reconstruction after sarcoma surgery also has unique circumstances and complications.[66] These reconstructions can include allografts, metal prostheses, or, alternatively, no reconstruction at all. Patient satisfaction varies, depending on volume of the pelvis removed and the age of patient at the time of resection. Patients who do not undergo reconstruction after pelvic resection (flail limb) have fewer complications and higher satisfaction scores.[66]

Soft Tissue Sarcomas

Most soft tissue sarcomas occur in adults, although the complications are quite similar in some soft tissue sarcomas in children, except for those related to growth. Soft tissue sarcomas are commonly treated with surgical resection and radiation therapy, which are responsible for complications. Radiation therapy involving the growth plate of a bone may halt growth in that bone. In addition, short- and long-term complications from treating soft tissue sarcomas can be related to surgery when combined with radiation therapy. Wound healing complications and fibrosis are the most common complications.

Preoperative radiation therapy is delivered in a lower dose to a smaller field, but the short-term insult to the skin interferes with early wound healing, which can lead to further stiffness, given the need for surgical debridement and wound care. Stiffness reduces the range of motion, limiting mobility and increasing pain. Radiation therapy after surgery provides a larger field and a higher dose, which can contribute to larger areas of stiffness and lymphedema. Radiation to large, deep, high-grade sarcomas can also contribute to radiation necrosis, with short- or long-term effects, including bone fractures requiring intramedullary fixation and the need to remove necrotic bone.[64] Once the bone has become necrotic, attempts to support bone healing without resection are fraught with complications, including multiple surgical procedures, pain, and unsatisfactory results.[67]

CONCLUSION

Worldwide, more than 28 million people live with cancer. This number could triple by 2030. With the increasing number of patients and improvements in cancer management that continue to reduce cancer death rates, the number of survivors is projected to increase rapidly, especially among those afflicted during childhood. In children and adolescents, the survival rate has jumped from fewer than 50% in the mid-1970s to 80% today. The growing population of childhood survivors is notable for its vulnerability to adverse health outcomes, many of which may not become clinically apparent until years after therapy has been completed.[38] Loss of fertility, cardiotoxicity, and orthopedic complications are three such adverse outcomes.

For prepubertal patients, preserving and perhaps transplanting testicular and ovarian immature tissue should be discussed as experimental options. The data support the use of the cardioprotectant dexrazoxane for all children who require anthracycline therapy for treatment of osteosarcoma to mitigate or prevent the development of cardiotoxicity, and developments in limb-salvage surgery should improve the orthopedic outcomes in these patients.

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