Review Article

Musculoskeletal Effects of Cancer and Cancer Treatment

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Abstract

Improvements in cancer treatment have led to prolonged survival and increased rates of cure. An estimated 14 million cancer survivors live in the United States. The cornerstones of cancer treatment, including radiation, chemotherapy, and surgery, give rise to a host of chronic health conditions, some of which affect the musculoskeletal system. As survivorship continues to improve, orthopaedic surgeons across all subspecialties will be tasked with managing these complications of treatment. This article reviews orthopaedic health concerns secondary to cancer treatment that are likely to present to orthopaedic surgeons for evaluation, such as osteoporosis, osteonecrosis, secondary malignancies, radiation-associated fractures, exercise tolerance, and perioperative evaluation.

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Improvements in the treatment of childhood cancers have led to 5-year survival rates of up to 75% to 80%, with many patients living into adulthood.[1] Currently, there are nearly 380,000 adult survivors of childhood cancers,[1] and an estimated 14 million cancer survivors are alive today. Many pediatric cancer survivors face health challenges during adulthood as a result of cancer treatment. The Childhood Cancer Survivor Study analyzed data from a cohort of more than 20,000 childhood cancer survivors and found that two-thirds of long-term survivors develop at least one chronic health condition,[2] and more than one-third develop a serious or life-threatening health condition as a result of cancer treatment. A longitudinal study of survivors of Ewing sarcoma showed that musculoskeletal complications were the most common chronic conditions in this patient population.[3] Long-term cancer survivors are at risk of developing musculoskeletal conditions such as osteopenia, osteoporosis, fragility fractures, and osteonecrosis that require an orthopaedic surgery consultation. Chemotherapy and radiation therapy can cause chronic health conditions that may place survivors at a higher risk of perioperative complications when undergoing elective surgery. The orthopaedic surgeon should be knowledgeable of these risk factors when treating this population.

In this article, we review common musculoskeletal conditions that affect long-term cancer survivors. Perioperative risk assessment after cancer therapy is addressed. In addition, we examine how the type and duration of chemotherapy exposure may necessitate patient-specific exercise regimens, and we provide exercise recommendations for this unique population.

Osteoporosis and Osteopenia

Effects of Childhood Cancer Treatments

Both cancer and various treatments, such as high-dose steroids, ablative

Table 1

Common Chemotherapeutic Agents With Musculoskeletal Effects

Drug Class	Commonly Used Drugs	Types of Cancers	Manifestation
Alkylating agents[a]	Mechlorethamine (nitrogen mustard), oxazaphosphorines (cyclophosphamide and ifosfamide), melphalan, nitrosoureas (lomustine and carmustine), and busulfan.	HL, NHL, sarcomas, germ cell tumors, testicular, leukemias, lung, breast, and ovarian	Can cause hypogonadism and early menopause, which can lead to secondary osteoporosis, and second malignant neoplasms
Anthracyclines[b]	Doxorubicin and daunomycin	ALL, AML, bone and soft-tissue sarcomas, Wilms tumor, and neuroblastoma	Second malignant neoplasms (cardiotoxicity)
Antimetabolites	Methotrexate, mercaptopurine, and cytarabine	ALL, NHL, osteosarcoma, chronic myelogenous leukemia, and histiocytosis	Osteoporosis and methotrexate osteopathy
Corticosteroids	Dexamethasone and prednisone	ALL, NHL, Hodgkin disease, histiocytic disorders, and brain tumors[d]	Osteopenia and osteonecrosis
Epipodophyllotoxins[c]	Etoposide and teniposide	Pediatric solid tumors and ALL	Secondary malignancies (eg, AML)
Heavy metals	Cisplatin and carboplatin	Pediatric solid tumors	Nephrotoxicity, neuropathy, and ototoxicity

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, HL = Hodgkin lymphoma, NHL = non-Hodgkin lymphoma
[a] Highly carcinogenic, mutagenic, and teratogenic.
[b] Approximately 40% to 50% of childhood cancer survivors were treated with anthracyclines.
[c] For example, topoisomerase II inhibitors, very oncogenic.
[d] Also used to treat cancer-related complications (eg, nausea/vomiting, anorexia, and hypercalcemia).

cytotoxic chemotherapy, and radiation, negatively affect bone health and place survivors of cancer at risk of osteoporosis and osteopenia. Children and adolescents who fail to reach their expected peak bone mass will have lower bone mineral density (BMD) throughout adulthood and are at a greater risk of osteoporosis and fragility fractures later in life. Chemotherapy, radiation therapy, poor oral intake, and reduced physical activity levels associated with treatment all contribute to decreased bone accumulation and growth. The St. Jude Lifetime Cohort Study reported that osteoporosis occurred at a rate of 9.6% among adult survivors at a median age of 32 years if they had been exposed to therapies known to affect bone metabolism.[4]

Most long-term survivors have been treated with multiagent chemotherapy. Table 1 lists common anticancer therapeutics that affect bone metabolism. While receiving systemic treatment, many children develop nausea, gastritis, and mucositis and are unable to eat a balanced diet. Consequently, they become malnourished and may experience cessation of growth until calorie intake improves. The incidence of malnutrition ranges from <10% to 50%, depending on the severity of the cancer and type of chemotherapy regimen. Compounding the issue is a decrease in physical activity during treatment, further compromising bone acquisition during a time of peak bone acquisition. As a result, these children may reach a lower peak bone density in adulthood, which may predispose them to osteoporosis later in life.[5,6]

Steroids are used to treat several childhood malignancies, such as leukemia, lymphoma, and brain tumors, and to control cancer-related complications. High-dose steroids affect skeletal growth and BMD through direct and indirect effects on bone and calcium metabolism. In a recent meta-analysis investigating corticosteroid-induced osteoporosis, the authors found that BMD was lower among children receiving steroids than among healthy children. The rate of clinical fractures ranged from 6% to 33%.[7]

Methotrexate, the most commonly used chemotherapeutic agent for hematologic malignancies and pediatric sarcomas, alters bone metabolism. Methotrexate osteopathy, a constellation of osteoporosis, bone pain, and fractures, was first described in patients treated with low-dose methotrexate for leukemia but has been noted in patients with osteosarcoma. Ecklund et al[8] examined the radiographs and records of 87 patients with osteosarcoma who were treated with high-dose methotrexate. Eight patients (9%) exhibited signs of severe osteopenia, dense zones of provisional calcification, insufficiency fractures, and multiple bone involvement. They found that patients treated with high-dose methotrexate during the first decade of life were at the highest risk

of developing osteopathy compared with those treated during the second decade of life. Most children improve rapidly after discontinuation of methotrexate; however, progressive bone deformity may develop with continued treatment. Van der Sluis et al[9] found that children with acute lymphoblastic leukemia (ALL) were six times as likely to sustain a fracture during treatment or within the first 2 years after treatment compared with healthy controls because of poor bone health. In a separate study by the same group, 61 children with ALL were evaluated with dual-energy x-ray absorptiometry, body composition measurements, and serum markers of bone turnover at diagnosis, during therapy, and 1 year after cessation of therapy. Eleven fractures occurred in nine patients (15%).[10] No difference in BMD was found between those with and those without fractures; however, a decrease in BMD during the first 6 months of treatment was correlated with the occurrence of later fractures, suggesting that a decrease in BMD has a greater influence on fracture risk than does absolute BMD value.[10] Strauss et al[11] also found an increase in fractures among children and adolescents treated with steroids for ALL. The authors followed 176 treated patients over an 8-year period. With a mean follow-up of 7.6 years, they calculated a cumulative index for fracture at 5 years of 28% (±3%). Children older than 9 years, boys, and patients receiving dexamethasone were at an increased risk of fracture. Some studies suggest that treatment with craniospinal radiation is a greater risk factor for long-term decreased BMD, as well as reduced growth velocity, than is cumulative steroid or methotrexate dose because of its effect on growth hormone secretion.[12,13] Currently, cranial radiation is being used less frequently to treat ALL; therefore, rates of osteoporosis may decrease among long-term ALL survivors.[14]

Although it is intuitive to assume that a posttreatment reduction in BMD will increase the risk of osteoporotic fractures later in life among long-term cancer survivors, the published data are inconclusive. The Childhood Cancer Survivor Study evaluated more than 7,000 survivors at a median 23-year follow-up after cancer diagnosis and compared them with more than 2,000 siblings.[15] The self-reported prevalence of fractures was actually lower among survivors (35%) than among siblings (39%); however, this could be attributed to reduced activity levels in survivors. In a subgroup analysis, female survivors, those treated with methotrexate, Caucasian race, and individuals with balance difficulties sustained more fractures.[15] However, the mean age of participants at the time of the study was 36 years. Given the relatively young age, additional follow-up into late adulthood will be necessary to better determine osteoporotic fracture risk.

It is important for orthopaedic surgeons to be aware that cancer survivors and children undergoing treatment for cancer are more likely to have decreased BMD. Prevention of osteoporosis in this population begins with optimizing dietary intake of calories, calcium, and vitamin D and promotion of weight-bearing exercises. The Children's Oncology Group recommends 400 IU of vitamin D daily for all survivors, BMD testing using dual energy x-ray absorptiometry 1 year after bone marrow transplant, and a referral to an endocrinologist when a diagnosis of osteoporosis has been made by dual energy x-ray absorptiometry or a patient has a history of multiple fractures.[16]

Few studies evaluating diphosphonates have been performed in children with osteopenia or osteoporosis. Lethaby et al[17] performed an open-label, single-arm study of alendronate for the management of osteoporosis or osteopenia during treatment of ALL. They found that BMD Z-scores at the lumbar spine increased in 14 of 15 children after at least 6 months. No short-term toxicity secondary to the medication was evident, and all children tolerated the weight-based dosing, which ranged from 20 to 70 mg orally each week. However, diphosphonate use in children remains controversial. The long-term effects of diphosphonates for childhood osteoporosis and osteogenesis imperfecta are not entirely known. Previously described adverse effects in adults, such as osteonecrosis of the jaw and atypical femur fractures, reinforce the need for multidisciplinary input when considering diphosphonate treatment in children. Reid[18] reviewed the literature on the use of diphosphonates for pediatric osteoporosis and recommended optimizing nutritional sources of calcium and vitamin D and reserving diphosphonate treatment only in the setting of clinical trials or with careful consideration of the benefits and adverse effects for children.

Effects of Adult Cancer Treatments

Several studies have shown that adult cancer survivors have increased rates of osteoporosis.[19] The Women's Health Initiative Observational Study compared rates of osteoporosis as defined by BMD testing of the spine and hip. Survivors of breast cancer had a 27% rate of osteoporosis compared with 19% in the reference group. The authors estimated that women with a history of breast cancer experience 68.6 more fractures per 10,000 person-years compared with women without breast cancer.[20] Khan et al[21] compared long-term health outcomes among breast, colorectal, and prostate cancer survivors to age-matched controls. They found an increased rate of osteoporosis among all survivors, and the highest rates

were among prostate cancer survivors (hazard ratio, 2.49 versus 1.26 for breast cancer, and 1.41 for colorectal cancer). Cancer itself, as well as the treatments, can lead to osteoporosis. Survivors of breast and prostate cancer are at risk because of hormone suppression, in addition to traditional chemotherapy that affects bone metabolism, such as alkylating agents and ablative chemotherapy.[19] An osteoporotic fracture can be devastating and cause long-term effects on function, quality of life, and life expectancy.[22,23] The American Society for Clinical Oncology and the US Preventive Services Task Force recommend 1,200 mg of calcium and 600 to 800 IU of vitamin D daily for postmenopausal women and cancer survivors.

Skeletal Growth

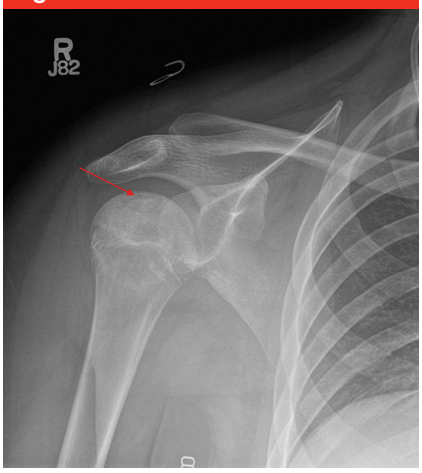
Ionizing radiation has known deleterious effects on skeletal health, including radiation-associated fractures, osteoradionecrosis, and growth retardation. The magnitude of growth arrest and deformity are proportional to the dose given and inversely proportional to the patient's age at the time of treatment. The bone is often not considered a dose-limiting normal tissue when planning for radiation in an adult; however, it is of major concern when planning radiation in children.[24] Total body irradiation is often used for myeloablation before bone marrow transplantation and is used in conjunction with high-dose chemotherapy. Locally, radiation interferes with chondrogenesis and reabsorption of calcified matrix, leading to short stature. It has been shown that microscopic growth retardation occurs after low doses of 600 cGy to the epiphysis. However, doses between 2,000 and 6,000 cGy cause clinically relevant growth disturbances in a dose-dependent fashion when involving an open epiphyseal plate.[25] Jentzsch et al[26] reviewed the imaging of 22 patients who received 5,000 cGy to the extremity for treatment of Ewing sarcoma in conjunction with chemotherapy. Nine patients had greater than 1.5 cm leg-length discrepancy with moderate to severe functional limitations, and one patient required an amputation. Age less than 16 years was associated with a poor functional outcome. Impaired growth can also be seen in patients treated with cranial radiation therapy who develop subclinical hypothalamic/pituitary dysfunction and decreased growth hormone levels and, less often, hypogonadotropic hypogonadism. Scoliosis and kyphosis are documented late effects after radiation to the abdomen for Wilms tumor. Paulino et al[27] followed up 42 patients for a minimum of 5 years after abdominal radiation for Wilms tumor. Forty-two percent of patients developed scoliosis, and 7% developed kyphosis. Scoliosis seemed to be dose dependent, with an expected rate of 74% at 15 years after treatment among those who received more than 24 Gy. Both scoliosis and kyphosis developed late in this group, suggesting that prolonged clinical observation of these patients may be warranted. Of note, only one patient in this cohort required an orthopaedic intervention. Varus and valgus limb deformities have been reported among children who receive asymmetric radiation to the limbs near an open epiphyseal plate and often require corrective surgery.[24] Slipped capital femoral epiphysis can also be associated with radiation around the hip, with the highest risk in children treated with radiation doses >25 Gy when they are younger than 4 years. The risk of slipped capital femoral epiphysis in this population is younger than the average at approximately 9 to 10 years.[28] Radiation directed at or near the epiphyseal plate, as well as whole-body radiation, can result in osteochondromas. Finally, many patients treated with cranial radiation therapy develop subclinical hypothalamic/pituitary dysfunction and decreased growth hormone levels and, less often, hypogonadotropic hypogonadism, which can also affect growth.

Osteonecrosis

Osteonecrosis is a late-onset and potentially debilitating complication of cancer treatment most commonly occurring in survivors of adult and pediatric leukemia (Figure 1); however, osteonecrosis can occur among survivors of solid tumors as well (Figure 2). The most common locations among cancer survivors are the femoral head, distal femoral condyle, and humeral head, although multiple sites can be involved. Padhye et al[29] reported an overall 7% incidence of osteonecrosis in children treated for ALL in the Australian and New Zealand Children's Haemotology/Oncology Group, with an incidence of 29% in children aged >10 years. The median time to development of symptoms was 1.15 years after treatment. Most patients who developed osteonecrosis had radiographic progression of the disease and persistent pain despite diphosphonate therapy.

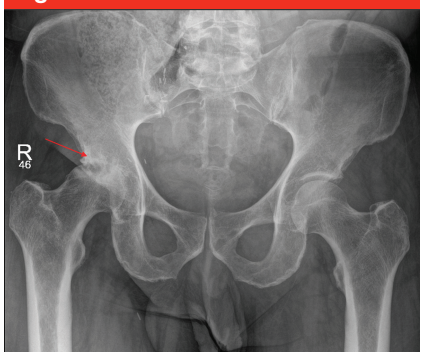
Several risk factors for the development of osteonecrosis have been identified, including steroid exposure, chemotherapy, graft versus host disease, female sex, radiation exposure, and older age. Karol et al[30] studied a cohort of 2,285 children treated for ALL with the goal of identifying genetic risk factors for the development of osteonecrosis. They found that osteonecrosis was associated with inherited variations near glutamate receptor genes.[30] Interestingly, these osteonecrosis-associated glutamate receptor variants were also associated with other vascular complications, including cerebral ischemia, arterial embolism, and thrombosis.

Figure 1



AP right shoulder radiograph of a 14-year-old girl who underwent bone marrow transplant for leukemia. Sclerotic and cystic changes (red arrow) demonstrative of osteonecrosis are seen in the humeral head.

Figure 2



AP pelvic radiograph of a 69-year-old man who had undergone radiation therapy to the groin 10 years earlier for treatment of nodal metastases from melanoma. End-stage osteonecrosis (red arrow) is evident in the right hip.

These findings are compelling in that the genetic alteration may provide a potential target for intervention.

Table 2[31-39] summarizes the outcomes of nonarthroplasty interventions for the treatment of osteonecrosis of the femoral head. Currently, no consensus recommendation exists on the optimal nonarthroplasty treatment for osteonecrosis. The role of diphosphonates is uncertain. Kotecha et al[33] treated pediatric ALL patients with osteonecrosis as determined by MRI with a diphosphonate or pain management alone, depending on severity. Nine patients received oral alendronate or intravenous pamidronate, and eight patients were treated with observation and pain control. All nine patients in the diphosphonate group showed clinical improvement; conversely, seven of the eight patients treated conservatively worsened clinically, and two required joint replacement surgery.[33] In contrast, Padhye et al[40] reported that only 5 of 20 children with osteonecrosis treated with zoledronic acid experienced symptom relief, with most showing progressive radiographic abnormalities and 25% requiring arthroplasty. Core decompression with bone marrow implantation is a promising joint-sparing technique. Hernigou and Beaujean[36] reported a 6% rate of total hip arthroplasty at 5 to 10 years after core decompression plus bone marrow aspirate injection in patients with precollapse lesions (Ficat I and II) compared with 56% in patients with Ficat stage III or IV. Fibular autografts have been used after core decompression, and several studies have reported superior results using free vascularized fibular autografts after core decompression in patients with precollapse lesions compared with nonvascularized fibular autografts, with a survival rate of 86% compared with 30% at 7 years.[41,42] Taken collectively, these interventions are promising, but the long-term results vary considerably. Lastly, several low-level-evidence interventions, such as extracorporeal shock wave therapy, pulsed electromagnetic therapy, and statins, have been investigated with limited evidence of efficacy.

Radiation-associated Fractures

Radiation osteitis refers to radiographically evident changes to bone within a radiation field and is seen in 2% to 22% of patients.[43-45] On conventional radiographs, the affected bone has a mottled appearance, osteopenia, coarse trabeculae, and areas of focally increased bone density. The pathophysiology leading to the radiographic changes is poorly understood, although it seems to be dose related and can become evident 2 to 3 years after radiation treatment.[46] The radiographic signs are similar to those of osteomyelitis, recurrent malignancy, and radiation-induced sarcoma. In radiation osteitis, however, the osseous changes are seen only within the radiation field, and there are no systemic signs suggestive of infection, nor is there an associated soft-tissue mass, which often occurs in radiation-induced sarcoma.[25,46,47] MRI can be helpful to distinguish between radiation osteitis and a secondary sarcoma or lymphoma. Ugurluer et al[43] reviewed 122 MRI scans of patients who had received pelvic radiation. They found radiation osteitis in 4.1% of patients, with MRI characteristics of decreased T1 signal along with decreased and mixed signal areas on T2 sequences representing fibrosis, whereas most tumors show increased T2 signal.

Pathologic fractures have been reported in 1.2% to 6.6% of patients treated with surgery and radiation for extremity soft-tissue sarcomas and in >20% of patients who also demonstrated radiation osteitis.[48] Risk factors for radiation-induced pathologic fractures include high doses of radiation (>50 Gy), >64% maximum dose to a 2-mL volume of bone, periosteal stripping, cortical removal, and underlying metabolic bone disease such as osteoporosis.[48] Most radiation-induced fractures

Table 2

Nonarthroplasty Treatments for Osteonecrosis of the Femoral Head

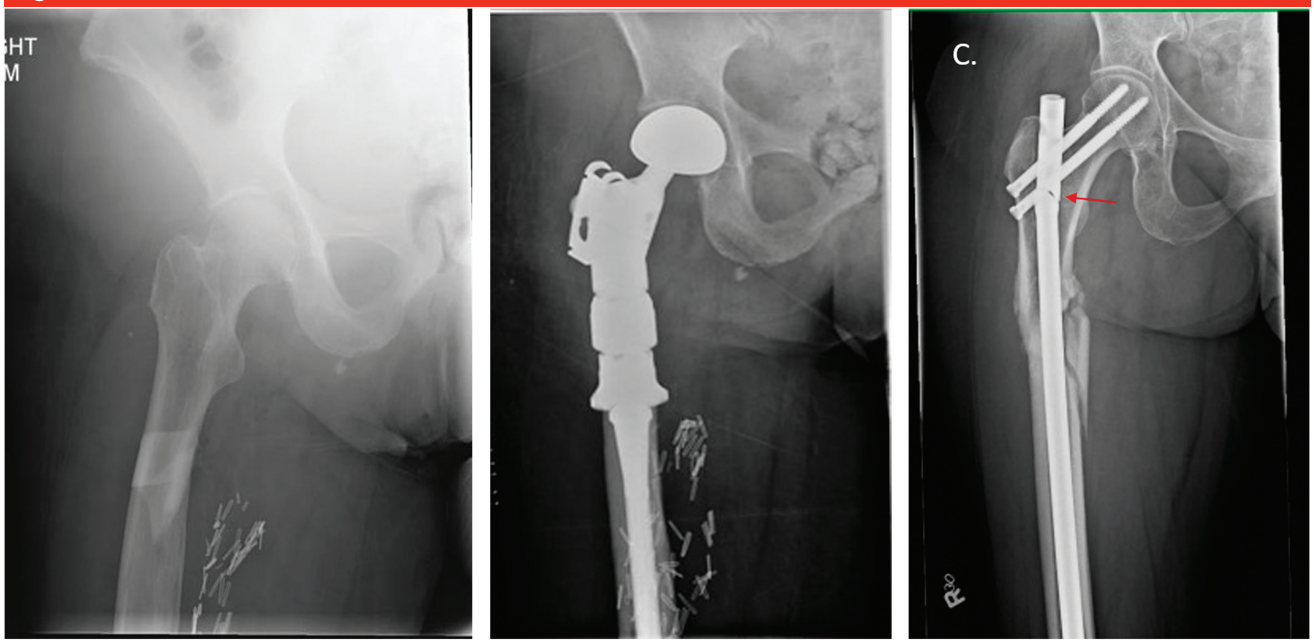
Study	Treatment	Population		Outcomes
		n	Details	
Nonsurgical treatment				
Agarwala et al[31]	Alendronate	60 adults	Various etiologies	At 1 yr, improved range of motion and decreased pain; 6/60 patients required surgery within 37 mo.
Lai et al[32]	Alendronate (70 mg weekly)	40 adults (20 treatment/20 controls)	Nontraumatic etiology	At 2 yr, 16/25 hips in the control group and 1/29 in the intervention group required THA.
Padhye et al[40]	Intravenous zoledronic acid	22 patients	Any joint	At 1 yr, 25% pain-free; hip joint destruction progressed despite treatment
Kotecha et al[33]	Oral alendronate or intravenous pamidronate	17 children (9 treatment/8 controls)	Secondary to ALL	9 patients treated with diphosphonates improved clinically. Condition deteriorated in 7/8 patients treated nonsurgically.
Scherer et al[34]	Hyperbaric oxygen	20 children (12 treatment/8 controls)	On chemotherapy	Both groups showed progression of osteonecrosis by MRI during treatment.
Surgical treatment				
Gangji et al[35]	Core decompression + autologous bone marrow	13 patients (18 hips)	Ficat stage I or II	At 2 yr, 5/8 hips in the core decompression–only group progressed to stage III vs 1/10 in the bone marrow group.
Hernigou and Beaujean[36]	Core decompression + autologous bone marrow	189 patients	Ficat stages I-IV	At 10 yr, 9/145 hips with stage I or II vs. 25/44 hips with stage III or IV required THA.
Israelite et al[37]	Core decompression alone	193 adults	Simultaneous bilateral vs unilateral decompression	45% of hips in the unilateral group and 32% of the hips in the bilateral group required THA.
Lieberman et al[38]	Core decompression + bone morphogenetic protein	15 patients (17 hips)	Ficat stage II stage III	3/17 hips had radiographic progression and required THA.
Yan et al[39]	Percutaneous decompression and autologous bone marrow infusion	28 patients (44 hips)	Ficat stage I-II	At 2-yr follow-up, the Harris hip score improved by 28 points; 4 hips progressed to stage V.

ALL = acute lymphoblastic leukemia, THA = total hip arthroplasty

occur more than 1 year after radiation, although a wide range has been reported in the literature (4 months to 25 years).[49,50] Although some surgeons recommend prophylactic fixation at the time of sarcoma resection in the setting of periosteal stripping and perioperative radiation therapy, a period of implant-free MRI surveillance is desirable to monitor for local recurrence, although the availability of carbon fiber nails may obviate this concern.

It is important for orthopaedic surgeons to recognize that conventional trauma fixation techniques may be inadequate to address pathologic fractures secondary to radiation (Figure 3). These fractures are very challenging to treat, with nonunion occurring in 45% to 75% of cases.[49,50] Treatment can require multiple surgeries, autogenous bone grafting, and vascularized fibular grafting. Lin et al[50] evaluated a cohort of patients with soft-tissue sarcomas of the thigh who had been treated with resection and radiation. Nine of 205 patients had fractures, only three of which healed. Of the remaining six fractures, two healed after secondary bone grafting, and four required endoprosthesis replacement

Figure 3



A B C

A, AP radiograph of the proximal femur demonstrating a transverse fracture pattern 3 years after radiation and surgery for soft-tissue sarcoma. Note the vascular clips in the medial thigh. **B**, The patient was treated with proximal femur arthroplasty to allow immediate weight bearing. **C**, A different patient was treated with an IM nail with the fracture going on to nonunion and broken implant (red arrow).

or amputation because of chronic nonunion. In a more recent study by Kim et al,[51] radiation-induced fractures treated by internal fixation failed to heal in 19 of 30 patients because of nonunion. The authors reported that the use of endoprosthetic replacement as primary treatment for radiation-induced fractures was associated with fewer complications than was open reduction and internal fixation or intramedullary nailing. More recently, onlay vascularized free fibula grafts have been used with success.[52]

Secondary Malignancies

Secondary malignancies are the most devastating complications from cancer treatment and are the most common cause of treatment-related death in long-term survivors. The Childhood Cancer Survivor Study found a cumulative incidence of secondary malignancies of 3.2% at 20 years after diagnosis and between 7.9% and 9.3% at 30 years.[53] Table 3 lists the commonly reported secondary malignancies in childhood cancer survivors, adapted from the Children's Oncology Group's long-term follow-up guidelines. Chemotherapy and radiation exposure are risk factors for secondary malignancies. In addition, genetic predispositions place patients with certain cancers at a much higher risk of developing second and third malignancies. Because chemotherapy and radiation are often used in the treatment of Hodgkin lymphoma, these patients are at risk of hematologic and solid malignancies and have up to a 20% risk of developing a secondary malignancy during the first 20 years after treatment.[57]

Radiation-associated secondary malignancies are defined as distinct, new malignancies arising within the radiation field at least 3 years after radiation treatment. They often develop more than 10 years after treatment. The overall incidence of radiation-induced secondary malignancies is between 2% and 10%, depending on the primary cancer, radiation field and dose, time since treatment, and genetic predisposition.[58] The Childhood Cancer Survivor Study, with a cohort of 12,268 childhood cancer survivors, reviewed the incidence and risk factors for radiation-related malignancies. They found a linear dose-response relationship from 0 to 50 Gy for all cancer sites except thyroid. The incidence of thyroid cancer increased up to 15- to 20-Gy exposure and then decreased. The rates of breast cancer were highest among patients with a history of Hodgkin lymphoma.[59] Several studies have shown that the incidence of all cancers increases without a

Table 3

Common Secondary Malignancies in Childhood Cancer Survivors and Screening Recommendations

Exposure	Malignancy	Latency	Incidence/Risk	Screening Recommendations
Epipodophyllotoxins (etoposide, teniposide), anthracyclines (not dose-dependent)	Acute myeloid leukemia	<5 yr	2%-4.2%[54]	Annual H&P to look for fatigue, easy bruising and bleeding with dermatologic exam, up to 10 years. CBC if clinically indicated. [sections 32 and 42, pages 39 and 52; COG guidelines v5.0][55]
Alkylating agents (dose-dependent effect)	Acute myeloid leukemia	5-7 yr	1%-4%	
Radiation of any field	Secondary sarcomas; skin cancers	>3 yr to decades	2%-10%	Annual H&P with inspection and palpation of the skin and tissue within the radiation field, with radiographs as clinically indicated. [section 43, page 54 COG guidelines v5.0]
Radiation to head/ neck, spine, TBI	Thyroid cancer	>3 yr to decades	14.6-18 relative risk compared with the general population[30] (highest risk with 20-Gy exposure)	Annual thyroid examinations, US and FNA as clinically indicated. [Section 67, pg 84 COG guidelines v 5]
Radiation to the chest, axillary region, TBI)	Breast cancer	>3 yr to decades	Up to 17% in survivors of Hodgkin disease	Monthly breast self-examinations; annual clinical breast examinations until age 25 then every 6 months; mammography yearly beginning 8 years after radiation or at age 25 (whichever occurs last), with adjunct magnetic resonance imaging beginning at age 25 or >8 years from radiation therapy (whichever occurs last). [Sec 72; pg 90 COG guidelines v5]
Radiation to the chest, axilla, TBI	Lung cancer	>3 years to decades	Cumulative incidence at 20 years 0.1% (95% CI 0-0.3%), 2.1% at 30 years (95% CI 0-4.4)[57]	Yearly H&P, consider spiral CT scan in high risk patients (smokers) [Section 75, pg 93, COG Guidelines v 5]
Radiation to pelvis, spine; Exposure to cyclophosphamide (dose dependent)	Bladder cancer	>3 years to decades	Low risk, (5/13,136 from CCSS)[60,61]	Yearly history focused on urinary symtpoms, urinalysis, urine culture, spot urine Cr/Ca ratio with positive history [Section 88, pg 109 COG guidelines v. 5]
Radiation of the abdomen, pelvis, spine (lumbar, sacral, whole), TBI	Colorectal cancer	>3 yr to decades	1.7 adjusted hazard ratio[17]	Colonoscopy (gold standard) every 5 years or multitarget stool DNA test every 3 years beginning 5 years after radiation treatment or at age 30 (whichever occurs later). [Section 85, pg 105, COG guidelines v 5]

TBI = total body irradiation; H&P = history and physical
Screening recommendation adapted from the *Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers*, Version 5.0, October 2018, used with permission.

Table 4

Systemic Toxicities of Common Chemotherapeutic Agents

Anatomic System	Toxic Agent	Adverse Effects	Screening	Special Considerations
Cardiovascular	Anthracyclines (doxorubicin and epirubicin), bleomycin, cisplatin, docetaxel, 5-fluorouracil, and paclitaxel	Arrhythmias, torsades de pointes, myocardial infarction, congestive heart failure, hypotension/ hypertension, cardiomyopathy, myocarditis, and pericarditis	Electrocardiography; echocardiography to evaluate cardiac wall contractility, left ventricular ejection fraction, and pericardial fluid; and cardiac MRI	Cardiac toxicity can be immediate or delayed and irreversible; treat as high risk of potential intraoperative cardiac complication.
Hematologic	Nearly all	Myelosuppression, neutropenia, and sepsis	Blood tests	Myelosuppression is usually completely or partially reversible 6 wk after completion of chemotherapy.
Nervous	Cisplatin, methotrexate, oxaliplatin, paclitaxel, and vincristine	Peripheral neuropathy, muscle pain, cranial neuropathy, seizures, orthostatic hypotension, and vocal cord paralysis (rare)	Full neurologic examination	Regional anesthesia should be used judiciously to prevent a "second-hit" phenomenon.
Pulmonary	Bleomycin, busulfan, cyclophosphamide, methotrexate, mitomycin, and nitrosoureas	Dr. cough, pulmonary fibrosis, pneumonitis, and pneumonia	Chest radiography to look for linear interstitial scarring, pneumothorax, and pneumomediastinum	If exposed to bleomycin, dose intraoperative O_2 to keep peripheral saturation between 88% and 92%.
Renal	Bleomycin, carboplatin, cisplatin, cyclophosphamide, ifosfamide, nitrosoureas, oxaliplatin, methotrexate, mitomycin, and vincristine	Renal tubular and glomerular damage and hypertension	Creatinine clearance and electrolyte measurements	Avoid dehydration intraoperatively and avoid concomitant nonsteroidal anti-inflammatory drug use.

plateau, during 10-, 20-, and even 30-year follow-up. Screening in this population consists of a meticulous annual physical examination of the skin and soft tissues within the field of radiation and possible radiographic evaluation.[55]

Perioperative Considerations

Cancer survivors are at an increased risk of a number of perioperative complications including venous thromboembolism (VTE), delayed wound healing, and cardiopulmonary toxicity. Comprehensive preoperative evaluation should be performed to minimize surgical morbidity.

Venous Thromboembolism

Patients with active cancer are at a 4- to 6-fold increase of developing VTE for which the cause is multimodal. A prospective study[62] evaluating symptomatic VTE for patients after cancer-related surgery found a 2.1% incidence, with 40% of cases occurring after 21 days. The overall death rate within 30 days after surgery was 1.72%, and 46% of deaths were caused by VTE, making this the most common cause of death within 30 days.[62] A recent international registry study demonstrated that patients who receive radiation therapy were at an increased risk of VTE implicating ionizing radiation as a prothrombic cause.

Metastatic disease to bone often requires orthopaedic surgical intervention. Recent studies in this population have shown high rates of VTE after fixation for impending and pathologic long bone fractures. Shallop et al[63] found a 7.1% rate of VTE among 287 patients treated for 336 impending or completed pathologic fractures. The rate of pulmonary

Table 5

Physical Activity Recommendations for Adult Cancer Survivors[ab]

Recommendation	Cancer Type				
	Breast	Prostate	Colon	Adult Hematologic	Gynecologic
General	Avoid inactivity; return to normal activity as soon as possible after surgery. Continue activities of daily living as much as possible during and after nonsurgical treatments.				
Aerobic training	Recommendations are the same as age-appropriate PAGs for Americans (ie, 30 min per d and 5 d per wk of moderate exercise).				
	Be aware of fracture risk from osteopenia, possible metastatic disease.	Potential increased risk of fracture.	Permission from the physician before contact sports (if the patient has an ostomy).	Avoid overtraining and very vigorous exercise (immune effect of vigorous exercise).	If peripheral neuropathy is present, consider stationary bicycle instead of walking/running.
Resistance training	Begin with supervised program of low resistance; increase at small increments. Watch for arm/shoulder symptoms, lymphedema. Be aware of fracture risk.	Add pelvic floor exercises to same-age general recommendations. Be aware of fracture risk.	For core strength, start with low resistance and increase slowly to avoid herniation at the stoma.	Resistance training may be more important than aerobic exercise in bone marrow transplant patients.	No safety data on resistance training in women with lower extremity lymphedema.
Flexibility	Recommendations are the same as age-appropriate PAGs for Americans.		Avoid excessive intra-abdominal pressure.	Recommendations are the same as age-appropriate PAGs for Americans.	

PAG = physical activity guideline
[a] Adapted with permission from Schmitz KH, Courneya KS, Matthews C, et al: American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010;42:1409-1426.[72]
[b] For patients with bone metastases

embolism (PE) was 3.9%. The authors found that 74% of these occurred within 15 days after surgery. Ratasvuori et al[64] performed a similar retrospective review of 306 consecutive patients with 343 non-spinal metastases over a 15-year period. They found a 10% rate of VTE within 3 months of surgery and a 3.3% rate of fatal PE. Both studies showed that lung cancer was a risk factor for VTE. Only 79% of patients in the study by Ratasvuori et al[64] received thromboprophylaxis, and the authors found a survival benefit among patients treated with 28 days of low-molecular-weight heparin. Some data suggest that patients undergoing prophylactic fixation for an impending long bone fracture may be at a higher risk of VTE than those with a complete fracture. Aneja et al[65] used the National Inpatient Sample database to compare rates of VTE among patients treated for an impending versus completed pathologic fracture during a 10-year period. The authors found higher rates of PE and deep venous thrombosis (DVT) in the prophylactic fixation group compared with the group treated for completed fracture (odds ratios = 2.1 for PE and 1.5 for DVT). Although no clear guidelines exist for the duration or type of thromboprophylaxis after surgery in patients with cancer, there is strong evidence that patients with cancer need extended thromboprophylaxis.

Wound Healing

Surgeons performing procedures in an irradiated area should be aware of lasting tissue damage as a result of radiation. Impaired wound healing is particularly relevant in cases of hardware implantation such as total joint arthroplasty. Acute skin damage peaks 1 to 2 weeks after completion of radiation therapy and typically resolves in 10 to 14 days. However, the late effects of radiation including fibrosis, skin atrophy, contraction, induration, and a dose-dependent decrease in wound strength persist forever. Even a remote history of radiation in an individual with no overt signs of skin damage will impart a slightly higher risk of delayed wound healing secondary to a decrease in collagen formation over time.[66] As such, particular attention to wound closure is crucial. In many cases, consultation with plastic surgery should be considered.

Anesthetic Considerations

Many chemotherapeutic agents can have lasting toxicities on the pulmonary, cardiac, hepatorenal, circulatory, hematopoietic, and nervous systems. This phenomenon may place cancer survivors at a higher risk of complications when undergoing general anesthesia. Table 4 lists common toxic

agents, their effects, and recommendations. In all patients, a careful preoperative assessment documenting all previous chemotherapy and radiation exposures, including doses, is essential for planning a safe operation and alerting anesthesiologists to potential hazards.

Pulmonary toxicity is a common complication in all patients undergoing systemic chemotherapy; bleomycin, which is used to treat germ cell tumors and Hodgkin lymphoma, is associated with a 6% to 10% rate of pulmonary toxicity and a lifelong risk of lung injury.[67] Pulmonary fibrosis is the most dangerous complication and can be fatal. High-inspired concentrated oxygen therapy, such as oxygen delivery during anesthesia, can lead to rapidly progressive pulmonary compromise.

Cardiac toxicity, immediate or delayed, is a well-known adverse effect of chemotherapy, particularly of anthracyclines such as doxorubicin. Long-term studies of cancer survivors have shown that 5% to 10% develop arrhythmias or severe cardiac conditions.[68] Using echocardiography, van der Pal et al[68] evaluated more than 1,200 adult survivors of childhood cancer and found that those who received treatment at least 30 years previously had an 8- to 9-fold increase in cardiovascular morbidity compared with age-matched controls. Risk factors for chemotherapy-associated cardiotoxicity include the following: preexisting cardiac disease; multiple, concurrent chemotherapy regimens; high doses of anthracyclines; age <5 or >70 years; female sex; and current or previous radiation to the mediastinum.[69] In these patients, cardiac clearance should be obtained to determine the need for additional workup.

Activity Recommendations in Cancer Survivors

There is growing evidence that regular exercise not only improves physiologic and psychosocial health in cancer survivors but may even extended survival in some cases. Exercise programs are safe in most cancer survivors; however, there are unique considerations when recommending an exercise regimen. Bellizzi et al[70] surveyed more than 7,300 survivors and 120,000 individuals with no history of cancer to determine health behaviors of both groups. They determined that 30% of survivors self-reported meeting the Centers for Disease Control and Prevention/American College of Sports Medicine physical activity recommendations (at least 30 minutes per day of moderate activity on 5 days per week or 20 minutes per day on 3 days per week of vigorous activity) compared with 37% of controls. However, after they controlled for physical disability, they found that cancer survivors were 9% more likely to meet physical activity recommendations.[70]

Many cancer survivors do not participate in adequate levels of physical activity.[71] In general, most cancer survivors should return to normal activity when possible and be encouraged to follow the general Centers for Disease Control and Prevention/American College of Sports Medicine guidelines of 30 minutes per day of moderate-level activity. The American College of Sports Medicine recently convened a roundtable to review the evidence concerning exercise programs in adult cancer survivors and to provide recommendations to fitness and healthcare providers interested in implementing an exercise program (these recommendations are summarized in Table 5).[72]

Conclusion

In the past three decades, cancer treatments have become more effective for childhood and adult cancers. Collectively, cancer treatments are associated with long-term adverse effects, with a high propensity for physical impairment of the musculoskeletal system. Chemotherapy, radiation therapy, and surgery can affect musculoskeletal health and leave survivors with conditions that require an orthopaedic evaluation. To provide effective care for the increasing number of cancer survivors, orthopaedic surgeons must be cognizant of the musculoskeletal complications facing this unique population and the current trends regarding treatment and activity.

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