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BONE AND SOFT-TISSUE SARCOMAS:
WHAT THE OPTIONS ARE, HOW TO ADVISE PATIENTS

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From the editors

Bone and soft-tissue sarcomas are relatively rare, yet their tendency to develop predominantly during adolescence and young adulthood makes these cancers particularly compelling and worthy of efforts toward early detection and effective management.

The past two decades have seen important advances in the management of patients with these musculoskeletal sarcomas, with resulting improvements in survival and quality of life. Whereas standard therapy for musculoskeletal sarcomas of the extremities used to be limb amputation, most patients today can be successfully managed with limb-sparing surgery. This progress has been made possible by advances in chemotherapy and radiation therapy as well as in surgical techniques.

We conceived of this supplement as an opportunity to provide information about these advances to physicians practicing outside of specialized tertiary care centers, for whom these sarcomas are rare but nevertheless occasionally encountered. *It has been written for nonspecialists in sarcoma, including family physicians, pediatricians, internists, and general surgeons.* Our aim is to help you better evaluate patients with masses suspicious for musculoskeletal sarcoma and advise your patients with confirmed sarcoma about their treatment options and post-therapy management.

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Clinical presentation and imaging of bone and soft-tissue sarcomas

◼ ABSTRACT

The clinical presentation of bone and soft-tissue sarcomas is varied. Constitutional symptoms are rare, and although bone sarcomas tend to be painful while soft-tissue sarcomas usually are not, there are exceptions to this general rule. A high index of suspicion is required for any unexplained mass with indeterminate imaging findings. Choosing the right imaging modality is critical to the diagnosis and management of patients with suspected sarcoma, and referring clinicians have a multitude of imaging options. After discovery of a malignant-appearing bone lesion by radiography, further imaging is obtained for better characterization of the lesion (typically with magnetic resonance imaging [MRI]) and for staging (typically with computed tomography of the chest). In contrast, radiographs are rarely helpful for evaluation of soft-tissue lesions, which almost always require MRI assessment.

Sarcomas are rare neoplasms arising from connective tissue elements of the body. Approximately 80% arise in soft tissue, while the remainder originate in bone.[1] Soft-tissue sarcomas are tumors of the mesenchymal system, and about half develop in the extremities. Bone sarcomas are characterized by their location in bone and sometimes produce osteoid, or immature bone.

The most common types of soft-tissue sarcomas are malignant fibrous histiocytoma (although this term has lost favor with some pathologists) and liposarcoma.

The most common types of bone sarcomas are osteosarcoma (a sarcoma that makes osteoid or bone), Ewing sarcoma (composed of small round blue cells with a characteristic chromosomal translocation), and chondrosarcoma (a sarcoma that makes chondroid tissue, or cartilage).

◼ EPIDEMIOLOGY AND PRIMARY BODY SITES

Approximately 10,600 new cases of soft-tissue sarcoma and 2,570 new cases of bone sarcoma were estimated to

have been diagnosed in the United States in 2009.[2,3] For perspective, the annual incidence of soft-tissue sarcoma is approximately 5.5% that of breast cancer and approximately 5% that of lung cancer.[3]

Most sarcomas develop in the lower extremities, although the age groups at greatest risk vary among sarcoma types.[4]

Soft-tissue sarcomas develop most commonly in the thigh and occur primarily in adults.[2]

Osteosarcomas are the most common bone sarcoma and develop most frequently in 10- to 20-year-olds; their most common location is the distal femur.[5–8] Metastatic osteosarcoma is found in approximately 20% of patients at the time of osteosarcoma diagnosis. Osteosarcomas mainly spread hematogenously, and the lungs are the most common initial site of metastases, being affected in up to 90% of patients with metastatic disease.[9]

Ewing sarcomas develop most often in the long bones of the extremities or bones of the pelvis. The large majority of cases develop in patients aged 10 to 15 years.[5–8]

Chondrosarcomas represent approximately 20% of all bone sarcomas and primarily affect older adults, with a peak incidence in the sixth decade of life.[10]

◼ OVERVIEW OF PRESENTATION AND EVALUATION

Presentation is highly variable

The clinical presentation of patients with bone or soft-tissue sarcoma is highly variable. Patients often present with a mass, typically one that is increasing in size. In general, bone sarcomas are painful and soft-tissue sarcomas are not, but there are exceptions to this general rule. Constitutional symptoms are rare in patients with bone or soft-tissue sarcomas, but symptoms such as fever, malaise, and weight loss can be seen, especially in patients with Ewing sarcoma.[11]

Delayed presentation and diagnosis are common

Particularly when a sarcoma is painless, patients sometimes do not seek medical attention until a suspicious mass becomes quite large. Certain tumors, such as synovial sarcoma, a high-grade soft-tissue sarcoma often seen in young adults, may present as a slowly growing or stable-appearing mass over several years. In one study of 33 children with synovial sarcoma, the mean duration of symptoms was 98
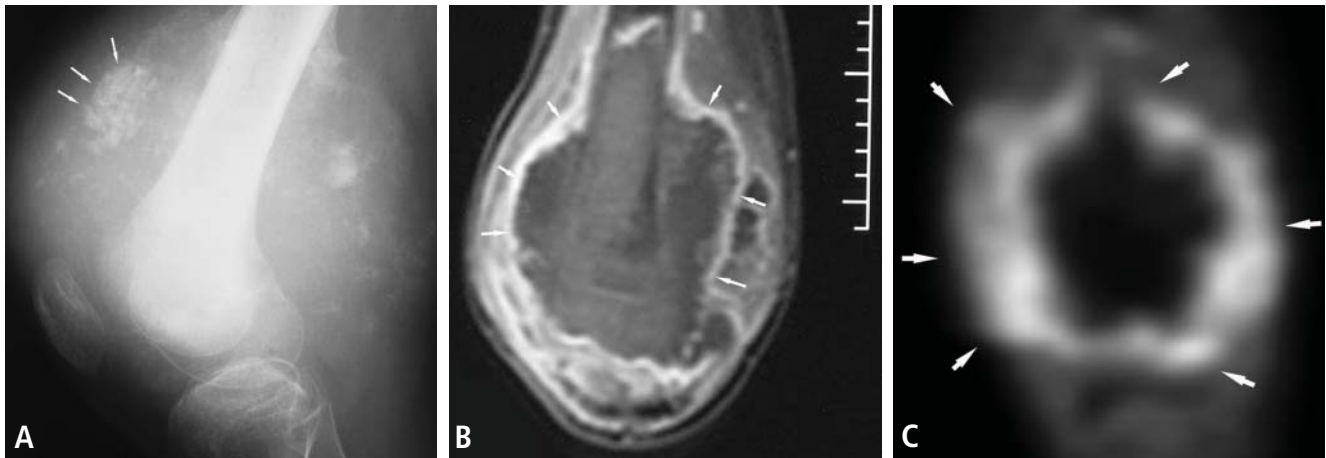
FIGURE 1. Imaging studies in a 14-year-old girl with a knee mass. **(A)** Lateral radiograph showing cloud-like osteoid mineralization (arrows) consistent with osteosarcoma. **(B)** Follow-up post-contrast T1-weighted MRI in the coronal plane shows evidence of significant tumor necrosis with enhancement confined to the tumor periphery (arrows), which correlates well with the absence of intratumoral metabolic activity centrally on a cross-sectional FDG-PET image **(C)**.

weeks (range, 2–364), the mean patient delay before a doctor was seen was 43 weeks (0–156), the mean doctor delay before a correct diagnosis was made was 50 weeks (0–362), and the mean number of doctors seen before referral was 3 (1–6).[12] For nearly half the patients in this study (15), the diagnosis was obtained only after unplanned excision, meaning that the surgeon did not expect a malignancy at the time of biopsy. Because delayed presentation is not uncommon in cases of bone or soft-tissue sarcoma, every patient with a mass with indeterminate imaging findings should be referred to or reviewed by an orthopedic or musculoskeletal oncologist.

Biopsy is gold standard for diagnosis

A comprehensive medical history and physical examination are essential at the initial presentation of patients with masses and/or pain suggestive of bone or soft-tissue sarcoma. Sarcoma simulators such as hematoma, metastatic disease, or infection can sometimes be ruled out by careful clinical examination, laboratory work-up, and appropriate imaging, but the gold standard for diagnosis is a biopsy. Moreover, an index of suspicion is required to rule out primary malignancy in any soft-tissue or bone lesion, and this index of suspicion will allow for referral or appropriate selection of the site for biopsy.

Biopsy considerations, as well as further detail on clinical presentation, are provided in the second and third articles in this supplement, which focus, respectively, on bone sarcoma and soft-tissue sarcoma. The remainder of this article reviews the use of imaging for the evaluation of suspected sarcomas, as imaging findings typically prompt or guide biopsy of a suspicious mass. Choosing the right imaging modality is critical to the diagnosis and management of patients with suspected sarcoma.

◼ CONVENTIONAL IMAGING MODALITIES

Radiography. Despite recent advances in cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI), radiographs remain valuable for characterizing osseous lesions and enabling accurate differential diagnosis of benign and malignant tumors **(Figure 1)**. Multiple lytic lesions in an adult older than 40 years almost always suggest metastases or multiple myeloma.[13] Bone sarcomas are rare, and the most common cause of a solitary destructive lesion in an adult is metastasis.

Despite their utility for evaluating osseous lesions, radiographs have limited to no value in the evaluation of soft-tissue sarcomas but can demonstrate matrix mineralization and erosion or destruction of adjacent bone.

Angiography. In the past, angiography was frequently used to assess the vascularity of sarcomas preoperatively. Diagnostic angiography has been replaced by conventional MRI and magnetic resonance angiography, but some vascular sarcomas may require presurgical embolization to prevent excessive bleeding during surgery.

Radionuclide bone scans have long been a reliable tool for detecting multifocal or disseminated osseous lesions and remain the mainstay for evaluation of osseous metastases. They also are helpful in identifying skip lesions of osteosarcoma (ie, smaller discrete foci of osteosarcoma occurring in the same bone or on the opposing side of a joint).[14] Advantages of this modality include whole-body scanning and low radiation at relatively low cost. Radionuclide bone scans demonstrate areas of bony repair and thus could be negative in purely lytic/destructive processes such as renal cell carcinoma metastases and multiple myeloma.

Chest radiographs are typically obtained in the initial stages of patient evaluation and are helpful in demonstrating large nodules or masses resulting from metastatic disease. In a patient with known sarcoma, a negative or equivocal chest radiograph should be followed by chest CT to definitively assess for metastasis.

FIGURE 2. MRI findings highly suggestive of soft-tissue sarcoma in a 79-year-old man with a large anterior thigh mass. **(A)** T2-weighted image reveals a large mass with heterogeneous signal and surrounding pseudocapsule (arrows). **(B)** Post-contrast image shows pockets of absent enhancement (arrowheads) suggestive of necrosis.

■ CROSS-SECTIONAL IMAGING WITH MRI AND CT

MRI preferred for evaluation of most masses

MRI is the examination of choice in the evaluation of soft-tissue masses in light of its superior contrast resolution and ability to demonstrate subtle changes in soft tissues.

Predicting the histology of most soft-tissue masses is difficult, with the exception of some benign vascular lesions (eg, hemangioma), ganglia, neurogenic lesions, and well-differentiated lipomatous lesions. Aggressive features of a soft-tissue neoplasm include size greater than 5 cm,[15] deep location, and absence of central enhancement, which is suggestive of necrosis **(Figure 1)**. Yet one third of soft-tissue sarcomas are either superficial or smaller than 5 cm, which highlights the relative nonspecificity of these features.[15]

A pseudocapsule or capsule is commonly seen around a sarcoma in the soft tissues, producing well-defined margins on MRI that do not reflect benignity **(Figure 2)**. MRI may show T2-weighted signal changes surrounding soft-tissue sarcomas. These abnormalities are considered to represent peritumoral edema. Tumor cells beyond the sarcoma margin were found within areas of peritumoral edema seen on preoperative MRI in 9 of a series of 15 cases.[16] Hematomas and abscesses typically have marked edema of surrounding soft tissue **(Figure 3)** and no internal enhancement after contrast injection. If MRI features of a suspected hematoma are equivocal, a follow-up study is warranted to exclude hemorrhagic sarcoma.

Nowadays, CT of primary soft-tissue tumors is rarely performed. Rare exceptions are patients with a contraindication to MRI (eg, presence of cardiac pacemaker) or for detecting subtle matrix mineral, if it will alter management.

MRI is also the preferred modality in the evaluation of the majority of bone sarcomas, given its ability to accurately define the extent of marrow changes and soft-tissue involvement. MRI should be performed prior to a biopsy to prevent misinterpretation of biopsy-related signal changes in the surrounding tissues, which may negate the value of MRI in sarcoma staging.

Several distinct roles for CT

CT is better at detecting subtle matrix mineral and for establishing the presence or absence of a thin rim of cortex around expansive lesions or masses containing calcific densities—findings that may have a bearing on the differential diagnosis **(Figure 4)**. Abdominal and chest CT remain particularly important tools in the staging process. CT is critical for evaluation of pulmonary nodules.

Chest CT should be obtained in all cases of known malignant neoplasms to evaluate for pulmonary nodules, masses, and lymphadenopathy. Despite the recent advances in MRI, CT remains the imaging modality of choice to evaluate the retroperitoneum, abdomen, and pelvis for masses, lymphadenopathy, or other signs of metastatic disease.

Post-treatment monitoring for recurrence

After definitive treatment, MRI remains the most sensitive imaging tool for diagnosing local recurrences of either bone or soft-tissue sarcomas. After surgery, hematomas or seromas often present as palpable soft-tissue masses and are easily diagnosed with contrast MRI **(Figure 5)**. Baseline examination is critical for visualizing the postoperative distortion of tissues. The presence of metallic hardware in postsurgical patients is not an absolute contraindication, and artifacts may be minimized by new MRI techniques **(Figure 6)**.[17]

■ ULTRASONOGRAPHY

Ultrasonography has a limited role in the initial diagnosis and follow-up of musculoskeletal tumors. Its main advan-
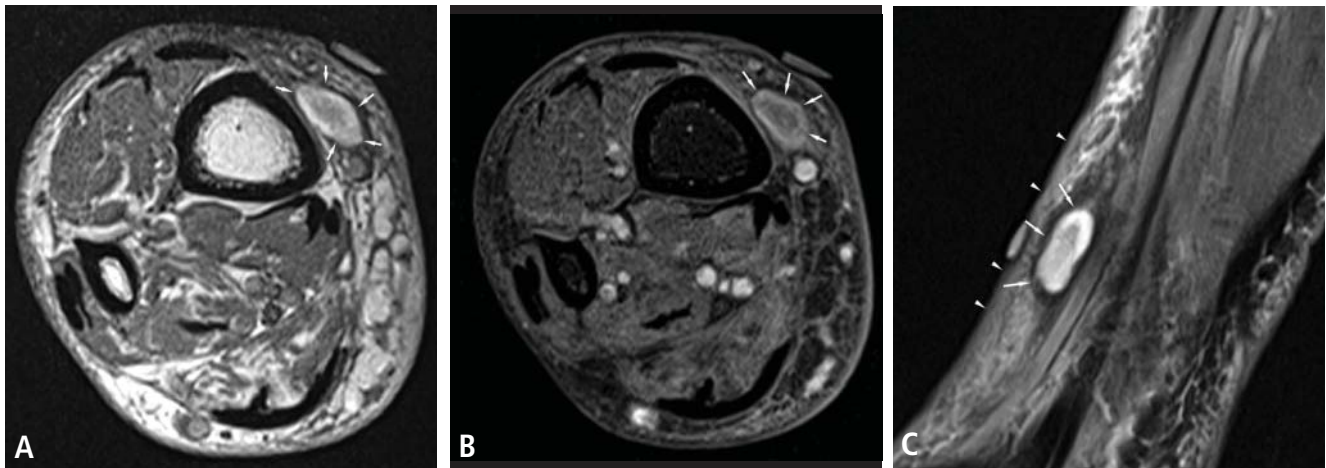
FIGURE 3. MRI findings in an 85-year-old man with a palpable right leg mass. **(A)** T1-weighted axial image shows a mass with increased signal (arrows) consistent with subacute blood products. **(B)** Post-contrast T1-weighted fat-suppressed axial image shows peripheral enhancement typical of a hematoma (arrows). **(C)** T2-weighted image in the sagittal plane demonstrates edema-like signal surrounding the hematoma (arrowheads).

FIGURE 4. CT of a 74-year-old man with a palpable mass along the sternum reveals a destructive mass with soft extension and chondroid-appearing calcifications (arrows) typical of a chondrosarcoma.

FIGURE 5. Follow-up MRIs in an 84-year-old man who had previously undergone surgical resection and radiation therapy for high-grade axillary sarcoma. **(A)** T2-weighted fat-saturated coronal image shows a mass-like structure with heterogeneous signal in the surgical bed (arrows). **(B)** Post-contrast image shows no internal enhancement typical of a postoperative hematoma or seroma. Note the diffuse surrounding edema and enhancement in the axillary area (arrows), which is related to the patient's prior radiation treatment.

tages are a lack of ionizing radiation and dynamic imaging capabilities. Doppler ultrasonography allows direct visualization of tumor vascularity, which may be important for diagnosis and presurgical planning. Unfortunately, bone lesions cannot be evaluated with ultrasonography, owing to the inability of sound waves to penetrate the bony cortex. Poor sound wave penetration may prevent visualization of deep-seated lesions, such as retroperitoneal sarcomas.

Ultrasonography is best used for differentiating solid masses from cystic structures and can provide image guidance in solid tumor biopsy and cyst aspiration. It also may play a role in detecting suspected tumor recurrence in patients in whom artifact from implanted hardware precludes cross-sectional imaging, and it can be reliably used for following up unequivocal soft-tissue masses such as ganglia near joints.

■ POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is a functional imaging technique that allows evaluation of tumor or physiologic tissue metabolism in vivo with positron-emitting radionuclides. [^{18}F]2-Deoxy-2-fluoro-D-glucose (FDG), the most commonly used radiolabeled tracer for PET imaging, demonstrates increased accumulation in several different types of benign and malignant neoplasms. PET/CT scanning of lesions offers a combination of concur-
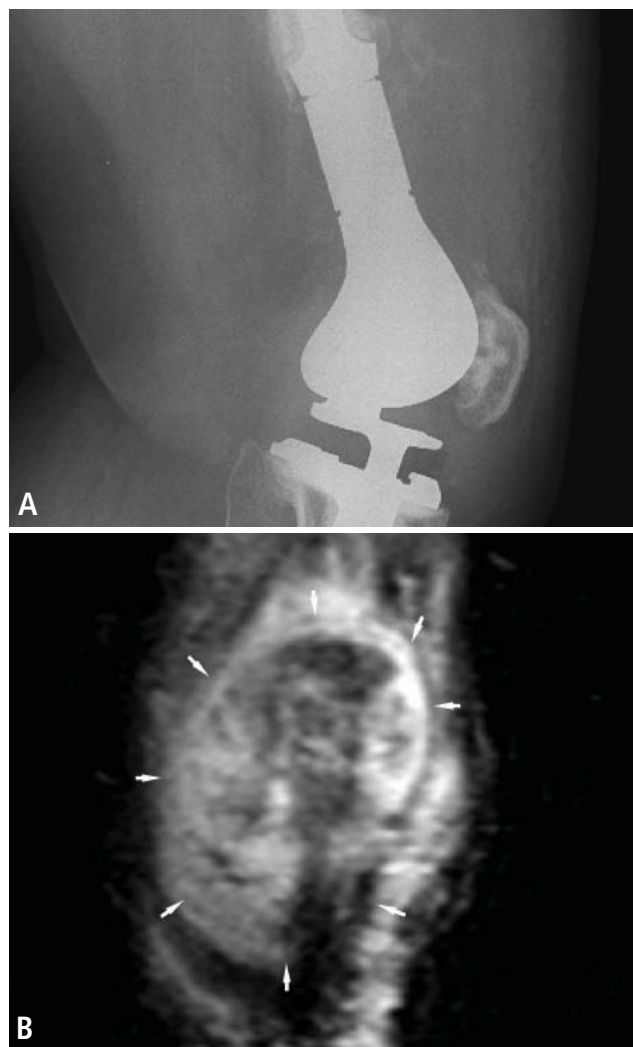
FIGURE 6. MRIs in a 36-year-old man presenting with an enlarging soft-tissue mass after a history of osteosarcoma resection 2 years earlier. **(A)** Lateral view of the knee shows surgical hardware and faint soft-tissue mineralization anteriorly. **(B)** Coronal short-tau inversion recovery (STIR) sequence demonstrates a large soft-tissue mass with heterogeneous signal (arrows) consistent with tumor recurrence.

FIGURE 7. (A) PET/CT scan in a 67-year-old man with a history of spindle-cell sarcoma of the groin showing increased metabolic activity in the right sacral area (arrowheads) suspicious for metastasis. **(B)** CT scan in bone windows from the same examination reveals an insufficiency-type fracture (arrows) with no evidence of a destructive tumor.

rent anatomical and functional imaging findings **(Figure 7A)**, and PET/CT scanner sales now account for more than 80% of the PET scanner market.[18] In the setting of sarcoma, FDG-PET is useful for detection of local recurrence and metastatic disease[19] as well as for evaluation of response to neoadjuvant chemotherapy.[20] Some initial studies have examined the ability of ^{18}F-FDG-PET to differentiate between benign and malignant bone and soft-tissue tumors,[21] which has been controversial because of the considerable number of false-positive and false-negative interpretations of lesions.[19] In addition to benign tumors, non-neoplastic findings such as fractures **(Figure 7)**, sarcoid, synovial chondromatosis, pigmented villonodular synovitis, and infection may demonstrate the maximum standardized uptake value (SUV_{max}) levels that are characteristic of malignant tumors.[19]

■ IMAGING-GUIDED INTERVENTIONS

Percutaneous imaging-guided procedures have increasingly replaced open surgical biopsies for bone and soft-tissue tumors. CT guidance is commonly used for percutaneous biopsy, whereas ultrasonographic guidance is sometimes used for superficial soft-tissue lesions. Although the shortest and most direct approach is desirable, this may not be possible in all cases due to the presence of nearby vital structures or the risk of contamination. Seeding of malignant cells along the biopsy tract is a well-known possible complication of image-guided biopsies, and en bloc resection of the needle tract is typically performed at the definitive surgery.

Knowledge of compartmental anatomy is paramount in planning the approach for these biopsies, and consultation with the referring orthopedic surgeon is recommended for optimal management. Expert histopathological interpretation of bone and soft-tissue specimens is essential for the

efficacy and high success rates of percutaneous imaging-guided biopsies. Such expertise is integral to the broader interdisciplinary collaboration that is needed to arrive at the most plausible diagnosis, especially in the setting of uncommon or atypical neoplasms.

Currently, MRI-guided interventions are in the initial stage of evolution and could provide valuable guidance for subtle marrow or soft-tissue lesions visible on MRI but not well seen on CT.[22] In the future, MRI could play an increasingly important role in imaging-guided procedures because of its lack of ionizing radiation and its ability to demonstrate subtle soft-tissue and bone marrow changes. Imaging-guided therapeutics are growing in their applications in musculo-skeletal oncology. CT-guided radiofrequency ablation and cryoablation have been used in the treatment of a variety of tumors[23] as well as in the palliation of metastatic bone pain.[24]

■ SUMMARY AND CONCLUSION

Bone and soft-tissue sarcomas are rare neoplasms with variable clinical presentations. A high index of suspicion is required for any unexplained mass with indeterminate imaging findings. Recent advances in imaging technology, including cross-sectional MRI and CT, have significantly refined the diagnosis and management of bone and soft-tissue sarcomas. When faced with a possible sarcoma, the clinician's selection of imaging modalities has a direct impact on diagnosis, staging, and patient management.

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Bone sarcomas: Overview of management, with a focus on surgical treatment considerations

◼ ABSTRACT

Outcomes for patients with bone sarcomas have improved dramatically over the past 40 years, and most bone sarcomas today are treated with surgery and chemotherapy. The most common clinical findings in patients with bone sarcomas are pain and an enlarging bone mass, although pain is not generally a good indicator of malignancy. In general, any patient with a bone mass with indeterminate imaging findings should be referred to an orthopedic oncologist. Bone sarcomas are diagnosed after a biopsy, which is best performed by the surgeon who will be doing the curative resection. Postresection reconstruction of the affected limb is generally done with an allograft-prosthetic composite or a modular metallic prosthetic joint replacement device. Post-therapy follow-up at frequent and regular intervals is critical to assess for recurrence and lung metastasis.

Prior to the 1970s, bone sarcomas were routinely treated with amputation, yet most patients still died from metastatic disease.[1] The advent of the use of chemotherapy for bone sarcomas in the 1970s was shown to increase long-term survival,[2–5] contributing in part to tremendous subsequent advances in the treatment of the most common bone sarcomas—osteosarcoma and Ewing sarcoma. Today, long-term disease-free survival rates of about 60% to 80% are observed for patients with Ewing sarcoma or osteosarcoma with no metastasis at presentation.[6,7] In addition to the chemotherapy advances, modular metallic prosthetic limb reconstruction systems are now readily available, eliminating the need to wait for custom reconstructive hardware. Moreover, these systems can be used in combination with large bone allografts or vascularized bone flaps.

The majority of patients with bone sarcomas require multimodal treatment, primarily with surgery and chemotherapy. Patients with chondrosarcomas are the primary exception, as chondrosarcomas are generally treated with resection alone. Thus, management of most patients with bone sarcomas requires a multidisciplinary team that includes orthopedic, medical, and radiation oncologists as well as plastic and reconstructive surgeons, physical therapy specialists, pathologists, and radiologists with expertise in bone tumors.

Despite this broad need for multimodal therapy, surgical resection is fundamental to the management of virtually all bone sarcomas and is the primary focus of this article. The roles of chemotherapy and radiation therapy for bone sarcomas are detailed in the final two articles in this supplement.

◼ INITIAL EVALUATION OF SUSPICIOUS BONE MASSES

Figure 1 outlines a general stepwise approach to the evaluation and management of the patient with a bone mass suspicious for sarcoma—an approach detailed in the section below.

History and physical examination

As noted in the preceding article in this supplement, most bone sarcomas (particularly osteosarcomas and Ewing sarcomas) occur in pediatric patients and young adults and develop in the extremities (especially the distal femur) or pelvis.

In terms of history, most patients with a bone sarcoma will report pain, but pain is not a good indicator of malignancy, as some patients with no pain or an improvement in pain have sarcomas while many patients with pain do not have malignancies.[1]

The other most common finding in patients with a bone sarcoma is an enlarging mass. The presence of a mass, as well as its location, depth, size, and overlying skin quality, can be determined on physical examination. An accurate neurovascular exam should be performed as well, although damage to neurovascular structures is a late finding in sarcoma patients.

Imaging

Radiographs are important in any patient with prolonged unexplained bone pain and will almost always reveal an aggressive lesion in the patient with a bone sarcoma. Lengthy delays in the diagnosis of a bone sarcoma are nearly always explained by failure to obtain a radiograph.

Magnetic resonance imaging (MRI). Questions about whether a radiograph of a lesion is determinate or not are best resolved by MRI, which is the primary imaging method for evaluating bone lesions, their exact location, and their proximity to neurovascular structures. While "determinate" and "indeterminate" are most precisely used to refer to imaging studies of a lesion, these terms are often used in clinical parlance to refer to the lesions themselves. As such, "determinate lesions" by imaging are those that can be accurately judged malignant or benign with a high level of certainty. Determinate benign inactive lesions such as enchondromas and osteochondromas, if asymptomatic and without severe bony destruction, do not require a bone biopsy. "Indetermi-

FIGURE 1. A general step-by-step approach to the patient with a bone abnormality on radiography.

*If widespread metastatic disease is found, then resection is not indicated for curative purposes but still can be useful for palliation.
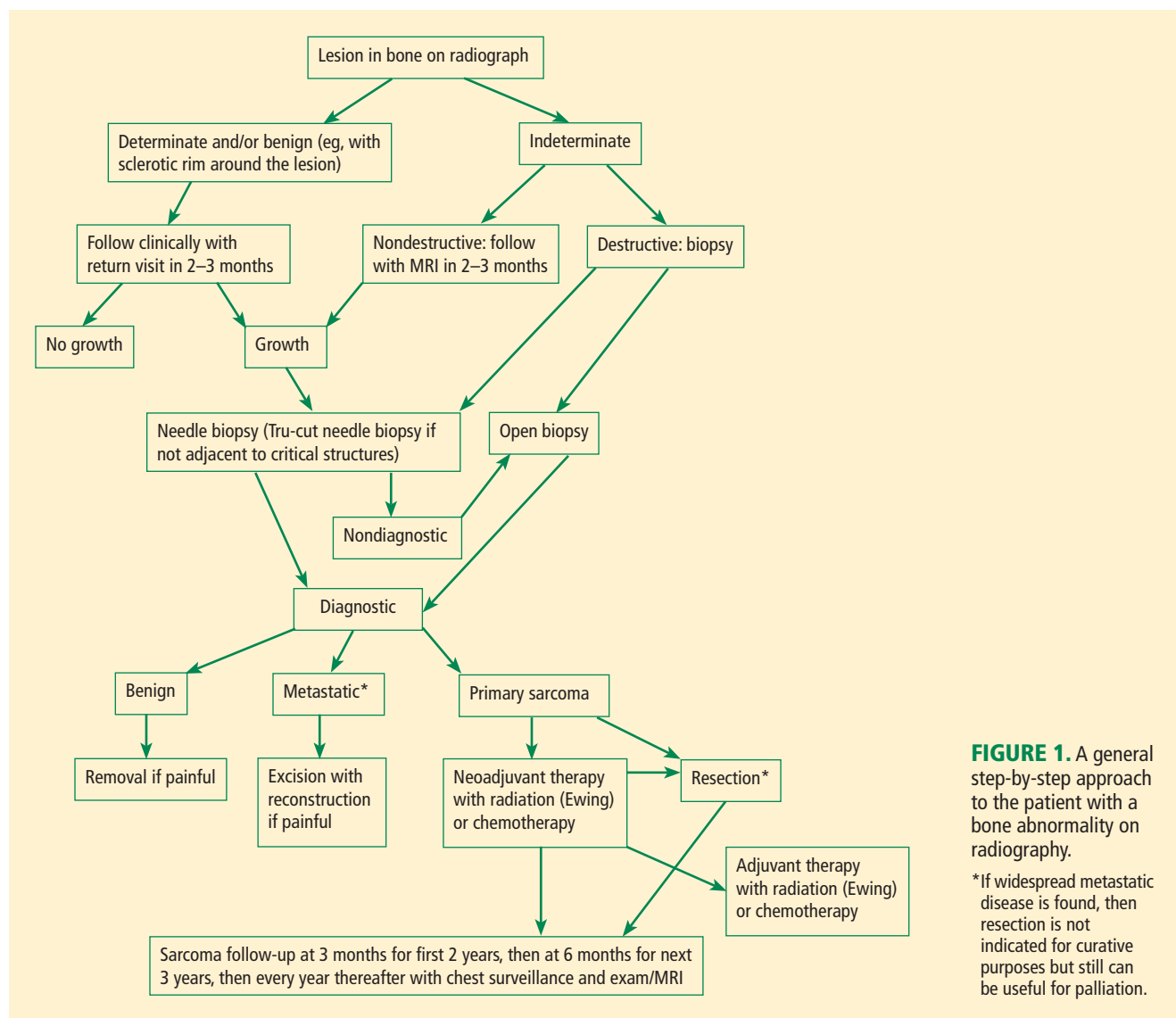
nate lesions" by imaging are those whose imaging findings are not clearly consistent with a single diagnosis, and nearly all of these lesions require a biopsy.

In general, any patient with a bone mass with indeterminate imaging results should be referred to an orthopedic oncologist.

Staging
When imaging findings are highly suggestive of bone sarcoma, efforts should be made to delineate how far the tumor extends and whether systemic disease is present. Bone sarcomas can metastasize to other bones, but their most common site for metastasis is the lung.

MRI of the lesion without gadolinium is indicated, and the entire bone is imaged to determine the extent of the external mass outside the bone and to look for medullary extension and skip lesions (eg, smaller foci of sarcoma occurring in the same bone or on the opposing side of a joint).

The precision offered by MRI has dramatically increased surgeons' ability to achieve negative margins during resection.

Radiography or computed tomography of the chest is required to accurately assess the lungs for metastasis. A nuclear medicine technetium scan can be obtained to look for other similar bone lesions (metachronous lesions) or metastatic bony disease.

Laboratory tests are not helpful in the staging of bone sarcomas.

■ BIOPSY
Biopsy is the gold standard for diagnosis of bone sarcoma **(Figure 1)**. The primary biopsy methods used are needle or open biopsy techniques, and Tru-cut needles or core bone biopsy needles are increasingly used. If the core needle biopsy is diagnostically inconclusive, an open biopsy can promptly be performed. Biopsies yielding specimens that

are too small can result in inconclusive pathology reports. Regardless of the biopsy technique, hemostasis is of paramount importance, and patients are generally advised to not use the affected limb for at least several days after the procedure to reduce the risk of a cancer cell–laden hematoma.

If a needle biopsy is performed, 2 to 10 minutes of gentle pressure is applied to the site. In an open biopsy, electrocauterization is used extensively. Aggressive hemostasis is achieved, and if a drain is placed it should be in proximity to the incision site itself so that the drain site will be resected with the specimen at the time of definitive resection. Open biopsies are performed in the operating room with regional or general anesthesia. Incisions are made longitudinally and never transversely.

Ideally, the biopsy should be performed or supervised by a physician experienced with limb salvage for bone sarcomas. Otherwise there is risk for an inappropriate biopsy tract or approach, misinterpretation of the radiographic studies, misinterpretation of the pathology, or biopsy complications. These errors may lead to undertreatment or even unnecessary amputation.[8,9]

■ RESECTION

For some bone sarcomas, such as osteosarcoma and Ewing sarcoma, there is a preference to treat the potential micrometastatic disease at the beginning of the course, prior to surgical treatment. This may result in reduction of the soft-tissue mass about the bone tumor and/or maturing of the mass, allowing for easier resection.

Importance of margins

The goal of resection is to achieve a margin or normal cuff of tissue around the pseudocapsule of the tumor. In general, the larger the margin, the less the chance of recurrence.[10–12] Ideally, the tumor and pseudocapsule should not be violated or exposed and a margin of at least 1 cm should be obtained. It has been postulated that margins of less than 1 cm may be associated with a very low rate of recurrence, although no well-controlled study has proven this and such a study would be difficult to perform given the rarity and heterogeneity of bone sarcomas and the variability in their assessment and surgical treatment.

Intralesional surgery is generally to be avoided

Intralesional surgery should not be performed on high-grade bone sarcomas because it will lead to a high risk of local recurrence regardless of whether the patient receives perioperative radiation therapy or chemotherapy. If intralesional surgery has been performed for a high-grade sarcoma at an outside institution, re-excision of the tumor bed is recommended, as it has reduced the rate of recurrence following intralesional surgery.[13] For low-grade chondrosarcomas, intralesional curettage (ie, violating the margin of the tumor by scraping it out thoroughly) with use of an adjuvant (freezing, phenol, methylmethacrylate, or argon beam) may be adequate and has been reported to have a low rate of recurrence.[14]

Preoperative planning

The resection procedure involves careful preoperative planning, typically guided by an MRI reviewed by a musculoskeletal tumor radiologist. General anesthesia is usually preferred because it can be used for a lengthy procedure, ensures complete muscle relaxation over the duration of the procedure, and allows for immediate postoperative nerve assessment. If neurovascular structures are not encased (ie, not more than 50% surrounded in the case of arteries or motor nerves), these structures are spared. If arteries are encased, arterial resection with reverse interpositional vein graft, synthetic graft, or vein allograft allows for bypass of the vessel and leaves the encased structure with the resection specimen for en bloc resection. In Ewing sarcoma, if the tumor is adjacent to but not encasing the neurovascular structures, the radiation oncologist is consulted about whether there is a preference for pre- or postoperative radiation therapy.

Limb salvage for Ewing sarcoma was originally with radiation only, but subsequently limb-salvaging surgery has been shown in several studies to have lower rates of local failure.[6,15–18] Whether primary radiation or surgery is performed after the initiation of chemotherapy is generally determined by a discussion between the surgeon and radiation oncologist about the feasibility of a negative margin with surgery and the inherent functional loss with resection. There are particular concerns about radiation in younger patients, who have a relatively high rate of postradiation sarcoma.[18]

In osteosarcoma and chondrosarcoma, radiation has been found not to be effective, so resection with a negative margin is especially important for preventing local recurrence.

■ RECONSTRUCTION

Allograft or metallic prosthesis?

For reconstruction after bone sarcoma resection, it is common to use costly modular metallic prosthetic joint replacements. We have found, however, that the most effective and easiest way to reconstruct the extensor mechanism sometimes is to use an allograft-prosthetic composite (APC) with a unicortical plate across the host bone–allograft junction. In the case of proximal tibial resection, for example, the APC consists of a proximal tibial allograft with soft-tissue patellar tendon and a rotating-hinge modular knee replacement prosthetic (**Figure 2**). In these proximal tibial resections, the soft-tissue envelope over the prosthesis is precarious and, depending on the quality of the remaining soft-tissue coverage, reconstruction over these complex components will usually require a local flap (gastrocnemius muscle) or occasionally even a distant free tissue transfer (free flap).

In the proximal and distal femur, modular metallic replacement prosthetic joint devices are used. Often a wafer of greater trochanter bone (if uninvolved in the tumor process) can be preserved and a "cable-claw" attachment to the metal component can be accomplished instead of using an allograft.
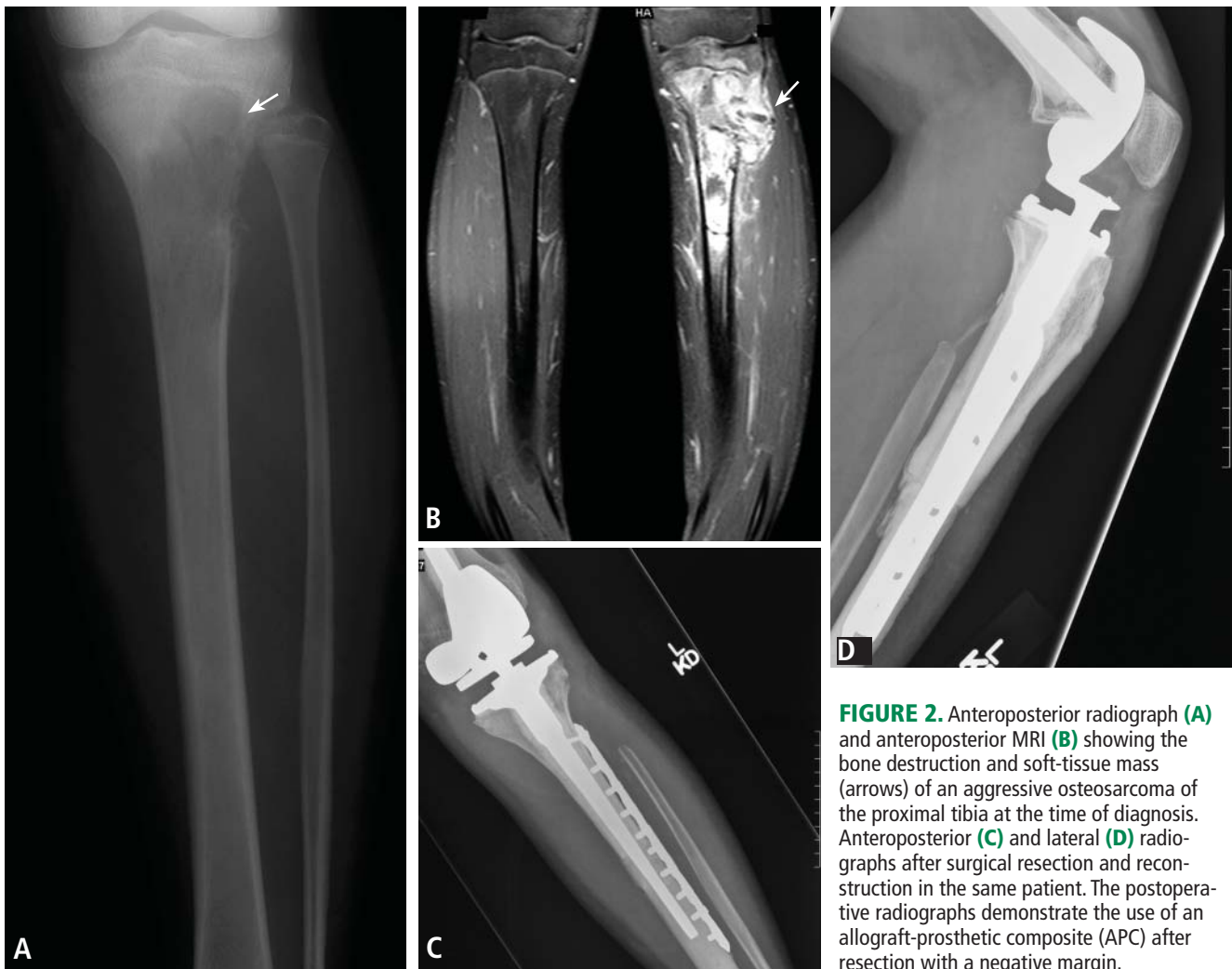
FIGURE 2. Anteroposterior radiograph **(A)** and anteroposterior MRI **(B)** showing the bone destruction and soft-tissue mass (arrows) of an aggressive osteosarcoma of the proximal tibia at the time of diagnosis. Anteroposterior **(C)** and lateral **(D)** radiographs after surgical resection and reconstruction in the same patient. The postoperative radiographs demonstrate the use of an allograft-prosthetic composite (APC) after resection with a negative margin.

Since the proximal humerus is not weight-bearing and because of the importance of the rotator cuff, use of an APC in the proximal humerus can be most helpful. Function is not good with a metallic proximal humerus implant alone, and the dislocation rate is high over long-term follow-up, owing to lack of healing of the rotator cuff remnant to the metal prosthesis.

In patients with scapular sarcomas, allograft or prosthetic reconstruction has not been consistently better than simply repairing the remaining muscles to each other, so we generally do not use allografts or prostheses after sarcoma resection in these patients.

Growing bones of youth pose special challenges

In growing children, who represent a large share of bone sarcoma patients, reconstruction after resection in the lower extremity is challenging, particularly in terms of addressing leg length inequality. In general, a prosthesis is used and if the end growth discrepancy will be greater than 3 cm, use of an expandable prosthesis is considered. Use of these expandable prostheses has been fraught with com-plications, however, and by their nature they require revision because of breakage. An alternative is reoperation to disconnect the modular prosthesis and insert an additional 1- to 2-cm segment to increase length when necessary. Allograft bones are a common method of reconstruction when the resection does not involve the joint.

Rotationplasty

Rotationplasty—which involves saving the portion of the extremity distal to the resection site and reattaching it after being rotated 180 degrees—is rarely performed for leg reconstruction, in light of the disfiguring nature of the surgery as a result of the 180-degree rotation.

When rotationplasty is performed, the lower tibia and foot generally are brought up to the middle or proximal femoral area and attached to the short proximal femur. Rather than a short above-knee amputation, the reversed foot functions as a knee, allowing for better prosthetic function (ideally similar to a short below-knee prosthesis), and adds length to a short above-knee amputation.

Another alternative is a tibial turn-up to add length to a very short above-knee amputation if the vessels are not involved with the tumor and limb salvage is otherwise not practical. In this procedure the ankle can be turned up to the hip and the proximal tibia ends up distal to the ankle.

■ AMPUTATION

When curative surgery is possible and limb-salvaging resection is unlikely to obtain a negative margin or a functionally viable extremity, amputations are still performed. For example, amputation is recommended in a patient with a high-grade calcaneal (heel bone) sarcoma with a large soft-tissue mass. However, amputation is not the usual approach for most bone sarcomas today and it is not benign in outcome. Notably, phantom limb pain and stump pain have been reported after amputation in the typically sensate tumor patient.

Meticulous hemostasis is necessary in all amputations, and myodesis, or direct suturing of muscle to the distal end of the bone, is important for soft-tissue coverage over the distal stump. In general, a fish-mouth incision is used for the upper extremity and thigh, and a posterior flap is used, when possible, below the knee. However, the choice of technique depends on factors such as the presence or absence of a biopsy incision and the location of tumor soft-tissue mass, so local tissue rearrangement or flaps may need to be used for stable coverage or closure.

For all amputation patients, early involvement of an acute pain specialist reduces the incidence of phantom limb pain.

■ SURVEILLANCE AND FOLLOW-UP

Post-therapy follow-up of patients with bone sarcomas is critical. Even among patients who receive appropriate surgery with negative margins there is a recurrence rate of approximately 9% (personal communication from Dr. Dempsey Springfield), and previously undetectable metastatic disease may become detectable in the postoperative period. In general, patients are followed at 3-month intervals for the first 2 years, at 6-month intervals for the next 3 years, and at yearly intervals thereafter. Follow-up evaluations must include examination of the the involved extremity and imaging of the chest, with radiography or computed tomography, to assess for metastasis.

Rehabilitation is specific to the site of resection and the reconstruction. In general, range of motion is important around the knee, whereas in patients with resection and reconstruction involving the shoulder, hip, or pelvis, it is more important that the affected muscles be given time to heal (6–12 weeks) before aggressive rehabilitation is begun.

Many patients limp postoperatively, particularly in the initial period, and the degree of limp depends primarily on the amount of muscle and the bony insertion sites that are resected with the tumor. Improvements in function are common over time, even at several years after surgery.

■ FUTURE DIRECTIONS

Despite the advances in bone sarcoma outcomes in recent decades, sarcomas of the pelvis continue to carry a worse prog- nosis than those of the extremities and thus represent an opportunity for improvement. Among the improvements hoped for is an ability to accomplish partial pelvic resections—eg, of the wing, ischium, or ramus—without need for reconstruction for these smaller localized tumors. Options include amputation (hemipelvectomy) with loss of leg; internal hemipelvectomy (where the pelvis is resected but the leg is left attached without reconstruction of the defect); or resection of the pelvic/acetabular area but with reconstruction using pelvic allografts/total hip composites or large metallic prostheses.

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Soft-tissue sarcomas: Overview of management, with a focus on surgical treatment considerations

■ ABSTRACT

Patients with soft-tissue sarcomas generally present with a mass that is increasing in size; the presence or absence of pain is not typically predictive of malignancy. While magnetic resonance imaging (MRI) can identify a few soft-tissue lesion types as benign, diagnosis of most lesions requires a careful biopsy, preferably performed by or in consultation with the surgeon who would do an eventual resection. If biopsy confirms a diagnosis of sarcoma, MRI-guided surgical resection with a wide margin is the mainstay of treatment. Neoadjuvant radiation therapy and chemotherapy have not been of proven benefit in well-controlled studies but are frequently used as adjuncts. Resections with wide margins are generally associated with a low (< 10%) risk of recurrence.

Soft-tissue sarcomas are tumors of the mesenchymal system, and half develop in the extremities.[1] Although patients with soft-tissue sarcomas have been treated with a combination of surgery, radiation therapy, and chemotherapy, it remains unclear whether either radiation or chemotherapy improves outcomes for these patients. Soft-tissue sarcomas are therefore currently treated with surgical resection when possible, with or without chemotherapy or radiation.

Even though multimodal therapy for patients with these tumors is controversial, a multidisciplinary conference among the many providers who may be involved in the management these patients—orthopedic, medical, and radiation oncologists, as well as the referring primary care physician, plastic and reconstructive surgeons, physical therapists, and radiologists and pathologists with expertise in these tumors—is helpful.[2] This article presents an overview of the management of these patients, with a focus on the mainstay treatment, surgical resection. The roles of chemotherapy and radiation therapy for soft-tissue sarcomas, while touched upon here, are detailed in the final two articles in this supplement.

■ HISTOLOGIC GRADING AND THERAPY IMPLICATIONS

The prognosis of soft-tissue sarcomas correlates with histopathologic grade, and a three-grade system appears to be

more accurate than a two-grade system.[3] In general, low-grade lesions (grade 1) are unlikely to metastasize and are therefore less likely to need treatment with chemotherapy or radiation, as the risks of these therapies would most likely outweigh any benefit in terms of local control.

Specifically, the risk of radiation involves debilitation of local wound healing and the chance of dedifferentiation of low-grade lesions to higher-grade lesions with more metastatic potential. Grade 2 and 3 lesions are usually considered high-grade and are more likely to be treated with radiation and chemotherapy. Radiation is frequently used in patients with high-grade lesions when anticipated margins or actual margins are less than 1 cm.[4–6]

Chemotherapy's lack of proven efficacy for soft-tissue sarcomas likely stems from poor understanding of the pathophysiology, molecular biology, and even some aspects of the natural history of these uncommon and heterogeneous tumors. There are more than 50 subtypes of soft-tissue sarcoma,[7,8] and this heterogeneity has likely contributed to the difficulty of identifying chemotherapeutic agents that are highly active against these diseases.[9]

■ THE ROLE OF FAMILIAL GENETICS

Developing effective chemotherapeutic strategies may depend on grouping soft-tissue sarcomas more homogeneously. To compare like lesions with like lesions, molecular analysis and even molecular signatures may be of assistance. Along these lines, critical mutations and translocations have been described for several soft-tissue sarcoma subtypes.

Li-Fraumeni syndrome is an autosomal dominant cancer predisposition syndrome caused by germline mutations (ie, in every cell) in the p53 gene.[10] Patients with Li-Fraumeni syndrome have an increased risk of developing soft-tissue sarcomas.[1,11]

Neurofibromatosis type 1 is caused by germline mutations in the NF1 gene, and malignant peripheral nerve sheath tumors occur within neurofibromas in neurofibromatosis patients and typically have additional mutations in CDKN2A or p53.[9] INI1 loss is seen in all cases of extrarenal rhabdoid tumors and has been reported in a subset of epithelioid sarcomas (those occurring in proximal/axial regions).[9,12] Delineation and greater understanding of these genetic abnormalities may lead to more effective medical therapy.

■ EVALUATION OF SUSPICIOUS SOFT-TISSUE MASSES

Soft-tissue sarcomas occur primarily in adults, and incidence rates rise gradually with age.[1] About half of these tumors develop in the extremities (primarily the lower

FIGURE 1. A general step-by-step approach to the patient with a soft-tissue mass suspicious for sarcoma.
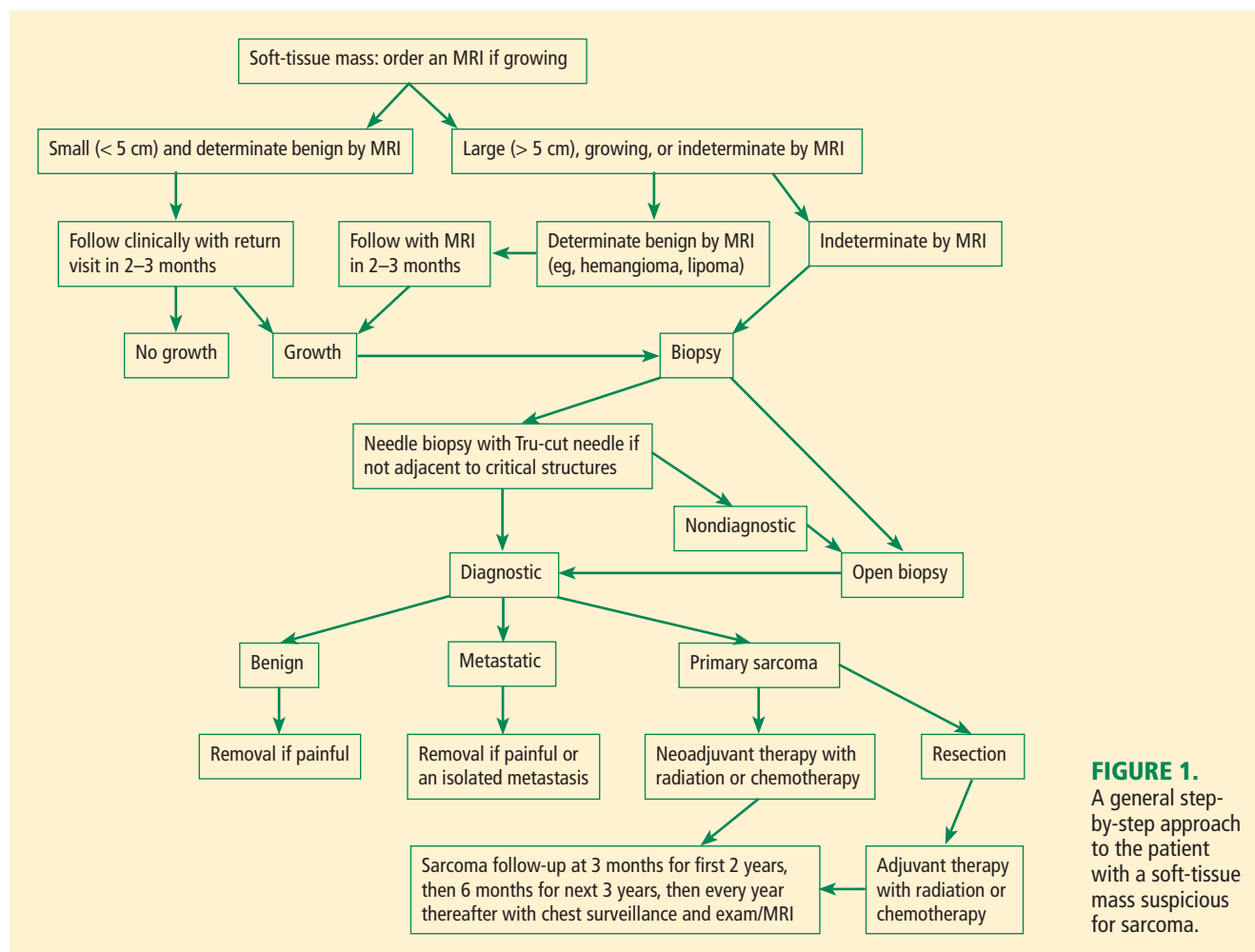
extremities), with the remainder occurring in the retro-peritoneum, the trunk, and other less common sites.[1]

Figure 1 presents in flow chart form our general approach to the evaluation and management of patients with a soft-tissue mass suspicious for sarcoma—an approach detailed in the text below.

History and physical examination

Patients with soft-tissue sarcomas present with a mass that generally is increasing in size. The location and depth of the mass can be assessed on physical examination. In general, the deeper the mass, the more likely it is to be a sarcoma.[13] Unlike bone sarcomas, soft-tissue sarcomas frequently are not associated with pain, so lack of pain does not make a mass more likely to be benign. In general, the only way to be sure that a mass is not malignant is to biopsy it. However, there are certain symptoms and signs that make a benign diagnosis much more likely. For example, very soft superficial masses that have not changed in size in years tend to be benign lipomas, and discolored lesions that go away with elevation of the affected body part tend to be hemangiomas.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is the primary imaging method for soft-tissue sarcomas. The benignity of a lesion such as a lipoma or hemangioma may be able to be determined with high certainty on MRI, in which case we call the imaging of the lesion "determinate." Such lesions with determinate imaging (often referred to as "determinate lesions") usually do not require a biopsy. However, the nature and identity of most lesions cannot be determined by MRI; although the MRI is still useful to help plan the biopsy in these cases, these lesions are termed "indeterminate" by MRI and should usually be biopsied.

Lesions that can be deemed determinate and usually be diagnosed as benign based on MRI findings include lipomas, hemangiomas, granuloma annulare, and ganglion cysts. However, most other soft-tissue lesions are indeterminate on MRI and, except in rare circumstances, require a biopsy to determine what they are and how they should be treated.

■ BIOPSY

The primary biopsy procedures for soft-tissue sarcomas are needle or open biopsy techniques and, in general, are
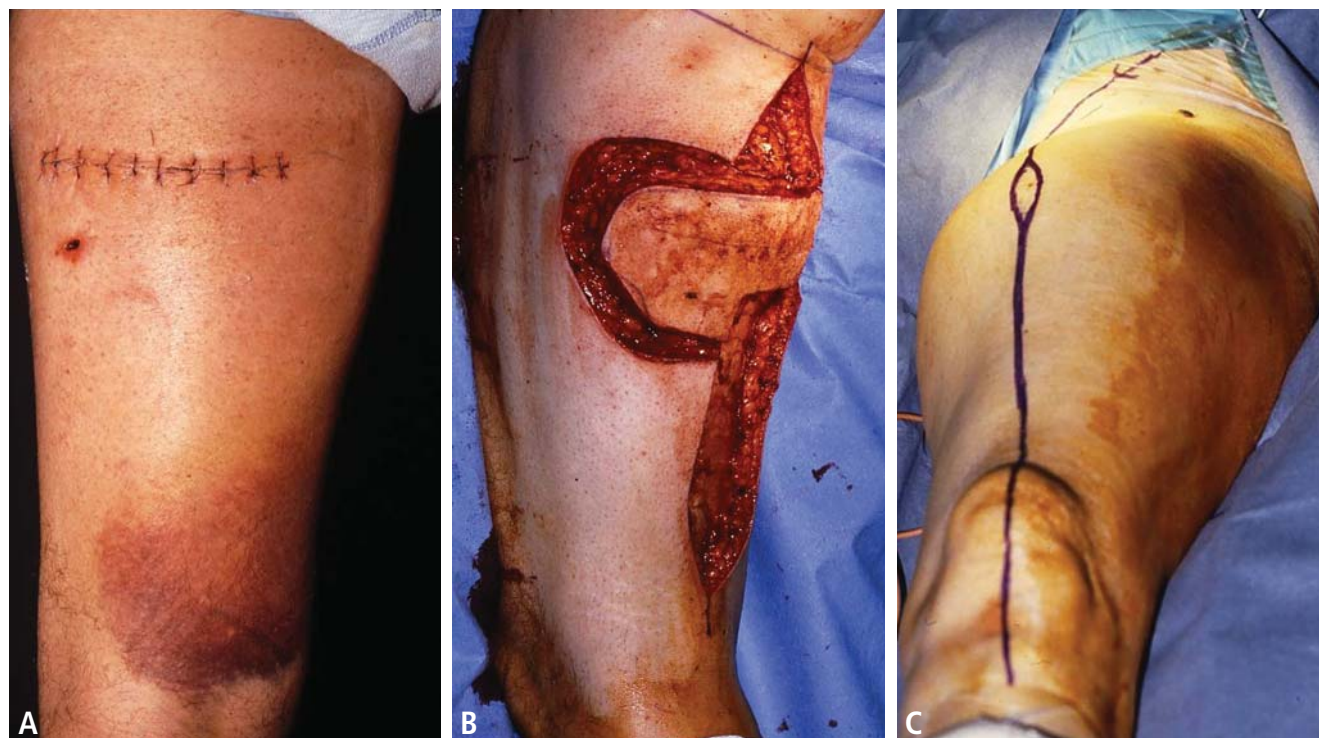
FIGURE 2. (A) Transverse incision for a biopsy of a soft-tissue sarcoma and **(B)** the subsequent resection of the biopsy tract required as a result of this transverse incision. Contrast this with the minimal additional soft-tissue resection that will be required with a properly performed needle biopsy **(C)**.

similar to those for bone sarcomas, as reviewed in the previous article in this supplement. Regardless of the biopsy technique, hemostasis must be meticulous and patients are generally advised to not use the affected limb for at least several days after the biopsy to reduce the risk of a cancer cell–laden hematoma. It is preferable for the biopsy to be performed by or in consultation with the surgeon who will do the resection, if required.

Avoid transverse incisions
Transverse incisions require that substantially more tissue be resected with removal of the biopsy tract **(Figure 2, A and B)** and should therefore be avoided. In general, small longitudinal incisions with no drains should be used if open biopsies are performed, and we prefer needle biopsies because much less tissue must be taken with the biopsy tract **(Figure 2C)**.

Lymph node biopsies
Lymph node biopsies are not generally indicated in patients with soft-tissue sarcoma. However, lymph node assessment and management should be considered in cases of clear cell sarcoma, epithelioid sarcoma, angiosarcoma, and embryonal/alveolar rhabdomyosarcoma, each of which has a greater than 10% incidence of lymph node metastasis.[14] In this subset of soft-tissue sarcomas, a 5-year survival rate of 46% has been reported with therapeutic lymphadenectomy with curative intent versus nearly 0% with no lymphadenectomy or noncurative lymphadenectomy.[14]

Our approach in these sarcomas that go to the lymph nodes with increased relative frequency has been to first resect the sarcoma and then, after the margin is determined to be negative on the permanent pathology report, to schedule a nuclear medicine radiotracer study to analyze the drainage of the surgical bed. With this information we take the patient to the operating room and assess the location of the sentinel node (ie, node with the highest level of activity) through the skin using a radioactive counter with a sterile probe. We then make an incision in this area and find the lymph node. Upon removal of the "hot" lymph node, we reassess the radioactivity of the resected node and its node bed to be sure that we have the sentinel node. If this node or any node in the dissection has tumor in it, we do a therapeutic lymphadenectomy to remove all the lymph nodes in the area. For example, in the lower leg the lymphatic drainage is to the popliteal area, the inguinal area, or both. In the lower arm the lymphatic drainage is to the epitrochlear area and the axilla.

■ RESECTION
The resection surgery involves careful preoperative planning, almost always with an MRI and subsequent review by musculoskeletal tumor radiologists. In the operating room, general anesthesia is preferred to avoid ineffective blocks or overly effective blocks, which prevent neurologic examination immediately after the operation. If the functional loss is not too great, resection of the entire muscle or muscles involved is performed. If neurovascular structures are not

encased (ie, not more than 50% surrounded in the case of arteries or motor nerves), then these structures are spared. If arteries are encased, the vessels are bypassed and the encased structure is left with the resection specimen. If the tumor is adjacent to but not encasing the neurovascular structures, the best course is to discuss with the radiation oncology team whether they prefer preoperative or postoperative radiation therapy. In general, for a high-grade lesion with adjacent neurovascular structes and no plane between the tumor and these structures, we ask our radiation oncologist colleagues to see the patient and discuss preoperative or perioperative (brachytherapy) radiation therapy. Postoperatively, where there is less than a 1-cm margin with no fascial boundary, we generally recommend radiation.

Margins

In our experience, margins of 1 cm or greater or resections with a fascial boundary are adequate and will leave patients with a much lower than 10% risk of recurrence. Others have postulated that margins that are smaller than this can have a very low rate of recurrence if perioperative (preoperative, intraoperative, or postoperative) radiation is given (personal communication from Drs. Jeffrey Eckardt and Dempsey Springfield). However, no well-controlled study has demonstrated how close the margin can be while still achieving an acceptable recurrence rate, and such a study would be very hard to perform given the rarity and heterogeneity of soft-tissue sarcomas and the variability in their assessment and surgical treatment.

Intralesional surgery leads to recurrence

Intralesional surgery will always lead to recurrence if the lesion is truly a soft-tissue sarcoma, even in spite of radiation therapy, chemotherapy, or both. Myomectomy and compartmental resections are frequently necessary to achieve a negative margin (normal tissue around the entire resection specimen). If intralesional surgery has been performed at an outside institution, we have generally recommended resection of the tumor bed, and in our experience this has reduced the recurrence rate after intralesional surgery to levels near those obtained when we perform the biopsy. In our experience, intralesional surgery without tumor bed resection will result in recurrence in nearly every case.

Reconstruction

Postoperative reconstruction of the defect involves closure of the fascia and skin with minimal tension, if possible. If there is tension, a vacuum-assisted closure dressing is placed on the wound and the patient returns for definitive closure, usually with a muscle flap. If the flap is a straightforward rotational flap, such as a medial gastrocnemius, or if only a split-thickness skin graft is required because there is healthy muscle in the floor of the open wound, this can be performed by experienced orthopedic surgeons. If these straightforward solutions are not possible, consultation with plastic surgeons is required, and they will cover the area with a complex rotational flap or, occasionally, with a free flap. For split-thickness skin grafts, it is prudent to

make certain that the width of a #15 knife blade can pass between the blade and the housing of the Padgett dermatome and to take the skin from the extremity ipsilateral to the sarcoma (even with negative margins) to ensure that skin will not be contaminated with errant sarcoma cells.

Reconstruction following sarcoma resection is discussed in further detail in the next article in this supplement.

■ OUTCOMES AND FOLLOW-UP

The recurrence rate for soft-tissue sarcomas resected at Cleveland Clinic over the past 15 years has been less than 10%. This rate is comparable to the rates at other institutions that perform a high volume of sarcoma resections, but at institutions without a group dedicated to these procedures or without substantial experience in them, the recurrence rate is much higher, particularly with positive margins.[15]

Cure for soft-tissue sarcomas depends on being disease-free not only locally but also systemically. Most metastases from soft-tissue sarcomas are to the lung and, less commonly (as noted above), the lymph nodes. We assess local recurrence and metastatic disease at 3-month intervals for the first 2 years. Among patients who are disease-free at 2 years after the definitive surgery, the cure rate is 80% to 85%. After 2 years, we assess patients for presence of disease at 6-month intervals for the next 3 years and at yearly intervals thereafter.

Patients who have a recurrence are at increased risk for metastatic disease, and it is often very hard to achieve local control, as these patients frequently have had tumor contamination of the wound. At that point, unless the entire wound is excised or an amputation is performed, recurrences will continue. A nomogram has been validated for evaluating 10-year soft-tissue sarcoma–specific survival[16] and is freely available at *www.nomograms.org*.

■ FUTURE DIRECTIONS

Future research challenges in this area include breaking down soft-tissue sarcoma subgroups more homogeneously, possibly with genetic markers, to better determine which lesions might benefit from chemotherapy. The goal of improved subtyping is to decrease the metastatic rate of soft-tissue sarcomas in much the same manner that directed chemotherapy has improved the metastasis and cure rates for patients with Ewing sarcoma and osteosarcoma.

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Considerations surrounding reconstruction after resection of musculoskeletal sarcomas

■ ABSTRACT

The defects left by resection of bone and soft-tissue sarcomas often require reconstructive surgery to provide adequate wound coverage, preserve limb function, and optimize cosmetic results. Immediate reconstruction should always be considered after resection with a negative margin, and should be attempted whenever possible. The choice of reconstructive method and tissue flap depends on multiple factors, including body site, donor site morbidity, functional requirements, size of the vascular pedicle, and aesthetics. Preoperative planning before the resection should anticipate the defect size and resulting functional and cosmetic deficits; the success of such planning depends on a collaborative approach between the teams performing the primary resection and the reconstruction. Vigilant postoperative care and flap monitoring is key to avoiding flap or graft failure, hematoma, infection, and other reconstruction-related complications.

Advances in the management of soft-tissue and bone sarcomas—referred to collectively as "musculoskeletal sarcomas" hereafter—have resulted in significant improvements in survival and quality of life.[1–3] Several factors have likely contributed to these advances, including improved surgical technique and the development of referral centers for sarcoma treatment that have embraced a multidisciplinary approach.[1,2]

The goal of treatment for musculoskeletal sarcomas is to optimize oncologic outcome and maximize functional restoration.[2,3] Surgical resection has been the mainstay of therapy,[1–7] as detailed earlier in this supplement. In patients with musculoskeletal sarcomas of the extremities, limb-sparing resection has been shown to be significantly superior to amputation.[1,7–9] Wide local excision of the tumor along with its muscle compartment, followed by adjuvant chemotherapy and radiation therapy, has allowed limb salvage without an increased risk of recurrence in many patients.[3] However, wide tumor resection can leave large defects that are not amenable to coverage by mobilization of the surrounding tissues, particularly if those tissues have been irradiated. As a result, resection can expose neurovascular structures, bone without periosteum, alloplastic materials, and internal fixation devices.

■ GOALS OF RECONSTRUCTION

Reconstructive surgery after musculoskeletal sarcoma resection aims to provide adequate wound coverage, preserve function, and optimize the cosmetic outcome.[1–3] Tumors can be found on areas crucial to limb movement or may involve tissues vital to limb function. Reconstruction to repair these deficits can take many forms. In certain situations, amputation is still inevitable. In those cases, the reconstruction should provide stable stump coverage with durability and the ability to fit well with an external prosthesis.[3]

■ TIMING OF RECONSTRUCTION

Immediate reconstruction should be pursued if possible
Immediate reconstruction after a negative margin should always be considered and should be attempted when possible. Immediate reconstruction allows the reconstructive surgeon to benefit from better evaluation of the defect and exposed structures, as no scar tissue is present to distort the anatomy. Likewise, patients benefit from faster recovery and can receive adjuvant treatment (if necessary) sooner, as well as earlier rehabilitation. Patients may also benefit psychologically from immediate reconstruction.[1,3]

Indications for delayed reconstruction
Delayed reconstruction is primarily indicated when there are wound healing problems or there is uncertainty about the tumor margins. Secondary indications for delayed reconstruction are wound dehiscence and unstable soft-tissue coverage. If hardware is exposed, the recommendation is for early intervention and wound coverage with well-vascularized tissue to protect and cover the implant or prosthesis.

What about radiation therapy?
A very important consideration in reconstruction is the need for neoadjuvant or adjuvant radiation therapy.[3,10,11] Irradiated wounds have a higher incidence of complications, including a tendency to dehisce. In patients who have been previously irradiated, the best practice is to perform immediate reconstruction with well-vascularized tissue, most likely a free tissue transfer.[4,6,11,12] This practice reduces hospital stay, costs, and morbidity and increases limb salvage and patient satisfaction.[13]

■ SYSTEMATIC PREOPERATIVE PLANNING NEEDED

Reconstruction after musculoskeletal sarcoma resection should be planned systematically within a process that involves preoperative anticipation of the defect size

and the resulting functional and cosmetic deficits that might need to be addressed. A preoperative visit to the reconstructive surgeon can be very helpful for presurgical planning.

During surgery it is usually preferable to allow the surgeon doing the tumor resection (eg, surgical oncologist or orthopedic oncologist) to complete the resection because the dimensions of the defect are not certain until negative margins are obtained.[14] If tumor margins are unclear at the time of initial resection, the surgeon should consider delaying the definitive reconstruction until the permanent sections confirm negative margins. Temporary closure can be achieved with wound dressings, skin grafts (either allograft or autograft), or negative-pressure wound therapy. In the same context, if neurovascular structures are exposed it is reasonable to use a muscle flap without "tailoring" the flap to the defect. This approach allows the flap to be advanced or repositioned in case of positive margins, and the skin graft can be applied to the muscle surface in a second procedure.[3]

■ RECONSTRUCTIVE METHODS: A BRIEF OVERVIEW

Several methods can be used to close musculoskeletal sarcoma excision defects. Smaller defects can be closed primarily, although most defects are large and not amenable to primary closure. If fascia or muscle is preserved with only the skin coverage missing, the wound can be covered with either split-thickness or full-thickness skin grafts.[1,4,6] Split-thickness skin grafts can be obtained in larger amounts and often heal faster than full-thickness skin grafts. However, most resections will require durable tissue coverage, particularly if adjuvant radiation therapy is planned.

In the case of long bone sarcoma resection, the resulting defect is usually large and complex and the traditional reconstruction is based on avascular allografts and local tissue flaps. However, allografts are associated with high rates of infection, nonunion, and fracture, leading to failure in about 50% of cases. Microvascular free flaps that contain bone, such as free fibula flaps, have been used instead of allografts with good success rates.[2]

Lately there has been growing interest in the use of the vacuum-assisted closure device (a form of negative-pressure wound therapy) to promote wound healing. It has been shown to improve the granulation and healing of open wounds by absorbing moisture, as well as to promote adherence after skin grafting, thereby reducing the risk of graft displacement.[1,3] This device can be used immediately after musculoskeletal sarcoma resection while definitive tumor margin results are pending. It also can be used to prepare the wound bed for grafting in high-risk patients who would not tolerate more complex reconstructions.

Local or adjacent fascial, fasciocutaneous, and dermal flaps can also be used in lower-extremity reconstruction. However, muscle or musculocutaneous flaps are the mainstay of reconstruction after resection of musculoskeletal sarcomas. This group also includes perforator flaps, which have grown in popularity in the last few years.[1,3]

■ LOCATION-BASED WOUND RECONSTRUCTION

Musculoskeletal sarcomas can occur in virtually any region of the body, and myriad reconstructive options are available for various body sites. Since lower-extremity musculoskeletal sarcomas represent about 75% of cases,[1] we will focus mainly on reconstruction of the lower extremity.

Factors driving choice of flap

Selection of an appropriate flap is essential to an optimal outcome. Flaps should be chosen with regard to donor site morbidity, functional requirements, length and diameter of the vascular pedicle, and aesthetic outcome.[3] Usually physical examination, palpation of peripheral pulses, and Doppler ultrasonography are sufficient to evaluate the circulation. A preoperative angiogram should be considered in patients with severe peripheral vascular disease or previous trauma, which can potentially compromise the reconstructive outcome.[15]

Each region of the lower extremity possesses unique anatomic and functional characteristics that must be evaluated. It is useful to categorize the thigh, lower leg, and foot into separate anatomic units when planning reconstruction. We further divided these units into several subunits, as previously proposed by Sherman and Law[15] and as outlined below.

Thigh

The thigh is usually well perfused and has several muscle groups, which facilitates reconstruction. Primary closure, skin grafts, or local flaps are acceptable options in most cases. The remaining musculature can be rotated or advanced to cover defects in the anterior or posterior thigh, providing bulk and adequate blood supply.

Hip and proximal/lateral thigh. Local muscle or myocutaneous flap options include tensor fascia lata, vastus lateralis, and rectus femoris flaps, all of which are based on the lateral circumflex femoral artery.

The tensor fascia lata flap is thin but has a long fascia extension that can be elevated from above the knee and can include a large skin paddle that is innervated by the lateral femoral cutaneous nerve. Some patients may experience knee instability after tensor fascia lata harvest.

The vastus lateralis muscle flap provides good bulk. Its arc of rotation reaches most of the inferior and posterior pelvis. It has little effect on ambulation.

The rectus femoris muscle flap is not so bulky, is easily mobilized, and has a wide arc of rotation. The donor site can be closed primarily. Harvest of this muscle can be associated with some strength loss during knee extension. For large defects of the upper third of the leg, a pedicled rectus abdominis muscle flap based on the deep inferior epigastric artery can be used. A vertically oriented skin island can be extended up to the costal margin, improving the reach. When the nature of the wound precludes use of pedicle flaps, free tissue transfer is indicated, with the latissimus dorsi muscle flap being used most commonly.[15,16]

Mid-thigh. Wounds in this location often can be closed with skin grafts or fasciocutaneous flaps. If the femur is
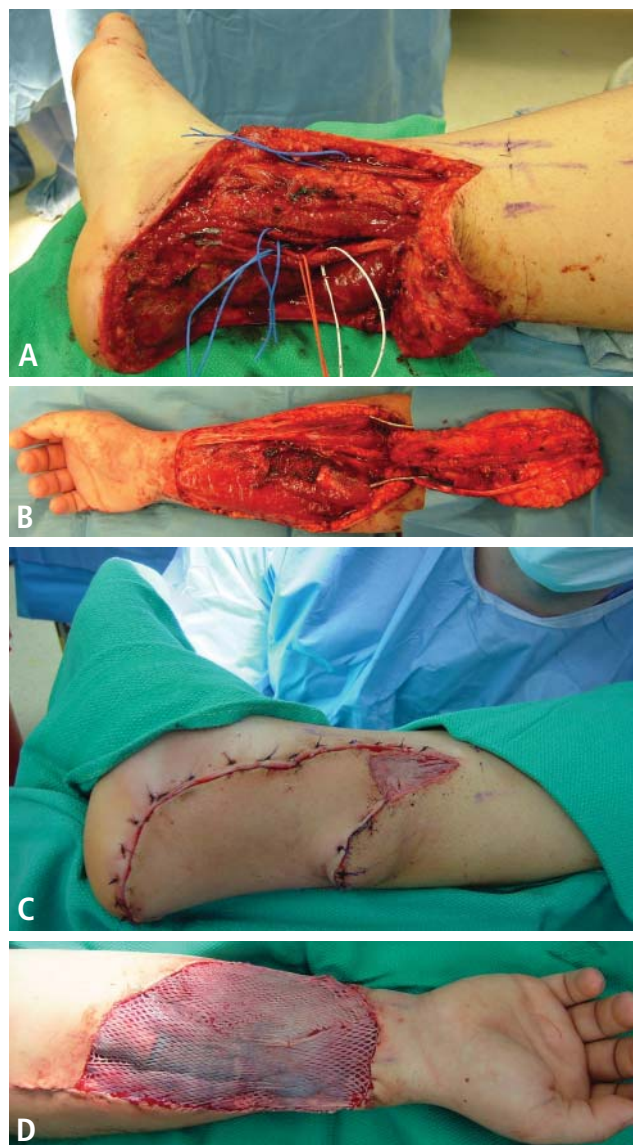
FIGURE 1. (A) Defect in the lower third of the leg and the foot in a patient following excision of a soft-tissue sarcoma (clear-cell sarcoma) with negative margins. Note the exposed tendons and neurovascular pedicle. **(B)** Radial forearm free flap elevated from donor site. **(C)** Flap inserted to recipient site. **(D)** Flap donor site with split-thickness skin graft applied.

exposed, however, a muscle flap will be required. As above, the tensor fascia lata, vastus lateralis, and rectus femoris can be used as flap options. If the lateral circumflex artery is unavailable, other flap options include the gracilis, vastus medialis, and rectus abdominis muscles. The gracilis muscle flap is based on the medial circumflex femoral artery and is useful for covering the medial aspect of the mid-thigh. Although this is a thin muscle, it can be used to cover long defects. The vastus medialis muscle flap is supplied by perforators from the profunda femoris and superficial femoral arteries. It can be rotated medially and advanced distally to

cover patellar defects.

Supracondylar knee. The knee is a location where sarcoma resection is particularly likely to leave a defect with exposed bone, tendons, or ligaments that will need coverage. The gastrocnemius muscle flap combined with a split-thickness skin graft remains a consistent and reliable reconstructive option for this area. Other options are an extended medial gastrocnemius muscle flap or myocutaneous flap, which incorporates a random fasciocutaneous extension. For larger defects, free flaps should be considered, such as the anterior thigh flap, rectus abdominis muscle flap, or latissimus dorsi muscle flap. If tendons or ligaments need to be reconstructed, we favor autologous tissue, such as the fascia lata and plantaris tendons. These are easy to harvest and provide long-lasting joint stability.

Lower leg

Proximal third of the tibia. Defects here can usually be covered with a medial or lateral gastrocnemius muscle or myocutaneous flap, or a combination of the two. These muscles have a dominant vascular pedicle—the medial and lateral sural arteries. They can be harvested as an island for better reach, and they are reliable and have minimal donor site morbidity.[15] The soleus muscle flap is another option that can be used alone or in combination with the medial or lateral gastrocnemius. Defects that are not amenable to closure by these flaps will most likely require free tissue transfer. The rectus abdominis or latissimus dorsi muscles are the first options. The latter can be combined with the serratus muscle if more bulk is needed.

Middle and lower thirds of the tibia. The soleus flap is frequently used for small or medium-sized mid-tibial defects. It is based on branches of the popliteal artery and posterior tibial artery. Larger defects require a combination of soleus and gastrocnemius muscle flaps or free tissue transfer.

Thinner flaps should be used to provide better contour of the distal tibia and ankle. Distally based fasciocutaneous flaps, such as the reverse sural flap, can be used for small wounds. If more tissue is needed, a more suitable option is a fasiocutaneous free flap from the anterolateral thigh, the radial forearm **(Figure 1)**, or the temporoparietal fascia.

Foot

Ideal reconstruction of the foot should provide thin and durable skin that will tolerate mechanical stress, and achieving this can be quite difficult. Skin grafts are seldom used for the foot, and are limited to non–weight-bearing portions with good underlying soft tissue.

Proximal non–weight-bearing areas (Achilles tendon and malleolar area). Local fasciocutaneous flaps are preferred. The lateral calcaneal artery flap, which is based on the peroneal artery branch, can cover exposed Achilles tendon, providing sensate coverage (sural nerve). The dorsalis pedis flap can be mobilized to cover the malleolar region and distal Achilles tendon, but donor site morbidity limits its use. Free tissue transfer is required for larger defects, and the the main options are flaps from the radial forearm, tem-

poroparietal fascia, or lateral arm.

Heel and midplantar area. For heel reconstruction, the medial plantar artery flap, dorsalis pedis flap, abductor myocutaneous flap, peroneal artery flap, or anterior tibial artery flap can be used. The most versatile flap of the foot is the medial plantar artery flap, which is available only when the posterior tibial artery is intact. If local flaps are not suitable, microvascular tissue transfer is indicated. The radial forearm flap, scapular flap, lateral arm flap, or anterolateral thigh flap can be used. The radial forearm flap is usually the first choice because it is thin, has a long pedicle, and is easy to harvest.

If the foot defect is associated with a large cavity, muscle flaps are the first choices, specifically the gracilis or anterior serratus. A split latissimus muscle can also be applied. The full latissimus or the rectus abdominis are often too large for the type of defects observed.

Distal plantar area and forefoot. Most wounds in this region will require free tissue transfer. Free muscle flaps with split-thickness skin grafts provide the most stable and durable coverage.

Amputation vs limb salvage

It is important to evaluate the effects of lower-extremity salvage on ambulation. Salvage of a nonfunctional limb is of little value for the patient. Likewise, patients with severe medical problems may not be good candidates for limb salvage procedures. In those situations, amputation of the lower extremity is indicated. Adequate soft-tissue coverage and good distal perfusion are necessary to ensure healing of an amputation. If possible, local tissue rearrangement may be enough to provide a good amputation stump to fit an external prosthesis. In the case of radiation damage to the tissue, a free tissue transfer is necessary. The calcaneal-plantar unit from the amputated limb is frequently used as a free flap. Other flaps from the amputated limb, called fillet flaps, are harvested immediately and converted to flaps transferred to the defect site. Studies show that they are oncologically safe and reliable.[17] Other flaps that provide good coverage for amputation defects are the latissimus dorsi muscle flap, the radial forearm flap, and the anterolateral thigh flap.

Upper extremities

Musculoskeletal sarcomas of the arm and hand present challenges because of these sites' unique anatomy. The arm and hand contain little soft tissue, and compartments are narrow. Amputation rates are higher for upper-extremity sarcomas, mostly because adequate margins are more difficult to obtain. Moreover, the sacrifice of important structures after wide resection can directly affect hand function.[15] Exposure of nerves, tendons, blood vessels, and bone will often require free tissue transfer. In that situation, immediate coverage is recommended, with free tissue transfer being the most available choice. A pedicled radial forearm flap can be used for smaller defects. For larger defects, the anterolateral thigh flap is indicated **(Figure 2)**. If bone is resected, a vascularized fibula free flap is used. In the case of sarcoma involving a digit, ray amputation is often required.

FIGURE 2. (A) Complex defect of the forearm after wide excision of an intermediate-grade soft-tissue sarcoma (spindle-cell sarcoma) with excision of the extensor digiti communis tendon. **(B)** Reconstruction was performed with tendon transfer from the extensor carpi radialis to the extensor digiti communis to fingers 2–5, and the wound was closed with an anterolateral thigh free flap.

For a single-digit ray amputation, defect transposition (such as index-to-middle finger or little-to-ring finger) can be used. A total thumb defect can be reconstructed with index finger transposition or a toe free flap.

■ POSTOPERATIVE CARE

Postoperative care following reconstruction after sarcoma resection requires a dedicated and trained team, particularly if a free flap is used for reconstruction.

Clinical evaluation of flaps includes color, temperature, and capillary refill. In cases of microsurgical reconstruction, postoperative care should include hourly examination of audible Doppler signals, at least for the first 36 hours. Free flap complications develop primarily in the first 24 hours, but they can occur during initial mobilization of the patient after a long period of bed rest. The surgical team should be aware of the potential problems and be able to act fast if necessary to reestablish blood flow to the flap.

In addition to flap monitoring, immobilization of the patient after surgery is extremely important. Postoperative swelling to the extremity should be avoided. Patients should be placed on bed rest until the postoperative swelling has subsided and the flap has adhered to the wound bed. Our protocol includes strict bed rest for about 7 days, followed by several days of dangling the extremity for short periods to ensure that dependent positioning will not alter the blood supply. A physical therapist should be involved to assist with crutches or a wheelchair. The patient should receive prophylactic anticoagulation during the resting period, in light of the high risk of deep vein thrombosis and pulmonary embolism. A compressive garment should be used to prevent lymphedema.

■ COMPLICATIONS ASSOCIATED WITH FLAPS

Once the flap is raised, it can still fail as a result of tension at insetting, inadequate blood flow, twisting of the pedicle, hematoma and/or infection, or the patient's condition (eg, coagulopathy, poor nutritional status, anemia). Failure to

correctly evaluate the direction of arterial flow, whether anterograde or retrograde, can cause flap loss. Instruments such as Doppler ultrasonographic equipment can be used to help to determine the flow. Partial or complete occlusion of the vascular pedicle can occur for several reasons (eg, twisting of the pedicle), and the consequences are disastrous if not recognized in time. If a pedicle problem is suspected in the case of a free flap, the patient should be taken to the operating room immediately and the flap should be explored. Rupture of the vascular anastomosis can occur as a result of technical problems, tension, and (in rare cases) infection.

Hematomas can cause mass effect, limit the venous return, and lead to flap necrosis. Hematoma formation also releases free radicals that can contribute to flap necrosis. Prevention is achieved through meticulous hemostasis. If a hematoma is suspected, the wound should be explored and the hematoma evacuated and washed out with normal saline.

The presence of an infected wound bed can also damage a flap by increasing its metabolic demand and causing the flap to be compromised by the infection itself. It is usually best to wait until the infection is controlled before planning the reconstruction.

Partial flap losses, skin graft losses, and wound dehiscence also are possible. Most of the time these require wound care, and patients' nutrition and general health should be optimized to help the healing process. In the case of partial or complete flap loss, a new flap is often required and should be planned at a proper time.

■ CONCLUSIONS

Soft-tissue reconstruction following musculoskeletal sarcoma resection can be as simple as allowing the wound to heal by itself, which is less ideal, or as complex as coverage with a microsurgical osteocutaneous free flap. Limb salvage for sarcomas of the lower extremity has demonstrated good final functional outcomes without adversely affecting the oncologic results. Moreover, patients feel better psychologically and have higher quality of life.[18,19]

We believe that soft-tissue coverage after a wide resection is the most critical factor for avoiding postoperative complications of the tumor resection, such as infection or fractures. For this reason, we recommend the use of well-vascularized coverage at the time of the initial operation, if possible. Careful preoperative planning is especially important. We believe that reconstruction following musculoskeletal sarcoma resection can be done effectively only by using a team approach. Every such team should include, at minimum, an orthopedic surgeon and a reconstructive surgeon, with the mix of other providers dictated by the individual case.

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Use of chemotherapy for patients with bone and soft-tissue sarcomas

■ **ABSTRACT**

For patients with bone sarcomas, chemotherapy has a proven role in the primary therapy of osteogenic sarcoma and Ewing sarcoma but no role for chondrosarcoma. Chemotherapy's role is currently more limited for patients with soft-tissue sarcomas, as it is generally used to palliate metastatic disease in most subtypes of soft-tissue sarcoma and remains largely investigational in the treatment of operable disease. The chemotherapy regimens for musculoskeletal sarcomas often carry significant potential toxicities, so the efficacy of less intensive and less toxic regimens is a focus of ongoing research.

Surgical resection is the mainstay of treatment for musculoskeletal sarcomas, as detailed earlier in this supplement, but chemotherapy also has a proven role in the primary therapy of most bone sarcomas and a potential role for some patients with soft-tissue sarcomas. This article provides an overview of the roles of chemotherapy for patients with bone and soft-tissue sarcomas and addresses key considerations surrounding chemotherapy in the context of overall patient management.

■ **BONE SARCOMAS**

Because most bone sarcomas occur in pediatric patients and young adults, studies of chemotherapy in this disease have often enrolled predominantly young subjects. As a result, very limited data are available in older adults. Single-institution experiences indicate that adults with bone sarcomas have inferior outcomes compared with their pediatric and adolescent counterparts,[1] but the literature on these tumors in adults is scant. Therefore, the following discussion on chemotherapy for bone sarcomas incorporates data from trials conducted predominantly in children and young adults (ie, generally younger than 30 years and with a very large majority younger than 20 years).

Chemotherapy for osteosarcoma

At present, neoadjuvant (preoperative) chemotherapy followed by definitive resection with subsequent adjuvant (postoperative) chemotherapy is the well-established approach to treatment of localized osteosarcomas. Chemo-

therapy can eradicate the micrometastatic disease that is believed to be present in the majority of patients with clinically resectable cancer.[2]

Efficacy. Historically, prior to the institution of effective chemotherapy, metastatic disease developed in 80% to 90% of patients who underwent curative resection with or without radiation therapy, which resulted in a long-term survival rate of less than 20%.[3] In the 1980s, clinical trials that randomized patients with resectable osteosarcoma to surgery alone or to surgery plus chemotherapy found that the addition of perioperative chemotherapy led to significant improvements in recurrence rates and survival.[4,5] More recent randomized trials have shown that treatment of such patients with modern multiagent chemotherapy regimens results in a 5-year survival rate of approximately 70%.[6] Additionally, response to neoadjuvant (preoperative) treatment has become the most important predictor of outcome, as the median survival of osteosarcoma patients who have greater than 90% necrosis in the resected specimen following neoadjuvant chemotherapy is about 90% at 5 years.[7,8]

Toxicity. Current chemotherapy regimens are based on high doses of methotrexate and leucovorin in combination with doxorubicin, ifosfamide, and platinum. Long-term effects of such regimens include the following[3]:

- Azospermia (in 100% of patients who received a total ifosfamide dose > 75 g/m^2)
- Subclinical renal impairment (in 48% of patients treated with high doses of ifosfamide)
- Hearing impairment (in 40% of patients treated with cisplatin)
- Second malignancies (in 2.1%)
- Cardiomyopathy (in 1.7%).[3]

In light of this, the development of equally effective but less intensive regimens for patients whose disease carries a better prognosis is highly desirable. Ongoing clinical trials are investigating this strategy.

Metastatic disease. Metastatic osteosarcoma is found in approximately 20% of patients at the time of diagnosis. Sarcoma mainly spreads hematogenously, and the lungs are the most common initial site of metastases, being affected in more than 60% of patients who develop metastatic disease.[9] Patients with metachronous lung lesions are initially considered for aggressive treatment with neoadjuvant chemotherapy and subsequent resection of clinically apparent disease, which results in event-free survival rates of 20% to 30%.[3]

Patients with disease limited to the primary tumor and no more than one or two bone lesions fare best. The pres-

ence of multiple metastases is associated with the poorest prognosis, as few patients with this profile live past 2 years.[10] In a review of 202 pediatric and adult patients with documented metastases at the time of osteosarcoma diagnosis, the presence of more than 5 metastatic lesions (which was reported in 91 patients) was associated with a 5-year overall survival rate of 19%.[9]

Chemotherapy for Ewing sarcoma

Perioperative chemotherapy in patients with localized Ewing sarcoma is believed to reduce the burden of micrometastasis that is thought to be present in most patients with early-stage disease. Five-year survival rates of 50% to 72% have been reported among patients with resectable Ewing sarcoma treated perioperatively with multiagent chemotherapy.[11,12] Notably, randomized trials that studied intense multiagent chemotherapy regimens (consisting of doxorubicin, cyclophosphamide, vincristine, and dactinomycin alternating with etoposide and ifosfamide) reported the best outcomes despite significant but acceptable toxicity. In a large randomized trial involving 398 patients with resectable disease, a 5-year survival rate of 72% was achieved with the above regimen, compared with 61% in patients treated with a less intense regimen that did not contain ifosfamide and etoposide (P = .01).[12]

Compressing these standard regimens to an every-14-day instead of every-21-day schedule improved event-free survival at 3 years from 65% to 76% (P = .028) without any significant increase in toxicity in a randomized trial involving 568 patients.[13] Data on overall survival from this trial are not yet published.

Metastatic disease. Metastatic Ewing sarcoma is found in 15% to 35% of patients with newly diagnosed disease and is treated with multiagent chemotherapy; resection of residual disease is considered in good responders.[3] This approach produces objective responses to therapy, but long-term survival is rare.

Toxicity. Myelodysplastic syndrome and acute myeloid leukemia are the most dreaded long-term complications of intensive multiagent chemotherapy for Ewing sarcoma and develop in up to 8% of patients.[14] Additionally, ifosfamide can lead to hematuria (~12% incidence), encephalopathy (mild somnolence and hallucinations to coma), chronic renal impairment (6% incidence), and hemorrhagic cystitis (though administration of mesna and generous intravenous hydration can minimize this latter complication).[15] Recent efforts are therefore focused on testing less-intensive regimens in patients who have good prognostic features.

Chondrosarcoma: No role for chemotherapy

Chondrosarcoma, which represents approximately 20% of all bone sarcomas and has a peak incidence in older adults (ie, in the sixth decade of life), is insensitive to chemotherapy. Radiotherapy is also of limited value and is reserved for patients treated in the palliative setting.[16] Definitive management of chondrosarcoma involves adequate surgical resection alone.

◼ SOFT-TISSUE SARCOMAS

Aside from recent advances in the treatment of gastrointestinal stromal tumors with the small-molecule tyrosine kinase inhibitors imatinib and sunitinib (which are beyond the scope of this article), an overall survival advantage with chemotherapy has not been demonstrated in adults with soft-tissue sarcoma.[17]

Resectable disease

The decision to use chemotherapy needs to be weighed against the magnitude of potential clinical benefit and the acute and chronic toxicities that can develop.

Toxicity. Chemotherapy regimens with activity against soft-tissue sarcomas often contain anthracyclines, alkylating agents, and taxanes. These agents can produce serious long-term toxicities, which is especially important in patients treated with curative intent. Doxorubicin and other anthracyclines, for example, may result in cardiomyopathy, the risk of which rises with increasing cumulative dose.[18] In addition, acute myeloid leukemia may develop in 2% to 12% of patients treated with anthracyclines or alkylating agents such as ifosfamide and dacarbazine.[3,19] Renal failure and an elevated risk of bladder carcinoma are uncommonly reported in patients with a history of ifosfamide treatment.[15] Sensory neuropathy associated with the use of taxanes (eg, paclitaxel and docetaxel) is dose dependent and reversible in more than half of patients. However, some patients treated with high doses of these agents can have persistent symptoms of paresthesias, burning, and decreased reflexes, which can be debilitating.[20]

Efficacy of adjuvant chemotherapy. Because chemotherapy puts patients at risk of such serious chronic toxicities, its use can be justified only if it results in significant benefit, such as prolongation of survival. A 1997 meta-analysis of 14 clinical trials evaluating adjuvant chemotherapy in patients with resectable soft-tissue sarcomas found chemotherapy to have an absolute benefit of 10% in recurrence-free survival at 10 years (ie, from 45% survival to 55% survival), with a hazard ratio of 0.75 (95% confidence interval [CI], 0.64–0.87; P = .0001) for recurrence or death.[21] However, when the analysis was limited to overall survival at 10 years, the survival difference between patients who received adjuvant chemotherapy and those who did not (54% vs 50%, respectively) was not statistically significant (hazard ratio = 0.89; 95% CI, 0.76–1.03, P = .12).[21]

The concept of adjuvant therapy has been revisited since the antisarcoma activity of ifosfamide was established. A large European trial randomized 351 patients with resected soft-tissue sarcoma either to placebo or to doxorubicin and ifosfamide given every 21 days.[22] The preliminary results, reported in abstract form at the 2007 annual meeting of the American Society of Clinical Oncology, showed a higher 5-year survival rate in the placebo arm (69%) compared with the chemotherapy arm (64%).[22] This and other trials using ifosfamide in various drug combinations showed no difference in survival, suggesting that adjuvant chemotherapy should not be considered to be standard practice

outside of a clinical trial.

Efficacy of neoadjuvant chemotherapy. Neoadjuvant chemotherapy also has been studied in patients with soft-tissue sarcomas. A retrospective analysis found that the greatest benefit is derived in patients with primary tumors larger than 10 cm, in whom neoadjuvant chemotherapy increased 3-year disease-specific survival from 62% to 83%.[23] However, differing results came from a prospective multicenter trial that randomized patients with large primary and recurrent tumors to either surgery alone or surgery preceded by three cycles of neoadjuvant doxorubicin and ifosfamide (all patients could also receive adjuvant radiation therapy, depending on grade and adequacy of resection).[24] The trial suffered from slow accrual, and only 150 patients were enrolled. At 5 years, survival was similar between the groups with and without neoadjuvant chemotherapy.[24] Therefore, neoadjuvant chemotherapy is not yet recommended pending results of larger randomized trials.

No clear role for recurrent disease. Local recurrence of the primary tumor after resection occurs in 10% to 50% of cases of soft-tissue sarcoma, with the specific rate depending on the primary tumor location. The highest incidence of recurrence is found in patients with retroperitoneal and head and neck sarcoma (40% and 50%, respectively), mainly because of the difficulty of obtaining clear margins. Chemotherapy has not been well studied in this setting and is of uncertain value.[3]

Metastatic disease

Metastatic soft-tissue sarcomas may respond to chemotherapy, but there is a lack of evidence that chemotherapy improves overall survival. Pulmonary lesions are the most common site of distant recurrence, and resection of such metastases is sometimes undertaken in well-selected patients. However, there is no level 1 evidence supporting chemotherapy in this clinical setting despite its common preoperative use. There is a paucity of randomized phase 3 trials that compare established palliative chemotherapy regimens to best supportive care. It is believed that some groups of patients do benefit, however, including those who are young and have good performance status, low tumor grade, absence of liver metastasis or pulmonary metastasis only, and a long interval between treatment of the primary tumor and development of metastatic disease.[3] Some histologies, such as uterine leiomyosarcomas and facial/scalp angiosarcomas, respond better to chemotherapy.[17]

Drugs found to have activity against metastatic sarcoma include doxorubicin, ifosfamide, platinum agents, gemcitabine, taxanes, and dacarbazine. Used either alone or in combinations, these drugs produce responses (ie, shrink metastatic tumors) in about 13% to 33% of patients.[3] Use of chemotherapy is frequently curtailed by the acute toxicity of these agents, which includes pancytopenia, transfusion requirements, febrile neutropenia, nausea, alopecia, and significant fatigue, as well as renal failure with ifosfamide or cisplatin and peripheral neuropathy with platinum agents or taxanes. Appropriate patient selection

for chemotherapy and exclusion of those who should be managed solely with best supportive care is an important challenge that oncologists often face when managing patients with metastatic soft-tissue sarcoma.

Future directions

Trabectedin (ET-743) is a novel compound with promising activity against soft-tissue sarcomas that acts by inhibiting cell-cycle transition from the G_2 to M stages. The drug covalently binds to the minor grove of the DNA molecule, changing its three-dimensional structure and impairing transcription and possibly DNA repair.[25] Phase 2 studies showed durable responses to trabectedin in 3% to 8% of heavily pretreated patients[26–28] and in 17% of treatment-naïve patients with advanced soft-tissue sarcomas.[25] Time to progression of up to 20 months has been reported in patients who respond or develop stable disease.[3]

Toxic effects of trabectedin include myelosuppression, fever, edema, arthralgias, hepatotoxicity, and (rarely) rhabdomyolysis. To date, these toxicities have been self-limiting. Larger clinical trials and longer follow-up is needed to assess whether this agent has any significant long-term toxicities.

Trabectedin has already been approved in Europe for treatment of chemotherapy-refractory soft-tissue sarcoma when given as a 24-hour infusion every 21 days.

More broadly, an active effort is under way to better understand the molecular derangements in a variety of soft-tissue sarcoma subtypes. The hope is that this understanding will lead to improved therapies that target aberrant proliferation, angiogenesis, and other biologic processes that drive the growth and metastasis of soft-tissue and bone sarcomas.

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Use of radiation therapy for patients with soft-tissue and bone sarcomas

■ ABSTRACT

Radiation therapy is recommended as an adjuvant to resection for intermediate- and high-grade soft-tissue sarcomas; its role in bone sarcomas is largely limited to select patients with Ewing sarcoma. Despite the integral role of radiation therapy in soft-tissue sarcoma management, its optimal timing—preoperative versus postoperative—is uncertain, with each timing scenario having advantages and disadvantages. Preparation for radiation therapy involves a detailed planning session to optimize and standardize patient positioning and determine the target volume. Side effects of radiation therapy may include skin changes, delayed wound healing and other wound complications, fatigue, reduced range of motion of the affected limb, pain, and bone fractures.

While radiation therapy (RT) has an integral role in the management of soft-tissue sarcoma, it has a limited role in that of bone sarcoma, with few exceptions (ie, Ewing sarcoma). In keeping with the rarity of these tumors, it has been demonstrated that patients treated at high-volume centers have significantly better survival and functional outcomes.[1–3] Accordingly, treatment should be delivered by a multidisciplinary team including orthopedic, medical, and radiation oncologists, as well as plastic and reconstructive surgeons, physical therapy specialists, and pathologists and radiologists with expertise in musculoskeletal sarcomas.[4] As the preceding articles in this supplement have addressed the major modalities in the treatment of sarcomas other than RT, this article will focus on how RT fits into the overall management mix, with a focus on soft-tissue sarcomas, where it figures most prominently.

■ BONE SARCOMAS: A LIMITED ROLE FOR RADIATION

The role of RT in the management of bone sarcomas is limited. Its primary application appears to be in Ewing sarcoma, for which curative treatment requires combined local and systemic therapy. For definitive therapy, limb-salvage surgery is preferable over amputation, but amputation may be an option for younger patients with lesions of the fibula, tibia, and foot. Based on the available data, postoperative RT is probably of benefit for all patients with

Ewing sarcoma with close margins and/or those with a poor histologic response.[5] Further discussion of Ewing sarcoma management is beyond the scope of this article (see the second and fifth articles in this supplement).

For osteosarcoma, the current standard of care is surgical resection combined with neoadjuvant and adjuvant chemotherapy. RT had been used years ago, prior to the advent of effective chemotherapy regimens, but its use for osteosarcoma has now been relegated to a few select situations. These include lesions not amenable to surgical resection and reconstruction, cases in which the patient refuses surgery, cases where there are positive margins after resection, and cases where palliation is needed for symptomatic lesions.

■ SOFT-TISSUE SARCOMAS: RADIATION HAS A CLEAR ADJUVANT ROLE

The primary management of localized soft-tissue sarcomas is surgical resection to achieve a negative margin when feasible. Historically, local excision of soft-tissue sarcomas resulted in local failure rates of 50% to 70%, even when a margin of normal tissue around the tumor was excised. As a result, amputation became standard treatment.[6] In a landmark National Cancer Institute study 3 decades ago, patients were randomized to amputation or to limb-sparing surgery with the addition of RT.[7] Notably, disease-free and overall survival were not compromised by limb-sparing surgery plus RT, demonstrating that although lesser surgery in the absence of RT may be insufficient, limb-sparing surgery with RT was equal to amputation. Consequently, limb-sparing approaches have become the favored surgery for the majority of cases of soft-tissue sarcoma, as advocated in a consensus statement from the National Institutes of Health.[1]

Indications vary by lesion grade

In general, adjuvant RT is recommended for all intermediate- and high-grade soft-tissue sarcoma lesions. A potential exception is a superficial tumor smaller than 5 cm with widely negative margins after resection. For low-grade lesions, re-excision is favored over adjuvant RT for positive or close margins, and RT is avoided in the setting of negative margins.

Optimal timing of radiation remains unclear

The optimal timing of adjuvant RT—preoperative versus postoperative—remains unknown. The relative advantages of preoperative RT include smaller and well-defined treatment volume, ability to use a lower dose, lack of tissue hypoxia, increased tumor resectability (smaller surgery), and improved limb function with less late fibrosis and edema. The disadvantages include inability to precisely stage patients

and higher risk of acute wound-healing complications.

The National Cancer Institute of Canada compared outcomes with preoperative versus postoperative RT among 190 patients with soft-tissue sarcoma in a prospective randomized trial.[8] Patients were stratified by tumor size (≤ 10 cm or > 10cm) and then randomized to preoperative RT (50 Gy in 25 fractions) or postoperative RT (66 Gy in 33 fractions).[8] There was no difference between the groups in local control, distant control, or survival rates, but a higher rate of late complications, including fibrosis and edema, was observed with postoperative RT.[8,9] On the other hand, the incidence of wound complications was higher in the preoperative group (35%) than in the postoperative group (17%).[8]

Likewise, the optimal sequencing and benefits of systemic therapy (chemotherapy) with relation to local therapy (surgery with pre- or postoperative RT) remain unclear. More than a dozen individual randomized trials of adjuvant chemotherapy, as well as a meta-analysis of 14 trials of doxorubicin-based adjuvant chemotherapy, have failed to demonstrate significant improvement in overall survival in patients with soft-tissue sarcomas.[10] With regard to neoadjuvant chemotherapy for soft-tissue sarcomas, there are studies suggesting improvement in local control but no consistent survival benefit.[11] Chemotherapy may yield a benefit in select cases, as detailed elsewhere in this supplement.

■ MECHANISMS OF ACTION: DIRECT AND INDIRECT

In simplified terms, radiation kills cancer cells through two basic mechanisms: indirect and direct.

The indirect effect (the most common mechanism) results from the generation of free radicals in the intracellular medium via ionization by photons. Free radicals, in turn, deposit large amounts of energy that damage DNA or some other vital component of the cell, resulting in cell death.

The direct effect is a consequence of photons themselves interacting directly with the cell in a lethal manner.

The goal of RT is to kill tumor cells selectively, without irreversibly injuring adjacent normal tissue. This is done by exploiting two abnormal aspects of tumor behavior: decreased ability for repair and increased susceptibility to ionizing radiation damage. Tumors are generally less able than normal tissue to repair DNA damage, owing to defective repair mechanisms. Tumor cells are also comparatively more radiosensitive than normal tissues, as they are more frequently in radiosensitive cell-cycle phases. Thus, dividing the radiation dose into a number of treatment fractions provides two advantages that further exploit the biologic differences between tumor and normal tissue: it allows DNA repair to take place within the normal tissues, and it allows proliferating tumor cells to redistribute through the cell cycle and move into the more radiosensitive phases.

■ TREATMENT PLANNING

Treatment simulation

Following initial consultation with a radiation oncologist, the eligible patient undergoes a simulation, or a treatment planning session in which he or she is positioned so as to allow treatment to be carefully designed and subsequently delivered with precision. This typically requires fabrication of a customized immobilization device to allow for consistent positioning over the treatment course. Sarcomas require that special care be taken to properly immobilize both the proximal and distal joints. Additionally, radiopaque wires are used to delineate the anatomic boundaries of the tumor or scar. Computed tomographic (CT) scans are then obtained to enable image-based three-dimensional treatment planning. The patient setup is photographed, and setup indicators are recorded and marked on the patient's skin, some with freckle-size tattoos and some with indelible marker.

The treatment fields are then designed on the CT-simulation data set with the aid of virtual reality–type techniques. In addition to delineation of tumor volumes, three-dimensional treatment planning is used to contour all nearby normal structures on each slice. The resulting structures can then be used to specify dose constraints and help determine the optimal beam geometries to ensure proper tumor coverage and minimize the potential for side effects by reducing the dose to organs at risk. In the case of sarcomas, several strategies for reducing the risk of side effects are especially relevant: (1) carefully sparing a portion of the circumference of uninvolved bone to minimize the risk of fractures; (2) carefully sparing a strip of normal tissue to minimize edema by permitting undisrupted lymphatic drainage from the extremity; and (3) keeping dosing to joint spaces and other adjacent organs below tissue tolerances as defined by Emami et al.[12]

Determining target volume

The target volume for RT is determined on the basis of physical examination, radiologic studies, anatomical considerations, and the natural history of the sarcoma.

In the preoperative setting, longitudinal margins of 5 cm beyond the tumor and tumor-associated edema and radial margins of 2 cm are treated to 50 Gy in 25 fractions. Surgery is undertaken approximately 4 weeks after completion of RT to allow for repair in normal tissues and minimize operative and postoperative complications. Following surgery, an RT boost may be added for positive margins (16 Gy) or gross residual disease (25 Gy).

In the postoperative setting, details on the extent of dissection or observations from the surgeons themselves must be considered. Information regarding the surgical approach must be noted and can influence the effectiveness of postoperative RT as well as the incidence of late side effects. When experienced surgeons are involved, scars and drain sites, which are at risk for subclinical disease, can be planned so that their inclusion in the RT portal allows for sparing a strip of skin to minimize complications. Surgical clip placement at the boundaries of the tumor bed also facilitates RT planning.[13] Finally, prophylactic bone stabilization may reduce the risk of subsequent fracture in cases where circumferential bone radiation in high-risk sites is anticipated.

Recommendations on the volume that must be treated vary among different authorities. Some advocate treating the entire compartment because of the risk for microscopic

seeding.[14] Others recommend margins around the tumor or tumor bed ranging from less than 5 cm up to 15 cm.[15] Most often the postoperative approach is to include the resection bed with a 2-cm radial margin, the incision, and any drain sites in the initial treatment volume and to base the longitudinal margin on the grade and size of the primary tumor (5–15 cm). This volume is treated to 50 Gy in 25 fractions followed by two sequential reductions in field size, with the total dose determined by the extent of resection: 60 Gy for negative margins, 66 Gy for microscopically positive margins, and 75 Gy for gross residual disease.

■ TREATMENT DELIVERY

Once treatment planning is completed, treatments begin and are given daily Monday through Friday. Each day, the patient is positioned in the immobilization device, the field measurements are set, and positioning is checked with measurement tools and external marking of the field borders on the skin. Daily image guidance techniques may be used to increase setup reproducibility. Typical treatment times, including setup and actual delivery, are roughly 20 to 30 minutes daily.

While external beam RT is most commonly delivered as described above, brachytherapy, or intraoperative electron beam techniques, as well as proton or other charged-particle therapies, are also applied in selected cases.[16–18]

■ SIDE EFFECTS

Side effects of RT in the setting of sarcomas can be divided according to their onset—ie, acute versus delayed.

Acute effects. Skin changes ranging from erythema to moist desquamation in the skin overlying the high-dose volume are common. Major wound complications (delayed wound healing or need for surgical intervention) occur in approximately 17% of patients after surgical resection with postoperative RT, and perhaps more commonly (35%) with preoperative RT,[8] though these rates vary widely in the literature. Another frequently reported acute side effect is fatigue.

Delayed sequelae after conservative resection and RT of extremity lesions include a reduction in range of motion secondary to joint contracture, edema, and fibrosis, as well as pain and bone fractures, all of which can significantly limit function of the preserved limb. In centers treating high volumes of patients with soft-tissue sarcoma, the incidence of moderate to severe late effects is less than 10%.[19] In contrast to acute wound complications, a higher rate of late complications, including fibrosis and edema, have been observed with postoperative RT relative to preoperative RT.[9] When necessary, high-dose RT does not appear to compromise the viability of skin grafts used to repair defects after sarcoma surgery if adequate time is allowed for healing.[20]

Regardless of the management approach, intensive rehabilitation led by physical therapy specialists is imperative in minimizing disabilities after treatment of soft-tissue sarcomas.

■ CONCLUSION

Outcomes of patients with musculoskeletal sarcomas are optimized at specialized sarcoma centers. For patients with soft-tissue sarcomas, effectively implementing an approach that combines conservative surgery and RT—and, in select cases, chemotherapy—achieves excellent local control rates while minimizing morbidity and maximizing long-term extremity function relative to aggressive surgery alone.

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