Advanced Modalities for the Imaging of Sarcoma

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There is a diversity of modalities available for the imaging of soft tissue and skeletal sarcomas. However, conventional radiography remains the first line imaging modality in the diagnostic work-up, as it provides superior spatial resolution for the evaluation of bone trabecular detail [1]. In the assessment of skeletal sarcomas, radiography is used for initial detection and characterization of the lesion. In the assessment of soft tissue sarcomas, radiography is less valuable for detection, given its poor contrast resolution compared with cross-sectional modalities, though it is often employed for the assessment of tumor calcification patterns that aid the characterization of these masses.

Cross-sectional imaging techniques have become essential for the comprehensive analysis of sarcomas, for the primary purpose of treatment planning and when additional characterization is needed beyond radiography. Magnetic resonance imaging (MRI) is most advantageous for the determination of the extent of newly discovered masses and for the assessment of tumors following treatment. MRI may allow further characterization of a mass, based on such features as the enhancement pattern, location, and signal strength. Computed tomography (CT) may be used for initial staging when MRI is contra-indicated, but is most valuable for the characterization of skeletal masses and soft tissue mineralization patterns. A final technique that has emerged is that of positron emission tomography (PET) imaging, which affords the advantage of whole body imaging rather than locoregional staging. This article focuses on the advanced imaging modalities of CT, MRI, and PET in the evaluation of sarcomas.

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doi:10.1016/j.suc.2008.03.003 surgical.theclinics.com
Computed tomography

CT is a noninvasive diagnostic technique that uses a rotational radiographic source to generate cross-sectional images [2]. It essentially maps the density of electrons in tissue to create an image. An important benefit of using CT is its ability to provide rapid image acquisition, which reduces the need for sedation. This feature is especially useful in the pediatric population and in critically ill patients [3,4]. CT is less expensive than MRI and provides excellent osseous cortical detail and definition of lesion matrix mineralization patterns. It can also be used to image those patients with contraindications to MRI. CT represents a cost-effective modality for a wide range of clinical problems and is widely available [1,2].

CT offers better spatial resolution than MRI, though it still remains inferior to radiography in this respect. However, it can provide a clear anatomic depiction of complex areas not well evaluated by radiography, such as the axial skeleton and small joints. With recent technologic advances and the introduction of thin-section multi-detector scanners (16-, 64-detector, and beyond), CT offers the capability of producing imaging datasets with isotropic resolution that result in improved image quality. Such datasets in turn allow the reconstruction of multiplanar reformatted images and three-dimensional (3D) CT images with optimal spatial resolution. In addition, faster gantry rotation speed allows more volume coverage at improved temporal resolution, decreasing motion artifact. Finally, more efficient X-ray tube usage minimizes beam-hardening artifact with metallic hardware, allowing for a better postoperative evaluation than MRI, in the presence of metal [2].

CT angiography is another facet of CT that is evolving. Technologic advances in this area include improved isotropic datasets and temporal resolution, allowing enhanced visualization of the vascularity of sarcomas. Specifically, CT angiography can delineate tumor size, extent, source, and degree of vascularity, which aids in establishing the grade of malignancy [5], though the contrast resolution afforded by CT is inferior to that of MRI. Intravenous contrast is necessary when evaluating soft tissue sarcomas, though not so for skeletal sarcomas, which are evaluated by their characteristic patterns of bone destruction rather than their contrast enhancement patterns.

Disadvantages of using CT include the exposure to radiation and its poor contrast resolution when compared with MRI. In addition, if the use of intravenous contrast is necessary, there is a risk of allergic reaction or contrast nephropathy [1,2].

With regard to the evaluation of the primary mass, CT is most frequently indicated for the characterization of the mass. Other indications include the assessment of surrounding bone destruction and fracture risk, the identification of potential tumor recurrence in the presence of hardware and, finally, the detection of metastatic disease. For example, metastatic disease to the
lungs is common with osteosarcoma and early detection improves survival rates. Therefore, as part of the diagnostic work-up, lung evaluation is required, and CT represents the most sensitive technique for detecting lung metastases [3,4,6].

**Skeletal sarcomas**

When evaluating skeletal tumors, CT is useful for characterizing the pattern of bone destruction, tumor margins, and matrix, to guide the diagnosis between benign and malignant lesions as well as to determine the histology of the lesion. Analysis of any matrix mineralization patterns can be helpful in offering a more specific diagnosis. Sarcomas may produce chondroid, osteoid, or fibrous matrix. Chondroid matrix tends to produce small punctuate or swirled areas of calcification, sometimes described as “arcs and whorls,” “popcorn” calcification, or “speckled,” as can be seen with chondrosarcoma (Fig. 1). Osseous matrix tends to appear dense and confluent, sometimes described as “cloud-like,” and is characteristically seen in osteosarcomas (Fig. 2) [4,7], while fibrous matrix is not calcified, occasionally with a “ground glass” quality.

To distinguish between a benign and a malignant process, CT evaluation includes the assessment of tumor margins and the pattern of cortical and periosteal bone destruction. Well-defined margins indicate a more benign process, whereas ill-defined or irregular margins are indicative of a destructive or malignant process. Regarding the periosteum, benign periosteal reaction is described as solid or continuous, while malignant periosteal reaction can have a number of appearances, described as interrupted, spiculated

Fig. 1. Axial CT image of the proximal tibia shows typical chondroid-type matrix with stippled and curvilinear calcifications, and cortical destruction in a chondrosarcoma of the proximal tibia.
As an example, Ewing’s sarcoma can demonstrate all of the aforementioned types of periosteal reaction, though the lamellated and hair-on-end appearances are classic descriptors. The Codman’s triangle and sunburst periosteal reaction are classically associated with osteosarcoma or chondrosarcoma [4,9].

Soft tissue sarcomas

Soft tissue sarcomas may contain components of varying densities, which can be demonstrated by CT. Most importantly, a solid lesion such as a sarcoma can be accurately differentiated from a simple cyst by the presence of enhancement within the lesion following contrast administration. Often, however, especially when large, sarcomas will have necrotic areas, which will appear cystic on CT (Fig. 3). Other densities may be observed within a mass that may allude to its histology. For example, lesions that contain fat (lipomatous lesions) are well characterized by CT and liposarcomas are fat-containing lesions that will also demonstrate soft tissue density, including thickened, irregular septa and nodular components [10] in addition to fat density, to differentiate them from their benign counterparts (lipomas). Another density characteristic that may be used to distinguish the histology of a lesion is high-density material, which may reflect proteinaceous or hemorrhagic content within the mass.

When evaluating soft tissue sarcomas, CT provides the capability for detecting mineralization (calcification or ossification) within a mass that may guide the diagnosis toward soft tissue chondrosarcomas or osteosarcomas.
However, known as the great mimicker, myositis ossificans circumscripta refers to localized bone and cartilage formation in the soft tissues and is usually post-traumatic. Often mistaken for a sarcoma, CT is essential for characterizing its benign nature through the presence of a peripheral zonal pattern of calcification (Fig. 4) [11]. While the mineralization pattern is typically peripheral, it is not contiguous with the underlying bone and does not cause periosteal reaction, characteristics that are nicely confirmed by CT.

**Magnetic resonance imaging**

MRI is a noninvasive technique that uses the proton within hydrogen atoms in the body to create an image based on an applied magnetic field [12]. Advantages of MRI over other imaging techniques include its high contrast resolution, superior to other cross-sectional imaging modalities, resulting in the visualization of exquisite soft tissue detail. In addition, it is more sensitive than CT for the detection of bone marrow abnormalities. MRI also requires no radiation exposure, but like CT, offers multiplanar imaging capability [4,12].
Disadvantages of MRI include a long imaging acquisition time, much longer than CT, which may require the use of sedation, a challenge in the pediatric patient. Additionally, there are numerous contraindications to the performance of MRI based on the fact that the strong magnetic field can move implanted metal structures in the body. Absolute contraindications include the presence of a cardiac pacemaker, implanted cardiac defibrillator, aneurysm clips, carotid artery vascular clamp, neurostimulator, insulin or infusion pump, implanted drug infusion device, bone growth or fusion stimulator, and cochler or otologic or ear implant. Patients suffering from claustrophobia

Fig. 4. Axial (A) and coronal volume rendered 3D (B) CT images shown with dedicated bone windows, and axial (C) CT image with dedicated soft tissue window of the distal thigh, show a peripherally calcified, well-defined soft tissue lesion with lobular borders and no evidence of underlying bone involvement in a case of myositis ossificans circumscripta. There is associated surrounding soft tissue edema.
may also be unable to tolerate the procedure, a problem also occasionally encoun-
tered with CT, although to a much lesser degree. More open configura-
tions for the magnet have been invented to circumvent this problem, but the quality of the images produced by such magnets is poorer [12].

MRI is the modality of choice for the locoregional staging of musculo-
skeletal masses. The particular sequences that are useful for tumor evaluation differ from other indications for MRI, such as for the identification of the internal derangement of joints. When evaluating tumors, whether soft tissue or osseous in nature, pure spin echo T1-weighted and fluid-sensitive sequences are indicated to detect the mass, characterize it, and determine its extent. T1-weighted images provide high signal-to-noise images for good anatomic detail of the affected structures and, in the setting of osseous tumors, are especially necessary for the identification of the tumor extent within the bone marrow. Also, most musculoskeletal tumors demonstrate increased fluid signal, so that fluid sensitive sequences (fat-saturated T2-weighted and short tau inversion recovery sequences) are also fundamental. Sarcomas may be homogeneous or heterogeneous. However, malignancies, by virtue of their very nature and potential for autonomous growth, are generally larger and more likely to outgrow their vascular supply with subsequent infarction, necrosis, and heterogeneous signal intensity on MR imaging. Consequently, the larger a mass is, the greater its heterogeneity, the greater is the concern for malignancy [12–15]. In addition to spin echo sequences, gradient echo sequences may be indicated to evaluate for the presence of calcification or hemosiderin [15].

Intravenous contrast administration is not absolutely indicated for the evaluation of de novo skeletal sarcomas, as routine noncontrast images are adequate for defining the presence of a mass. Contrast is, however, required for the assessment of de novo soft tissue masses and for the posttreatment evaluation of all sarcomas. For de novo soft tissue masses, contrast is used for characterization and is especially useful to distinguish simple cystic lesions (for example, ganglions) from solid tumors; it may also be used to guide the selection of a biopsy site (to a non-necrotic portion of the mass). Enhancement following contrast administration reflects tissue vascularity and tissue perfusion, and, in general, the rate of enhancement in malignant lesions is greater than that seen in benign lesions [16,17]. However, it should be noted that MRI with contrast has relatively low specificity for characterizing lesions for malignancy, estimated to be between 25% and 48% [17–19].

On the other hand, an important use of contrast lies in the assessment of tumors that have been treated, whereby contrast helps determines if viable tumor remains [12,14]. Following the treatment of sarcomas, MRI is used to monitor preoperative neoadjuvant therapy to predict the percentage of tumor necrosis, the most important factor differentiating treatment responders from nonresponders and one of the most reliable predictors of outcome. For this purpose, MRI may provide an estimate of the percentage of tissue necrosis that has occurred, but a change in the size of the lesion, the
most commonly used feature, is not an accurate measure of response. Other measures of treatment response include the use of dynamic contrast-enhanced techniques, but these are often cumbersome and provide information on only a portion of the lesion. Following surgery, MRI is the modality of choice for the distinction between residual or recurrent tumor and postoperative fibrosis or inflammation. For this purpose, there is some overlap in the features of benign postsurgical inflammation and the presence of subtle residual or recurrent disease. In fact, only when there is an absence of T2 signal can the MRI absolutely rule out the presence of tumor in the surgical bed [17,18], as increased T2 signal and contrast enhancement can be observed in tumor, as well as immature scar tissue and nonmalignant reactive tissue. It should be noted that a recent drawback for using contrast (gadolinium) has emerged in the form of nephrogenic systemic fibrosis, occurring in patients with pre-existing renal disease [20].

Advanced techniques, such as diffusion weighted imaging and MR spectroscopy, are under investigation and may become a fundamental part of the routine evaluation of sarcomas. These sequences do not require the use of intravenous contrast administration and may prove to add specificity to conventional MRI for the characterization of disease processes. Preliminary research has shown that diffusion-weighted imaging has the potential to differentiate between benign and malignant soft tissue masses. With MR spectroscopy, the metabolic make-up of a mass may be ascertained, with the focus on detecting metabolites that are characteristically elevated in malignancy. Recent studies indicate that the metabolite choline is elevated in malignant musculoskeletal lesions [21–23].

Skeletal sarcomas

When evaluating skeletal sarcomas, MRI is not particularly useful for characterization of the mass (which is typically done by radiography). However, it is the modality of choice for determining the extent of bone marrow involvement of a lesion, for the purpose of treatment planning, including the detection of any skip lesions. Tumors appear as a marrow replacement process on T1-weighted images and can have either well-defined or ill-defined margins. T2-weighted images are useful for defining the extent of masses into the adjacent soft tissues, but are not specific for this purpose [4]. Contrast is generally not required for de novo lesions, although occasionally, intravenous contrast may add specificity to the characterization of a mass by MRI. Contrast is used primarily in the setting of prior treatment for differentiating posttreatment residual or recurrent disease from fibrosis, and as a preliminary estimate of postneoadjuvant therapy response [12–14,16–18].

Many sarcomas have a nonspecific appearance by MRI. However, there are a handful of lesions with specific MRI characteristics. For instance, telangectatic osteosarcoma can have a distinctive appearance on MRI, demonstrating fluid-fluid levels, internal septations, enhancement and peripheral
heterogeneity (Fig. 5). However, such features must be considered in the setting of other findings that would suggest malignancy, because fluid-fluid levels may also be identified in benign processes, such as bone cysts, giant cell tumors, and any lesion with a fracture [14,16,17].

Low-grade cartilage lesions often have a distinctive appearance by MRI as well. Encondromas are typically ovoid in configuration, occurring adjacent to a physeal scar, containing increased T2 signal with a lobulated appearance, and occasional signal voids that signify calcifications. When a suspected enchondroma demonstrates more aggressive features of increased endosteal scalloping or cortical destruction, chondrosarcoma is likely. Osteochondromas can be diagnosed, as they are on other modalities, by the contiguity of their cortex and medullary canal with the host bone. MRI is particularly useful in assessing the thickness of the cartilage cap of osteochondromas to identify chondrosarcoma transformation [24]. With regard to contrast enhancement of chondrosarcomas, low-grade lesions show a lobulated pattern with enhanced septations after intravenous injection of contrast, while high-grade tumors do not have septations and show more diffuse, heterogeneous enhancement [16,19].

**Soft tissue sarcomas**

Soft tissue sarcomas originate in the mesenchymal tissues of muscles, connective tissue, vessels, joints, and fat. As such, MRI represents an ideal modality to evaluate them, given its superior contrast resolution compared with other modalities, particularly CT. When evaluating soft tissue

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**Fig. 5.** Axial (A) and sagittal (B) T2-weighted MRI images show a very large mass lesion extending from the distal femoral diaphysis associated with multiple fluid-fluid levels, internal septations, and heterogeneity characteristic of a telangiectatic osteosarcoma. Note the intramedullary component of the mass with extensive soft tissue component posteriorly.
sarcomas, MRI exquisitely defines the extent of the lesion with respect to compartmental involvement in the muscles, fascia, bones, and joints, as well as any involvement of the neurovascular bundles (Fig. 6). In addition, for posttreatment evaluation, MRI is the modality of choice for detecting residual or recurrent disease.

However, with respect to the characterization of disease, MRI allows for the accurate characterization of only a small number of soft tissue lesions and is frequently deficient in its ability to distinguish whether a mass is benign or malignant. As such, many soft tissue masses encountered in clinical practice will require a biopsy for characterization and diagnosis. There are several lesions, however that can be well characterized by MRI. Lipomas, for example, contain fat signal almost exclusively as seen on all pulse sequences and may occasionally demonstrate thin internal septations (Fig. 7). Cysts are well-circumscribed lesions of decreased signal on T1-weighted images and increased signal on T2-weighted images, with the hallmark that they do not demonstrate any internal enhancement with contrast administration. Vascular malformations have a characteristic infiltrating appearance, are of increased signal on T2 weighted images, and may contain flow voids if they possess an arterial component. There are also some lesions with a few, though not entirely, specific MRI characteristics, which include nerve sheath tumors, myxoid masses, giant cell tumors of the tendon sheath, and some fibrous tumors, such as elastofibroma and desmoid tumors [13].

As a general rule, contrast enhancement characteristics may help distinguish benign and malignant soft tissue lesions, even though there is much overlap in the enhancement patterns of benign tumors and sarcomas. Malignant masses tend to demonstrate greater heterogeneity, liquefaction, and rapid early enhancement than benign lesions [13,18,19], but overall, with MRI a correct diagnosis of a soft tissue mass is made in only approximately 25% to 40% of cases [25]. That being said, the characteristics that a lesion demonstrates on the various MR sequences will help direct the final decision as to whether it is benign or malignant. For example, liposarcoma is a common soft tissue sarcoma and, depending on the subtypes, will often demonstrate internal lipomatous tissue with intervening solid components and variable enhancement patterns (Fig. 8), features that will direct the management toward an invasive biopsy, differentiating it from a simple lipoma.

**Positron emission tomography**

PET is a noninvasive diagnostic technique that involves the acquisition of physiologic images by the detection of radiation emitted from positrons administered to the patient [26,27]. It is considered the gold standard in metabolic imaging and provides information about both the anatomic extent as well as the behavior of tumors, which, in turn, will guide therapeutic choices. The most widely used tracer for PET is fluorine-18 fluorodeoxyglucose (FDG). FDG is a glucose analog that accumulates in cells in proportion
to the rate of glucose metabolism. FDG provides a means of quantifying glucose metabolism as the radiotracer becomes trapped in a cell in proportion to the rate of glycolysis [28]. The standard uptake value (SUV) is a quantification measure of FDG uptake (metabolic activity) in a region of interest. Because increased metabolism is a recognized feature of malignant cells when compared with normal cells, PET is a useful tool for the assessment of malignancies. In addition, although there is much overlap, high-grade malignancies tend to have increased rates of glycolysis and FDG uptake (and therefore higher SUV values) than low-grade and benign lesions [26,28].

Studies suggest that PET is a reliable test for determining the biologic activity of a tumor and for predicting tumor necrosis after neoadjuvant therapy. For the evaluation of sarcomas, PET is showing promise for staging of the tumors, especially distant metastases and monitoring the effect of treatment. It has also shown some potential for targeting high-yield portions of a mass for biopsy [29–33]. Fig. 9 is an example of a mass with distant metastases in the lung.

Nevertheless, although promising, there are limitations to the use of PET. Clearly, PET imaging does not allow the prediction of the histology of a mass [27]. Also, when compared with CT and MRI, PET has poor spatial resolution and should, in fact, be interpreted in conjunction with a cross-sectional study. In this way, common pathologies, such as insufficiency fractures that may be found in oncology patients and have been shown to demonstrate increased FDG uptake, are not misinterpreted as metastatic disease on a PET study. PET/CT has become more widely available in recent years and helped to alleviate the challenges of interpreting PET examinations by themselves. PET/CT has high sensitivity for the initial staging of tumors as well as for the assessment of recurrence; the literature shows an overall 66% sensitivity and 96% specificity of FDG-PET for diagnosing recurrent sarcomas. While combined PET/CT has higher accuracy than either modality by itself, PET overall remains more accurate than CT [34].

Skeletal sarcomas

There has been limited work on the characterization of skeletal sarcomas by PET, although the grading of sarcomas using PET has been recently studied. For example, in general, the higher the grade of the cartilage lesion, the greater its SUV value [35]. However, this poses a diagnostic dilemma for low-grade chondrosarcomas, which can have values less than the cut-off typically observed with malignancy: 2.5. Additionally, SUV values may be above 2.5 with benign inflammatory lesions, such as osteomyelitis or eosinophilic granuloma, as well as any lesion with high giant cell or fibrous content [35,36], such as giant cell tumors, aneurysmal bone cysts, osteoblastomas, Paget’s disease, and fibrous dysplasia [26,36]. In such cases, PET will be deficient in distinguishing benign and malignant disease.
Regarding osteosarcomas, although FDG-PET may provide important information regarding the biologic features of the mass, it has a limited role in primary staging. First-line diagnostic tools remain radiography and MRI. But in the pediatric population, FDG PET may be especially useful to detect intraosseus skip metastases in cases of equivocal MRI findings because of physiologic marrow distribution [34].

PET is most valuable for detecting metastatic disease because it represents a whole-body imaging technique, whereas CT and MRI are limited to the body area scanned. In addition, the response to preoperative neoadjuvant therapy is the most important prognostic factor in sarcomas because the degree of drug-induced tumor necrosis is highly correlated with disease-free survival after therapy [26]. As a functional imaging tool, PET studies have shown that biochemical changes in tumors in response to treatment tend to occur sooner than morphologic changes, and as such, may be better detected with PET than with anatomic cross-sectional imaging [33,34].

Fig. 7. Coronal T1-weighted MRI image shows a well-corticated, slightly expansile lesion of increased signal in the proximal tibial metaphysis. Notice the T1 signal is similar to fatty tissue, and this lesion represents an intraosseous lipoma.

Fig. 6. Axial precontrast T1-weighted (A) and axial T2-weighted (B) MRI images of the thigh show slightly heterogeneous noncontrast intermediate T1 and increased T2 signal in a soft tissue mass adjacent to the osseous cortex of the femur. This lesion is displacing adjacent structures. Axial T1-weighted postcontrast (C) and coronal T1-weighted postcontrast (D) MRI images show heterogeneous contrast enhancement, mostly at the periphery of the lesion with central necrosis, more commonly indicating a malignant than benign state and negating the possibility of a cyst. Sagittal T2-weighted (E) MRI image shows an ovoid, hyperintense but heterogeneous soft tissue mass paralleling the long axis of the body, commonly seen with synovial sarcoma.
Fig. 8. Sagittal T1-weighted precontrast (A) MRI image shows a well-circumscribed, low signal intensity lesion within the soft tissues of the posterior thigh. Sagittal T2-weighted MRI image (B) shows that the lesion is increased T2 signal. Sagittal T1-weighted postcontrast MRI image (C) shows the lesion demonstrates heterogeneous enhancement internally, negating the possibility that it is a cyst, even though the precontrast features suggest the possibility of a cystic nature. This mass was proven to be a myxoid liposarcoma.

Fig. 9. Coronal PET image shows focal radiotracer uptake in a right upper lobe pulmonary nodule, representing a single distant focus of metastatic disease in a patient with newly diagnosed osteosarcoma.
Soft tissue tumors

An important feature of sarcomas, especially soft tissue sarcomas, is that they are often inhomogeneous, with different portions of the tumor having different degrees of aggressiveness and malignancy grades [26]. Biopsy is a key step in the diagnosis of these masses, but improperly performed biopsies are a frequent cause of misdiagnosis, amputation, and local recurrence [26,29]. As such, selecting a high-yield biopsy site is paramount. PET may allow the determination of the most metabolically active region of the lesion to be visualized, thus providing information on tumor biology, which is not done by any other imaging modality [27]. Targeting the area with the highest metabolic activity within the tumor helps determine the accurate histologic tumor grade and predicts outcome [30].

Summary

The advanced imaging techniques of CT, MRI, and PET available for the evaluation of soft tissue and skeletal sarcomas have been discussed in this article. There are benefits and disadvantages to the use of each modality and the choice of modality must be tailored to each patient and particular lesion. In general, CT is more suited to characterization of a mass while MRI will better define the extent of disease for treatment planning. PET is a promising tool for determining the metabolic activity of a lesion, and for use as a potential guide to biopsy and management. Often, however, a multi-modality approach to the evaluation of sarcomas is most effective, as complimentary information is gained from each technique.

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