RadioGraphics

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Multidisciplinary Management of Soft-Tissue Sarcoma[1]

TEACHING POINTS
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Introduction

Soft-tissue sarcomas are rare tumors (1) that can affect any age, gender, and anatomic subsite. They have unique growth features, tending to extend within compartments and along fascial planes on a path of least resistance. The extremities are the site of 50% of soft-tissue sarcomas, with 80% of those occurring in the lower extremities. Malignant fibrous histiocytoma is the most common histologic subtype, followed by liposarcoma (2). In the retroperitoneum, leiomyosarcoma and liposarcoma predominate. The natural history in this location is often characterized by large size at presentation despite slow growth owing to delay in diagnosis. Local control and survival vary according to anatomic site, largely because resection is less feasible and radiation therapy less easily administered in some regions. In patients undergoing curative treatment, outcome is best for extremity soft-tissue sarcomas and worst for retroperitoneal sarcomas and those arising adjacent to critical nonexpendable anatomy (in the head and neck, in the pelvis, and juxtaposed to the spine) (3).

Management of soft-tissue sarcomas provides a paradigm of the multidisciplinary approach for the optimization of local control, function preservation, and limb salvage. This article focuses on the imaging features related to detection, staging, and characterization of the primary tumor, as well as assessment for regional lymph nodes and distant metastatic disease. The anatomic characteristics for patient selection for different locoregional approaches and combined-modality treatment approaches with radiation therapy and surgery are briefly reviewed.

Abbreviations: EBRT = external-beam radiation therapy, PVNS = pigmented villonodular synovitis, SUV = standardized uptake value

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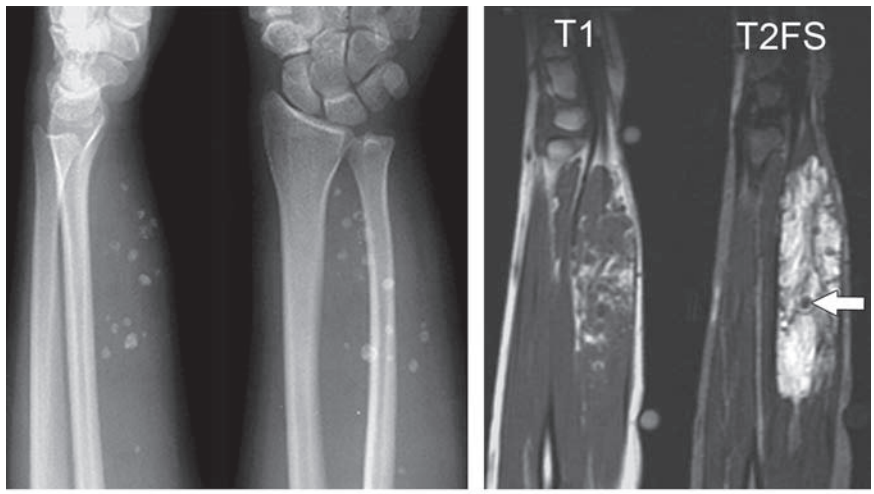


a. b.

Figure 1. Vascular malformation with phleboliths. **(a)** Lateral (left) and posteroanterior (right) radiographs show a hemangioma in the volar compartment of the forearm. The hemangioma contains multiple calcified phleboliths. **(b)** Sagittal T1-weighted (left) and T2-weighted fat-saturated (right) magnetic resonance (MR) images show the serpentine high T2 signal intensity characteristic of a hemangioma. There is also interspersed fat and rounded low-signal-intensity areas (arrow), which are related to the phleboliths.

Imaging

Radiographs are generally unrewarding in the work-up of soft-tissue tumors because soft-tissue masses are the same opacity as the surrounding muscle and are difficult to appreciate. However, radiography is still important in the imaging algorithm (4) and may provide useful information in specific cases, such as vascular malformations with phleboliths (Fig 1). Radiographs can help delineate any underlying bone lesion such as an exostosis, identify the presence of mineralization within the mass, and indicate whether there are changes in the adjacent bone, such as periosteal reaction and extrinsic cortical erosion (5).

Computed tomography (CT) is similarly useful in evaluating mineralized matrix and local bone changes. It can be very helpful in distinguishing soft-tissue sarcomas from myositis ossificans on the basis of the well-formed peripheral mineralization seen in the latter diagnosis (Fig 2). Distinction between a sarcoma and myositis ossificans can be difficult at MR imaging, as both can have nonspecific features on T1- and T2-weighted images (6).

Ultrasonography (US) is particularly valuable in the initial screening of soft-tissue lesions (7,8), particularly to distinguish solid masses from cystic lesions (which are common around joints) (Fig 3). Doppler US is useful in the evaluation of internal vascularity. US can also provide real-time guidance for aspiration or biopsy of masses.

MR imaging is ideally suited to the imaging of soft-tissue masses (9,10) owing to its excellent soft-tissue contrast, multiplanar capabilities, and lack of ionizing radiation. It is invaluable for local staging and surgical planning and can play a role in diagnosis of soft-tissue sarcomas. The technical factors relating to MR imaging, which include positioning, radiofrequency coil selection, and the pulse sequences chosen, are critical to proper imaging of soft-tissue sarcomas.

Teaching Point

Limb position should be chosen to optimize ease of the examination and patient compliance. In general, patients are imaged supine, but the prone position is useful for large dorsal lesions to avoid distortion and motion artifact, particularly for subcutaneous lesions. For upper arm masses, the arm is positioned above the head to place it in the isocenter of the magnet and improve image

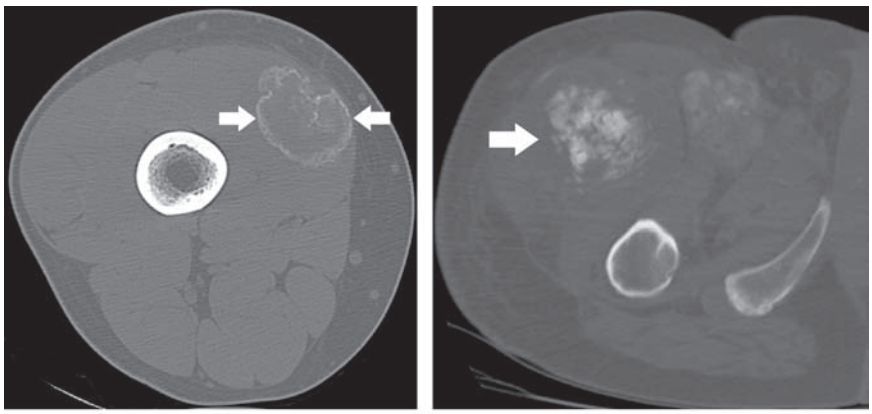


Figure 2. Myositis ossificans versus soft-tissue sarcoma. **(a)** Axial CT image shows myositis ossificans in the mid right thigh. The ossified mass has a zonal pattern of mature well-formed peripheral ossification (arrows). **(b)** Axial CT image shows a soft-tissue osteosarcoma in the proximal right thigh. The soft-tissue component is peripheral to the mineralization (arrow), unlike the ossification in myositis.

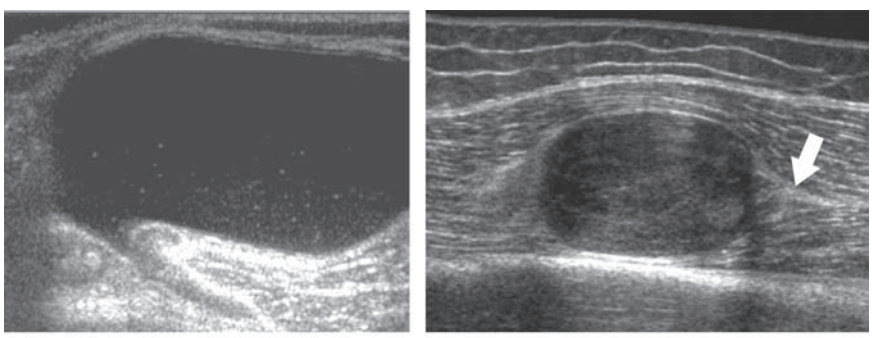


Figure 3. Cystic lesion versus solid mass. **(a)** Transverse US image shows a popliteal cyst, which demonstrates internal low-level echoes and posterior acoustic enhancement. **(b)** Longitudinal US image shows a peripheral nerve sheath tumor. The solid ovoid mass has internal echoes and a distal "tail" (arrow).

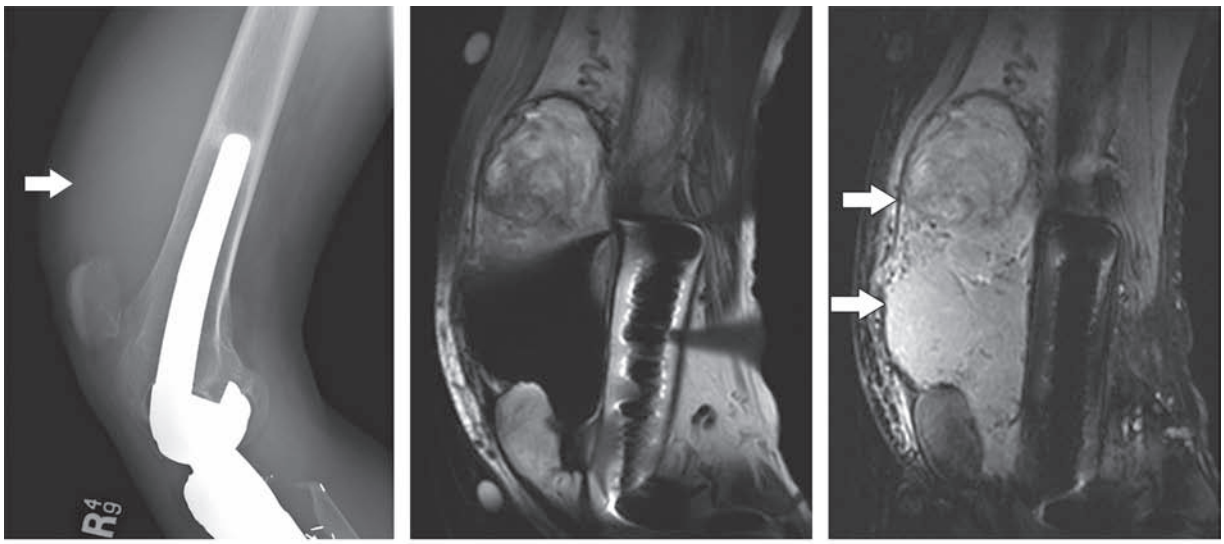
quality. Skin markers (vitamin E or gadolinium contrast material) can be placed at the site of any palpable abnormality, scar, or skin lesion.

A radiofrequency coil should be selected that provides adequate coverage of the lesion. Surface coils offer high signal-to-noise ratio, high resolution, and good off-center fat suppression and are used for the hand, wrist, and foot. Body coils cover a large field of view and are useful to localize soft-tissue lesions relative to an anatomic landmark such as a joint for surgical and radiation therapy planning. A combination of surface and body coils can be used to optimize the imaging study.

MR imaging pulse sequences for soft-tissue sarcomas include a large-field-of-view localizer, which allows quick assessment of lesion location and size and facilitates planning for the rest of the imaging planes. Orthogonal plane imaging is then performed with axial sequences and longitudinal plane sequences, which can be either coronal or sagittal depending on the lesion location. These planes should include both the proximal and distal extent of the lesion as well as any peritumoral edema to define the full extent of the tumor.

T1-weighted sequences are useful for determining soft-tissue anatomy related to the lesion. T1-weighted images are also helpful for lesion characterization, with fat, hemorrhage, and proteinaceous fluid all appearing high in signal intensity.

Fluid-weighted sequences allow sensitive detection of lesions and the associated reactive edema. Typically, some form of fat saturation is used with a T2-weighted sequence. A frequency-selective fat saturation technique requires a very homogeneous magnetic field. If this is not the case, the signal from fat is incompletely suppressed and may mimic soft-tissue edema. Heterogeneities can be caused by use of a very large field of view extending to the periphery of the



a. b. c.

Figure 4. Tumor recurrence in a patient who underwent placement of a tumor prosthesis for osteosarcoma. **(a)** Lateral radiograph shows soft-tissue fullness in the suprapatellar region (arrow). **(b)** Sagittal T2-weighted fat-saturated MR image shows significant artifact and poor fat suppression due to the metal hardware, which obstruct assessment of a locally recurrent tumor. **(c)** Sagittal short inversion time inversion-recovery image shows more homogeneous fat suppression. The recurrent tumor is seen more clearly (arrows) cranial to the patella.

magnet, imaging around metal, off-center imaging, and complex air-tissue interfaces. In these cases, an inversion-recovery technique can be employed, as it is less vulnerable to irregularities in the magnetic field and enhances the conspicuity of lesions (11) (Fig 4). The inversion-recovery technique produces comparatively lower signal-to-noise ratio, which is compensated for by obtaining more data acquisitions. However, the longer imaging times frequently also introduce undesirable motion artifact.

Use of gadolinium contrast material is controversial; it is not routinely employed at all institutions but may be used in suspected cases of hematoma and in distinguishing a cyst versus a myxoid or necrotic tumor. It is also valuable in the assessment of postoperative recurrence and in fibromatosis. In addition, gadolinium contrast material can help guide selection of a more viable area of the tumor to target for biopsy (12).

Teaching Point

Local evaluation of soft-tissue sarcomas is based on the location of the lesion, the lesion size, the amount of peritumoral edema, the compartmental extent of the mass, neurovascular involvement, and extension to the underlying bone or adjacent joint (13).

Anatomic compartmentalization of the mass is crucial to local assessment (Fig 5). In the arm, the compartments are defined as anterior and posterior. In the forearm, the compartments are volar (flexor) and dorsal (extensor), separated by the interosseous membrane. At the thigh, there are anterior (quadriceps), medial (abductors), and posterior (hamstrings) compartments. In the calf, the compartments are defined as anterior, lateral, and deep and superficial (soleus and gastrocnemius) posterior. The interosseous membrane separates the anterior compartment from the deep posterior compartment. Imaging helps define whether the mass is superficial or deep to fascia, is intra- or intermuscular, and whether it has breached fascia.

Neurovascular status is determined by the presence of a fat plane of separation between the neurovascular bundle and the tumor. The tumor can abut the neurovascular bundle, but the fat plane can still be preserved. If the fat plane is obliterated, the neurovascular bundle is presumed to be involved. It is also important to note whether the neurovascular bundle is encased by tumor. These features determine the surgical approach and are vital considerations in selecting between limb conservation-reconstruction and amputation.

Bone and lymph node involvement in soft-tissue sarcomas is rare (14). Involvement of bone by soft-tissue sarcoma has been shown to correlate with a higher frequency of disease-related death (15). MR imaging has good sensitivity and specificity for the detection of osseous invasion, as evidenced by changes in cortical and medullary

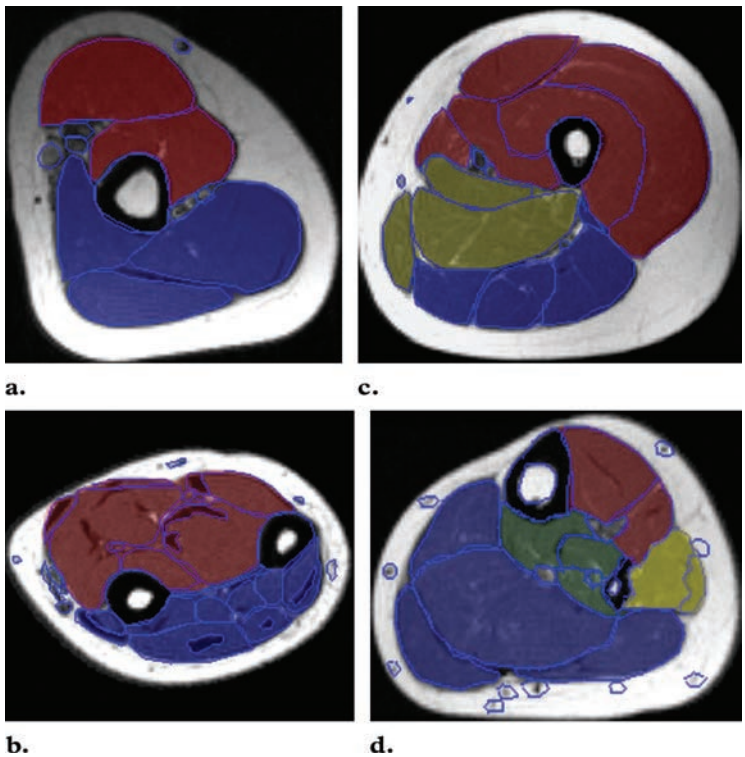


Figure 5. Anatomic compartments. **(a)** The upper arm is divided into anterior (red) and posterior (blue) compartments. **(b)** The forearm is divided into volar (red) and dorsal (blue) compartments. **(c)** The thigh is divided into anterior (red), medial (green), and posterior (blue) compartments. **(d)** The calf is divided into anterior (red), lateral (yellow), superficial posterior (blue), and deep posterior (green) compartments.

signal intensity (16). Rhabdomyosarcoma, clear cell sarcoma, and epithelioid sarcoma appear to have a higher tendency for lymph node spread than other soft-tissue sarcomas (17).

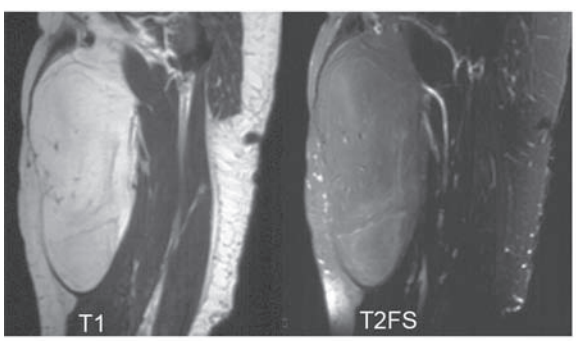
Positron emission tomography (PET) has an emerging role in the evaluation of soft-tissue sarcomas (18). It uses radiotracers specific for biologic processes to produce images of regional tissue metabolism. Fluorodeoxyglucose is the most commonly employed radiotracer in imaging of soft-tissue sarcomas. It behaves like glucose, but it is not a substrate for glycolytic enzymes and becomes trapped within the cell. The degree of fluorodeoxyglucose accumulation reflects the tissue glucose metabolism. Aggressive tumors often have higher fluorodeoxyglucose accumulation than benign tumors and low-grade neoplasms (5). Fluorodeoxyglucose concentration is normalized relative to the amount of radiotracer injected and the background tissue activity, resulting in a standardized uptake value (SUV) measurement. Higher SUV corresponds to higher metabolic rates.

PET results may allow distinction between low- and high-grade tumors (19) and direct the choice of a biopsy site to the more aggressive region of the mass (5). PET has not been proved in the distinction between low-grade tumors and benign lesions (18,20). SUV has been shown to be an independent predictor of survival and disease progression (21). SUV change after chemotherapy corresponds to treatment response, with no change or an increase in SUV in patients who do not show a response (22). Although chemotherapy treatment is not standard in soft-tissue sarcomas, patient who receive neoadjuvant chemotherapy and show a decrease of more than 40% in the tumor SUV have a better overall survival than patients with a stable SUV after chemotherapy (22).

Imaging Features of Specific Soft-Tissue Tumors

Although many benign soft-tissue masses can be correctly diagnosed at imaging (23), in general MR imaging is limited in its ability to permit a tissue diagnosis (24,25), particularly in the case of aggressive soft-tissue tumors. A correct diagnosis based on MR imaging features can be made in only 25%–50% of cases. The vast majority of lesions, whether benign or malignant, have low signal intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted images. However, MR imaging does have a high specificity for several specific lesions, as discussed in this section.

Lipomas are the most commonly encountered subcutaneous masses (26). A lipoma can be confidently diagnosed when the lesion is isointense to subcutaneous fat with all sequences, has no residual high signal intensity on T2-weighted fat-suppressed images, and has no internal



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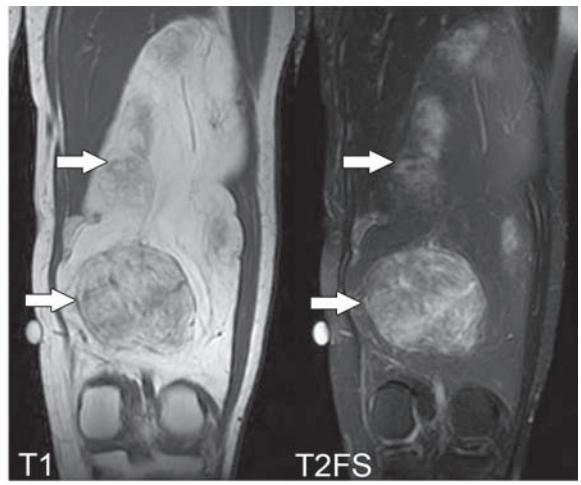

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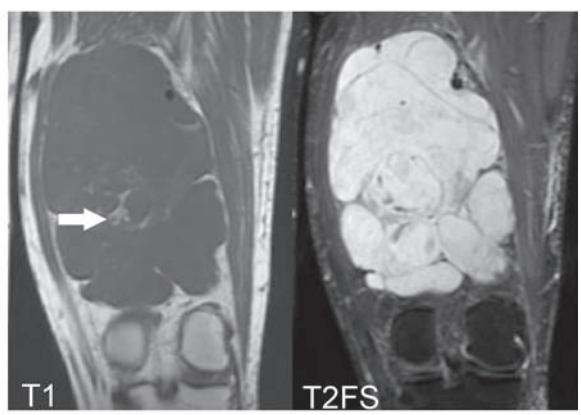


c.

Figure 6. Lipomatous lesions. **(a)** Sagittal MR images show a large lipoma in the thigh. Note the fat signal intensity throughout the lesion on the T1-weighted image (left). The fat signal is completely suppressed on the T2-weighted fat-saturated image (right). **(b)** Coronal MR images show a large well-differentiated liposarcoma in the distal thigh. Note the large soft-tissue nodules (arrows) on the T1-weighted image (left). Signal from these nodules is not fully suppressed on the T2-weighted fat-saturated image (right). **(c)** Coronal MR images show a large myxoid liposarcoma in the distal thigh. The signal intensity of the lesion follows that of water: low on the T1-weighted image (left) and very high on the T2-weighted fat-saturated image (right). However, the lesion has internal complexity, with septa and focal nodular areas of fat signal intensity (arrow).

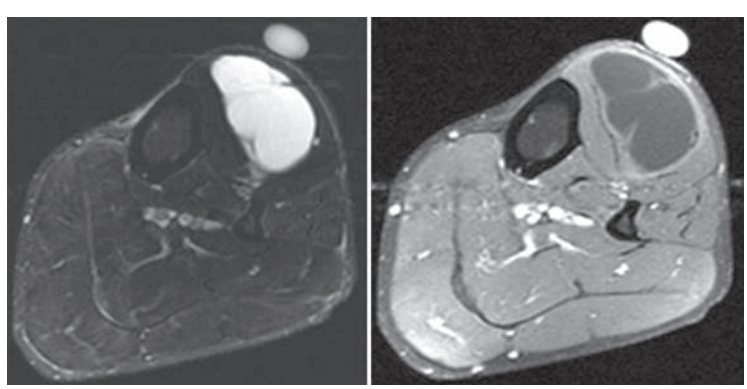


Figure 7. Intramuscular ganglion cyst. Left: Axial T2-weighted fat-saturated MR image shows a lesion with very high signal intensity in the left calf. Right: Axial gadolinium-enhanced T1-weighted fat-saturated MR image shows peripheral enhancement of the lesion.

complexity. Nonadipose areas within a fatty mass that remain hyperintense on T2-weighted fat-suppressed images or short inversion time inversion-recovery images can represent necrosis, fibrosis, inflammation, or sarcoma. Features that suggest a malignant lipomatous mass on standard T1- and T2-weighted images include increased patient age, lesion size greater than 10 cm, less than 75% fat content, and presence of a nodular enhancing component (27) (Fig 6).

Myxomas and cysts may be difficult to distinguish at MR imaging. Both are well defined, with low signal intensity on T1-weighted images and very high signal intensity on T2-weighted images

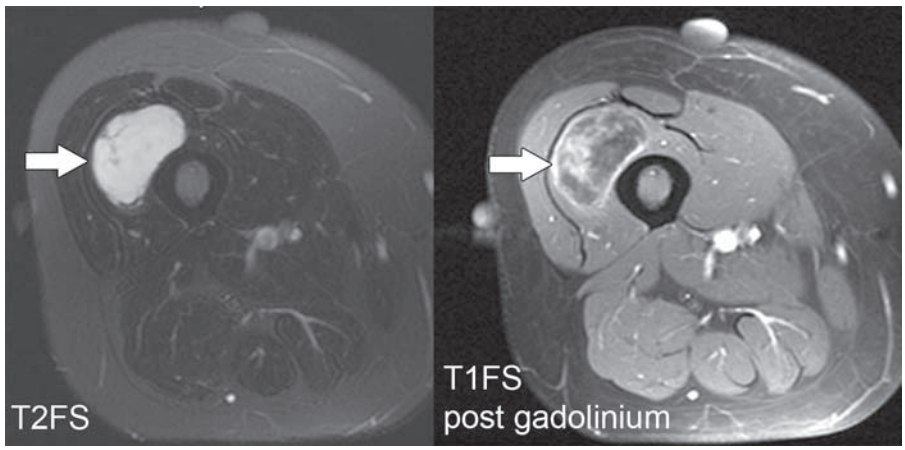


Figure 8. Myxoma. Left: Axial T2-weighted fat-saturated MR image shows a high-signal-intensity lesion (arrow) in the right thigh. Right: Axial gadolinium-enhanced T1-weighted fat-saturated MR image shows diffuse enhancement of the lesion (arrow); the enhancement is more prominent centrally. These findings are consistent with a solid lesion rather than a cyst.

Figure 9. Nerve sheath tumor. Sagittal T2-weighted fat-saturated MR image shows a fusiform mass in the thigh. The mass has central low signal intensity secondary to increased collagen content (arrowhead) and peripheral high signal intensity (arrow), which produce a target appearance.

(26). These lesions can be distinguished by administering gadolinium contrast material, which reveals peripheral enhancement in a cyst (Fig 7) versus mild diffuse enhancement in the majority of myxomas (28) (Fig 8).

Hemangiomas may have phleboliths, which can be demonstrated on radiographs. MR imaging features are characteristic: areas of high signal intensity on T1-weighted images corresponding to internal fat and very high signal intensity on T2-weighted images (28). The lesions are often infiltrative, with serpentine components representing vascular channels and spaces (26) (Fig 1).

Benign peripheral nerve sheath tumors are generally fusiform masses that are aligned along a fascial plane and have low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. The nerve can often be seen extending proximal and distal to the mass (29). A target sign on T2-weighted images is a characteristic feature, with the central portion of the lesion having low signal intensity due to increased collagen content and the periphery having high signal intensity due to myxoid components (30) (Fig 9).

Some benign locally aggressive tumors have a characteristic MR imaging appearance. Pigmented villonodular synovitis (PVNS) is a benign intraarticular locally aggressive mass that can be readily diagnosed with MR imaging, owing to the characteristic low signal intensity on T1-weighted images and heterogeneous low signal intensity on T2-weighted images (31). PVNS can be focal and nodular or have a more diffuse infiltrative

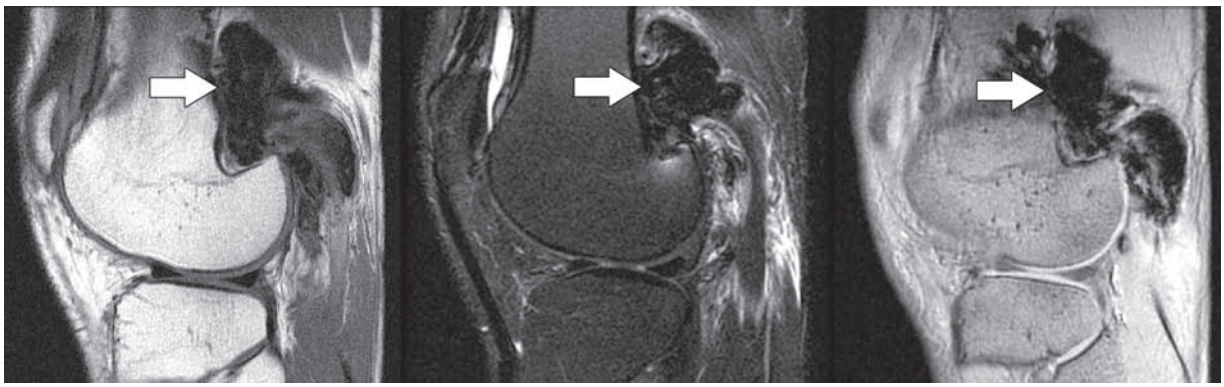


Figure 10. PVNS. T1-weighted (left) and T2-weighted fat-saturated (middle) MR images show a low-signal-intensity mass (arrow) in the knee. Right: On a gradient-echo image, the mass (arrow) demonstrates blooming artifact, which is due to the presence of hemosiderin and is a characteristic feature of PVNS.

Figure 11. Fibromatosis. Left: Axial T1-weighted MR image shows a lesion (arrow) in the proximal right thigh. The lesion is isointense relative to muscle. Middle: On a T2-weighted fat-saturated MR image, the lesion (arrow) has variable signal intensity, which depends on its cellularity. Right: Gadolinium-enhanced T1-weighted fat-saturated MR image shows enhancement of the lesion (arrow).

appearance. PVNS demonstrates blooming artifact on gradient-echo images (appearing larger and with lower signal intensity) due to susceptibility artifact related to magnetic heterogeneity induced by the presence of hemosiderin (Fig 10). Extrinsic erosions of the adjacent bone are seen in 50% of cases, most commonly at the hip, followed by the ankle, shoulder, and knee.

Fibromatosis is a benign locally aggressive infiltrative lesion that can often be diagnosed on the basis of its MR imaging features. It commonly has low signal intensity on T1-weighted images and also on T2-weighted images, although the T2 signal is variable (32) (Fig 11) corresponding to increasing collagenization. Areas of increased T2 signal can develop over time within the lesion (33) and may represent areas of increased cellularity. Often fibromatosis can enhance with gadolinium, making it more conspicuous. After radiation therapy, fibromatosis frequently demonstrates lower signal intensity on T1-weighted images. Local recurrence is common.

Aggressive sarcomas are generally nonspecific in their imaging features. Malignant fibrous histiocytoma usually manifests as a large aggressive intramuscular mass, with heterogeneous signal intensity on T1- and T2-weighted images. Suggestive features include a lack of adipose tissue and occurrence late in life. Synovial sarcoma has a variable appearance and can be well-defined or infiltrating. It commonly has low signal intensity on T1-weighted images and heterogeneously increased signal intensity on T2-weighted images, owing to areas of necrosis, hemorrhage, and calcification (34). Reactive periostitis may be seen in the adjacent bone in 11%–20% of cases (Fig 12). Radiographs show calcification in approximately 30% of cases (35).

Diagnosis and Staging

Local staging of soft-tissue sarcomas is primarily achieved with MR imaging, although CT is invaluable if there are contraindications to MR imaging. Distant staging is performed with chest radiography (for low-grade lesions and high-grade T1 lesions) or chest CT (high-grade, T2

Figure 12. Synovial sarcoma. **(a)** Lateral radiograph shows a soft-tissue mass in the anterior calf with underlying cortical scalloping (arrows). **(b)** Axial T1-weighted MR image shows the cortical scalloping and soft-tissue mass (arrow). **(c)** Axial T2-weighted fat-saturated MR image shows the soft-tissue mass (arrow) and abnormal marrow signal intensity (arrowhead), a finding consistent with marrow invasion by the tumor. Note the fluid-fluid levels in the tumor, which are secondary to hemorrhage and necrosis.

tumors). Currently, in most cases, CT of the thorax is performed. Additional investigations may be performed based on individual circumstances, including radiography, bone scanning, and PET/CT. Staging may be tailored to the disease situation (eg, myxoid liposarcoma may benefit from abdominal CT to exclude retroperitoneal disease or spinal MR imaging to exclude vertebral metastases).

Because imaging performs poorly in predicting the histologic characteristics of soft-tissue tumors, diagnosis of soft-tissue sarcomas depends on tissue analysis. Tissue is typically obtained with either a core needle biopsy or an incisional biopsy. Excisional biopsy is reserved for small superficial lesions. It is important to consider the approach for the biopsy so that the biopsy track remains within an involved compartment (36). Tumor regrowth along the biopsy track is a known complication, and the biopsy track is resected at the time of surgery (37). Consultation with surgeons and radiation oncologists about the biopsy approach is vital to ensure that the radiation therapy and surgical volumes are adequate to encompass the biopsy track. Pathologic analysis of the biopsy sample allows assessment of the histologic subtype and the grade of the tumor and evaluation of tumor margins (in the case of an excisional biopsy).

Soft-tissue sarcomas are classified according to the International Union Against Cancer–American Joint Committee on Cancer system, which stratifies patients into low-, intermediate-, and high-risk groups based on features of tumor grade, size, depth to fascia, and the presence of lymph node or systemic metastases. Of interest, the next edition of the stage classification, scheduled for introduction in 2010, reduces the impact of isolated lymph node metastasis by relegating this criterion to stage III from its current position in stage IV, on the basis of recent data (17).

Soft-tissue sarcoma is unique from other tumors because of the dominant position of grade in the management, a point that is emphasized by its inclusion in the stage classification. Thus, low-grade tumors remain stage I, irrespective of the size of the lesion or whether it is superficial or deep to fascia. High-grade small tumors or tumors larger than 5 cm that are superficial imply an intermediate risk and are considered stage II. Large deep tumors (stage III) or lesions associated with any lymph node or distant metastases (stage IV) are considered high risk from the standpoint of survival.

Histologic subtype does not generally influence management, except in a few specific cases. One such example is myxoid liposarcoma, which is unique in its radiation responsiveness (38). The reliable reduction in tumor size with preoperative radiation therapy translates into less extensive surgery and may contribute to an overall higher

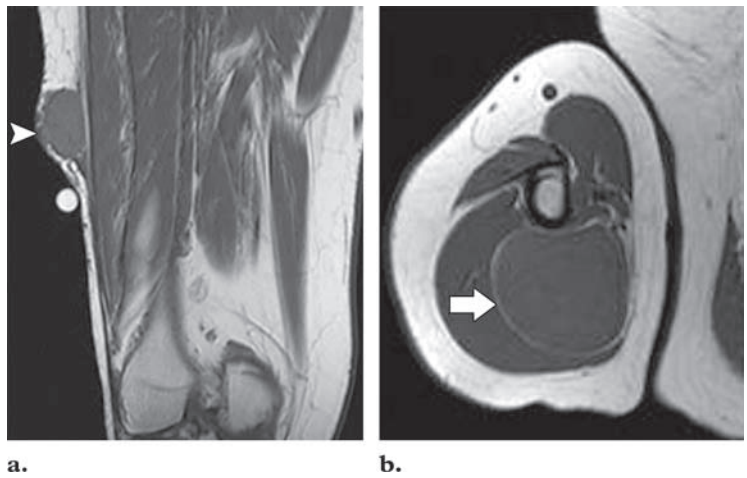


Figure 13. Treatment of small superficial sarcoma versus nerve sheath tumor. **(a)** Coronal T1-weighted MR image shows a small superficial soft-tissue sarcoma in the lateral aspect of the right thigh (arrowhead) with minimal surrounding edema. This lesion may be amenable to surgical management alone. **(b)** Axial T1-weighted MR image shows a malignant nerve sheath tumor centered within the posterior compartment of the right upper arm (arrow). Given the location of the lesion and its proximity to vital structures, a combination of surgery and preoperative radiation therapy would be used to reduce the risk of local recurrence.

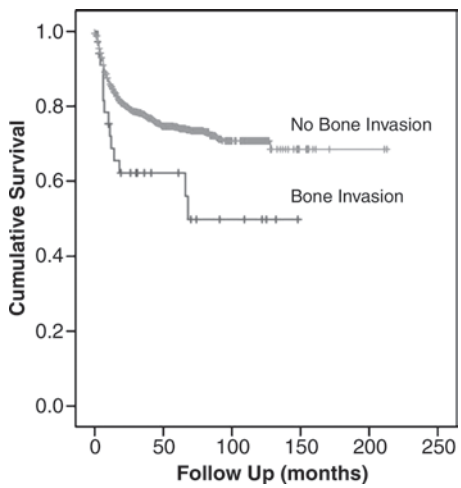


Figure 14. Kaplan-Meier curves comparing metastasis-free survival in patients with bone invasion versus patients without bone invasion. (Reprinted, with permission, from reference 44.)

survival than other types of soft-tissue sarcoma. Myxoid liposarcoma also has a much higher tendency for multifocality with nonpulmonary soft-tissue metastatic disease, classically seen in the retroperitoneum, shoulder region, and chest including the mediastinum. There is also a propensity for bone metastases (39), which can manifest as a solitary vertebral lesion many years after treatment of the primary tumor. Such metastases are frequently best identified with MR imaging of the spine, as they are often not identified on bone scans.

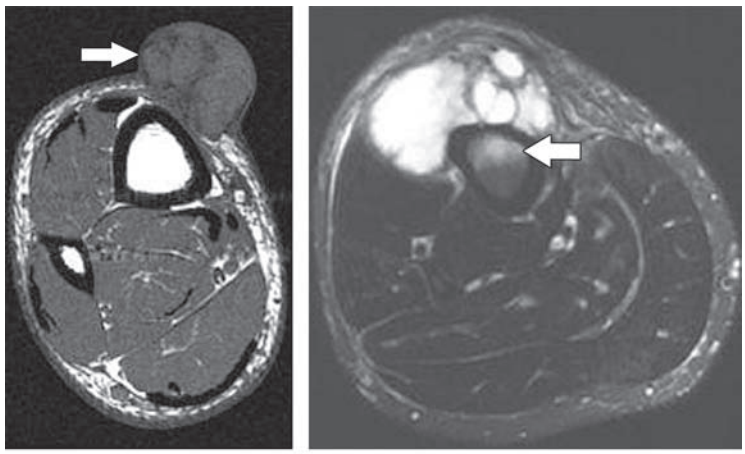
There is ongoing interest in molecular histologic characterization of these tumors. In many cases, soft-tissue sarcomas have complex karyotypes associated with dysfunction of p53 checkpoint function (40). However, some sarcomas have simple karyotypes, with specific genetic alterations encoding for chimeric proteins regulating tumor biology and pathogenesis. In the future, therapeutic targeting of these mutations may result in improvement in patient survival.

Treatment

Surgery

Surgery is the mainstay of management of soft-tissue sarcomas, with the goals of complete removal of the tumor and, if necessary, reconstruction of the adjacent soft tissue, bone, and neurovascular structures. Surgery can be considered as the sole treatment if the tumor can be removed with adequate wide margins, without sacrificing structures critical to functional outcome such as major nerves, blood vessels, and bone. This approach is generally reserved for small tumors that are superficial to fascia, irrespective of the tumor grade. With tumors that are large or deep to fascia, surgery alone is likely to leave microscopic disease behind for the sake of maintenance of critical structures. This increases the frequency of local recurrence; therefore, these tumors are usually treated with radiation in addition to surgical excision (41). With current treatment regimens, limb salvage surgery is possible in up to 95% of cases.

The surgical margin is an important concept. Intralesional excision, where the reactive zone of edema is peeled back to resect the tumor (often piecemeal), is inadequate. There is an unaccept-



a. b.

Figure 15. Sarcomas without bone invasion and with bone invasion. **(a)** Axial T1-weighted MR image shows a superficial soft-tissue sarcoma (arrow) of the calf. The lesion abuts the medial cortex of the right tibia without cortical scalloping or abnormal marrow signal intensity. **(b)** Axial T2-weighted fat-saturated MR image shows a high-grade synovial sarcoma that surrounds more than 50% of the tibia. In addition, there is cortical scalloping and high signal intensity in the medullary canal (arrow). These findings are consistent with bone invasion by the tumor.

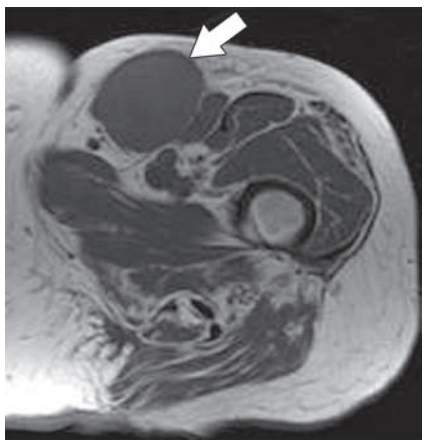


Figure 16. Sarcoma requiring adjuvant radiation therapy. Axial T1-weighted MR image shows a malignant fibrous histiocytoma in the left inguinal region (arrow). The femoral triangle does not have good fascial boundaries; therefore, this tumor requires adjuvant radiation therapy to ensure an adequate local margin and reduce the risk of local recurrence.

able risk of local recurrence of up to 40% with this approach owing to the presence of residual tumor (42). Unplanned positive margin intralesional surgery usually occurs when the aggressive nature of the mass is not appreciated preoperatively. Marginal excision is performed when the tumor is resected through the reactive zone of edema and also has a high risk of local recurrence due to the presence of residual microscopic disease. A wide margin indicates resection of the mass with a margin that lies outside the reactive zone. A radical excision includes the entire compartment containing the mass. This amount of resection can provide excellent local tumor control but can produce significant functional compromise.

Teaching Point

The goal of surgery is a wide excisional margin, which is defined as 2 cm of skin, fat, or muscle, to resect the adjacent microscopic disease. Fascia is an excellent barrier to tumor spread, such that 1 mm of fascia can still be considered a wide margin. The reactive zone of edema surrounding the tumor, which can often extend quite far from the mass, is considered to contain microscopic disease (43). For this reason, marginal excision is not adequate if surgery is the only treatment. Radiation therapy is necessary to address residual microscopic disease within the reactive zone of edema.

It is critical to determine if the tumor is superficial to the fascia. Although a small superficial lesion can usually be managed with surgery alone (Fig 13), there are several exceptions to this rule. For example, superficial lesions with edema or that appear infiltrative or multinodular generally require surgery and radiation therapy due to extensive microscopic disease.

Superficial tumors adjacent to bone often require combined management with radiation and surgery. Although histologic bone involvement occurs in less than 5% of soft-tissue sarcomas, it is an independent poor prognostic factor, associated with an increased risk of metastases, amputation, and decreased survival (44) (Figs 14, 15).

Superficial tumors in extracompartmental areas such as the axilla, femoral triangle, popliteal fossa, and antecubital fossa lack muscular fascia as a boundary. Such tumors are generally treated with a combined approach of surgery and radiation therapy to ensure an adequate margin (Fig 16).

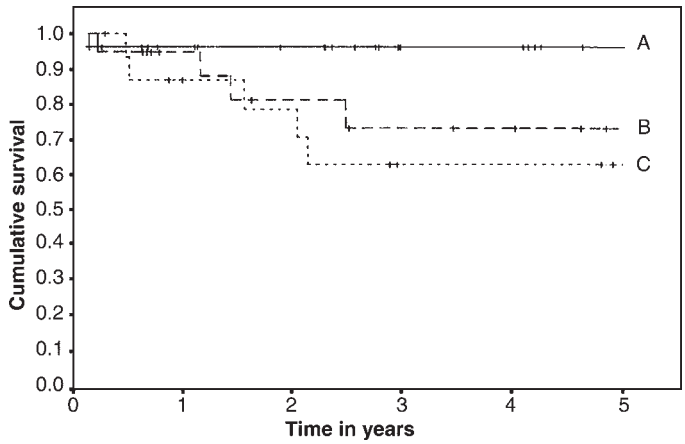


Figure 17. Kaplan-Meier survival curves show the rates of local recurrence in patients treated with limb-sparing surgery and adjuvant radiation therapy. *A* = planned positive margins against critical structures, *B* = positive margin at reexcision after an unplanned excision, *C* = unplanned positive margins. (Reprinted, with permission, from reference 42.)

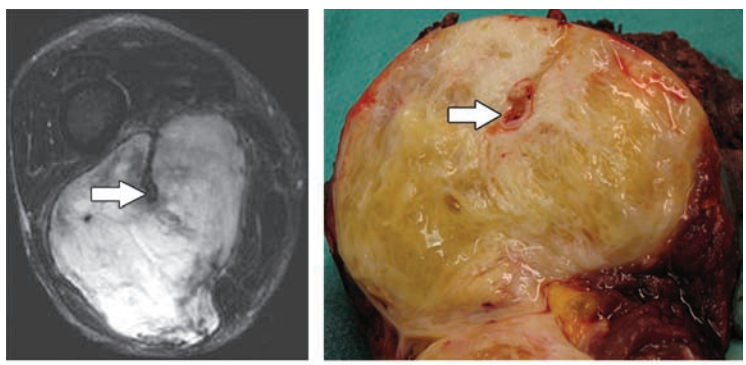


Figure 18. Tumor encasement of a critical structure. **(a)** Axial T2-weighted fat-saturated MR image shows a rhabdomyosarcoma in the right thigh. The tumor encases the sciatic nerve (arrow) and abuts distal superficial femoral vessels. **(b)** Photograph of the pathologic specimen shows the tumor surrounding the sciatic nerve (arrow).

Lesions that involve the fascia or are deep to fascia are generally managed with a combination of surgery and radiation therapy. This is because reliance on wide surgical excision alone would tend to involve resection of multiple critical structures, which would detrimentally affect functional outcome. The addition of radiation therapy allows closer surgical margins, thereby maintaining these critical anatomic structures without increasing the risk of local recurrence.

An exception to this approach is the low-grade lipomatous lesion. These tumors are generally resected via a marginal excision without radiation therapy, since they are predominantly grade 1 liposarcomas that have minimal risk of local recurrence and no risk of metastasis. Should a recurrence occur, radiation therapy can be considered in further management. If this approach is to be used, it is critical to preoperatively target the biopsy to the most aggressive portion of the mass (ie, high T2 signal intensity, nodularity, or enhancing foci), so that the grade of the tumor is not underestimated.

In certain circumstances, the surgical ap- proach may involve a "planned positive" margin along a critical anatomic structure such as a blood vessel, bone, or nerve. A planned positive margin is not associated with an increased risk of poor local control (42), as long as the remain- ing margins are adequate and adjuvant radiation therapy is included in the treatment regimen (Fig 17). The planned positive margin is akin to a "margin negative" marginal resection.

Teaching Point

When a critical neurovascular structure is circumferentially encased by tumor, the structure must be sacrificed and potentially reconstructed (Fig 18). The patient must be informed preoperatively of the functional implications. Although major motor nerve resection produces a significant deficit, function is still often better than an amputation. Newer techniques of nerve grafting and distal nerve transfer may help overcome functional limitations.

Vascular reconstruction of arteries commonly results in good long-term patency and extremity function. Venous reconstructions are prone to thrombosis, resulting in edema. A study comparing patients with and patients without vascular reconstruction found a higher risk of wound

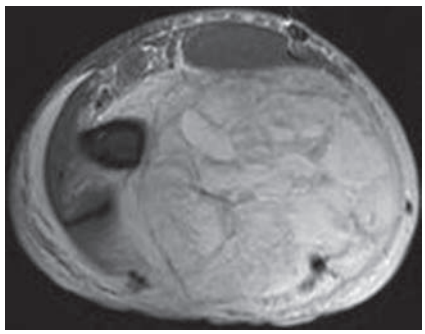


Figure 19. Sarcoma with vascular and neural involvement. Axial T2-weighted fat-saturated MR image shows a high-signal-intensity undifferentiated soft-tissue sarcoma involving the anterior and posterior compartments of the upper arm. The lesion abuts the humeral cortex and involves the brachial vessels and the median and ulnar nerves. Limb salvage could not be performed, and the patient was treated with shoulder disarticulation.

Figure 20. Nodal metastasis in a patient with an epithelioid sarcoma of the left arm. Axial T1-weighted MR image shows a lymph node metastasis (arrow) in the left axilla.

complications, deep venous thrombosis, and edema in the reconstruction group (45). These complications resulted in a higher risk of subsequent amputation, but functional results were excellent. Therefore, vascular reconstructions are preferable to amputation.

When vascular reconstruction is necessary, additional surgical expertise may be required. Therefore, it is helpful to delineate the extent of vascular involvement preoperatively. In cases with bone invasion as demonstrated by cortical changes or marrow edema at imaging, bone resection should be performed. Amputation is still considered in cases of significant coexistent vascular and motor nerve involvement, involvement of multiple nerves in the upper extremity, infected tumor, poor soft-tissue coverage, and poor expected functional outcome (Fig 19).

Lymph nodes are rarely involved by soft-tissue sarcomas (17) and are generally assessed with physical examination. In cases of epithelioid sarcoma, rhabdomyosarcoma, clear cell sarcoma, extraskeletal chondrosarcoma, and angiosarcoma, local MR imaging with attention to regional lymph node chains should be performed, as these histologic subtypes are associated with a higher risk of occult lymph node metastasis (Fig 20). Sentinel node biopsy has an uncertain role at this time. It may be warranted in the high-risk groups noted earlier. Isolated lymph node metastases have a much better prognosis than pulmonary metastases and have a prognosis comparable with that of a stage III large, deep sarcoma; this fact will be reflected in upcoming changes to the American Joint Committee on Cancer staging system. All lymph node metastases should be managed aggressively, including surgical resection, with radiation therapy considered for extracapsular spread or when the next station of lymph node drainage immediately beyond overt disease has not been dissected and may still harbor microscopic disease.

In the case of local recurrences, it is critical to have detailed information about previous treatment. If radiation has not already been given, the recurrence is usually treated as a primary tumor with surgery and radiation therapy. Again, treatment has to be individualized, based on local anatomy, reconstruction options, the likelihood of complications, and the projected functional limitations. The possibility of a new radiation-induced primary tumor should be considered, particularly if the histologic type is different from that of the original tumor and the interval after the original combined-modality treatment is very long.

Partially excised lesions that were not known to be sarcoma at the time of initial surgery pose management difficulties. In the case of piecemeal tumor removal, the zone of contamination is likely to be large, and preoperative radiation therapy should be considered. If the mass was removed en bloc through the reactive zone (ie, a marginal excision), the scar is reexcised; if there is residual microscopic disease with close margins, postoperative radiation therapy is performed.

Radiation Therapy

Teaching Point

Radiation therapy has an essential role in decreasing the need for amputation and improving functional outcome. With radiation therapy, the zone of microscopic disease around the gross tumor can be sterilized instead of resected, decreasing the size of the surgical margin required.

External-beam radiation therapy (EBRT), delivered preoperatively or postoperatively, and brachytherapy are the usual modes of administration. Radiation therapy requires multidisciplinary consultation, which should address the biopsy site and the anticipated resection technique (including whether the overlying skin is to be removed). Recent hypotheses have included selective radiation therapy techniques that avoid anticipated skin flaps (46), although studies are ongoing to address the benefit of this approach. The dose to adjacent organs must be considered, such as to the liver, which is most vulnerable to the effects of radiation therapy in cases of right-sided retroperitoneal sarcoma.

In a large Scandinavian study of the outcomes of various management strategies for soft-tissue sarcomas (amputation, wide-margin excision, radiation therapy, or chemotherapy) with a median follow-up of 7 years, there was a disappointing local recurrence rate of 18% in large deep lesions (41). The local recurrence rates may reflect the lack of a combined surgical and radiation therapy treatment approach in this series, which spanned a period of two decades.

A landmark randomized trial of amputation versus wide local excision combined with radiation therapy, performed more than two decades ago at the National Cancer Institute, changed the management of soft-tissue sarcomas by demonstrating similar local recurrence rates between the two groups, with no influence on survival in the limb preservation group (47). The contribution of radiation therapy to limb preservation surgery has also been studied in two randomized trials, with similar benefit identified in both studies from the addition of radiation therapy. Yang et al (48) reported on the use of external-beam therapy as the local adjuvant approach in a second study from the National Cancer Institute. Pisters and colleagues (49) at Memorial Sloan-Kettering Cancer Center also described the benefit of brachytherapy in the same setting in a randomized trial.

Brachytherapy has several advantages over EBRT. It can be promptly initiated after surgery, is more easily administered with chemotherapy (when this is part of the treatment regimen) because the skin is relatively protected, and has a shorter overall treatment time (typically 4–6 days vs 5–6.5 weeks for EBRT). However, brachytherapy is a very complex technique that demands multidisciplinary collaboration and interaction between radiation oncologists, surgical oncologists, and radiologists; such collaboration and interaction are not available at all centers. It is possible that these challenges have led to the popularity of the external-beam approach for local adjuvant treatment.

Of interest, in the Memorial Sloan-Kettering Cancer Center trial, brachytherapy in combination with wide local excision was not shown to be as effective in reducing local recurrence in low-grade tumors compared with the clear benefit seen in the high-grade lesions (49). Speculation exists as to why this may be the case. A putative rationale includes the potential slower kinetics of low-grade tumors; these slower kinetics may not permit sufficient radiation exposure over the relatively short dwell times used in brachytherapy, which is completed in a matter of only several days, compared with many weeks of treatment in the case of EBRT. Notably, the "grade effect" was not evident in the external-beam therapy trial performed by Yang and colleagues (48), where low-grade tumors fared exceptionally well.

The timing of radiation therapy has always been a central focus in the discussion surrounding optimal radiation therapy in the adjuvant treatment of soft-tissue sarcomas. The controversies and issues surrounding this question have recently been addressed (50). In essence, radiation therapy can be given preoperatively or after surgery. In a randomized trial from our group comparing wide excision with either pre- or postoperative radiation therapy, the overall survival, local control, rates of regional and distant metastasis, and progression-free survival were identical between the two groups at 5 years.

Advantages and disadvantages exist for both approaches. With preoperative radiation therapy, a lower dose is used (50 Gy compared to 60–66 Gy) and applied to a smaller volume of tissue, resulting in less edema and fibrosis. However, the rate of wound complications is statistically significantly increased with preoperative radiation therapy (35% vs 17%) (50,51). Despite the early disadvantage of preoperative radiation therapy, at 1 year the clinical outcomes are similar between the two groups (52). Postoperative radiation therapy is associated with an increased risk of fracture

due to the higher dose administered (53,54) and an increased risk of subcutaneous fibrosis (52).

There are specific situations where radiation therapy may not be warranted. It remains important to emphasize that not all patients require radiation therapy; it is best avoided where possible, particularly in younger patients, who are at greater risk of developing late tissue damage, including induction of second malignancies within or adjacent to the radiation therapy volume. Other long-term sequelae include tissue fibrosis and fracture, which can occur in up to 10% of patients receiving 60–66 Gy and are very difficult to manage. Thus, in the treatment of small superficial lesions, radiation therapy is unlikely to add additional benefit. If functional outcome after surgery is anticipated to be poor and the decision is made to perform an amputation, there is rarely a need for radiation therapy either, since the ablative surgery usually accomplishes the necessary tumor clearance. Exceptions to this rule include a complex proximal lesion arising in the shoulder or pelvic girdle, where anatomic constraints, particularly neurovascular structures, may result in insufficient surgical clearance.

Radiation therapy planning is generally based on a CT simulation process, with the patient positioned and immobilized in the treatment position. Simulation with a wide-bore CT unit is also advantageous in many cases, since it permits better limb positioning for the planning CT data acquisition. MR imaging is not generally used in radiation therapy dosimetric planning, owing to differences in extremity positioning within the MR unit for imaging purposes compared to the position required for radiation therapy. The lack of ionizing radiation with MR imaging means that attenuation-correction factors required for radiation therapy planning are unavailable.

Nevertheless, MR imaging remains a cornerstone of tumor delineation owing to the better soft-tissue visualization it affords. If care is taken to acquire both MR imaging and CT simulation data sets in similar positions, image fusion techniques may enhance target delineation on radiation therapy planning workstations owing to the ability to perform the image segmentation process on an MR image, even if dosimetric calculations were performed only on the planning CT data set. In the future, the development of suitable and accurate translation algorithms may also permit some capability for using MR imaging for the dosimetric optimization process.

Target delineation for radiation therapy may be complex and requires judgement and experience. The existence of subclinical disease in proximity to the primary tumor presents a frequent dilemma. The size and extent of the putative "risk zone" depend on a number of factors. These include any disturbance to tissue planes or barriers to tumor spread that may already be in place, including scars and drain sites. Such areas need to be included within an appropriate margin and should be identified with radiopaque markers at the time of the planning CT simulation acquisition. In the postoperative setting, strategic placement of clips by the surgeon at the time of resection may greatly enhance target delineation in areas at highest risk; this emphasizes once more the collaborative interaction required for the radiation therapy planning process.

In the preoperative setting, the gross tumor volume is typically represented by the radiologically defined tumor, but the acceptable volume margin remains problematic, depending on the results of the prior biopsy, the anatomic containment of the lesion, and the imaging characteristics of the lesion, including high T2 signal change evident on MR images beyond the overt tumor. This finding is thought to be due to increased water content and has therefore been labeled "peritumoral edema." However, it is not clear whether this MR imaging finding is actually the result of tissue edema, corresponding to the reactive zone noted earlier, or microscopic disease. Evidence from studies performed by our group suggests that tumor cells may reside in this area of high T2 signal (43), and it has been our policy to consider this region within the radiation therapy target volume.

Within the framework of uncertainty that has been described, our policy has been to use a 3.5-cm clinical target volume margin that encompasses the zone of potential microscopic involvement. In practice, this approximates to a traditional 5-cm field margin to permit the addition of a planning target volume margin, which accounts for machine setup uncertainty and the influence of lower dose due to the penumbral effects at the edge of the beam. The clinical target volume margin is located at the mentioned distance beyond any imaging abnormalities, including peritumoral edema, or areas of surgical disruption irrespective of grade or size of the tumor. However, practice is variable, and there have been no randomized trials in this area, to our knowledge.

In brief, modern radiation therapy approaches are confined to the use of megavoltage beams in the 4–10-MV range. These permit sufficient superficial tissue to be irradiated without undue skin irradiation, and the megavoltage photon ranges maintain the dose to bone to a minimum. Although accurate setup and immobilization are essential, there remains the possibility of day-to-day variance, resulting in interfraction variability and even intrafraction variability due to patient motion. It is customary in the contemporary era to deliver radiation therapy with some form of verification, which may include simple online radiation port verification on a daily or weekly basis. In some centers, sophisticated daily online tumor volumetric imaging is performed with radiation therapy units that have the capacity to acquire CT data, for comparison with the planning CT data set obtained at the initial CT simulation.

Various platforms exist to accomplish online image guidance, but their availability is not universal across all centers. Further technological enhancements may include the development of prompt fusion and autosegmentation algorithms to permit evaluation and replanning, in the event of an unacceptable change in target geometry as tumors swell or shrink during the treatment course. At our center, most patients are treated with the inverse planned intensity-modulated radiation therapy approach. This permits optimization of radiation therapy targeting and enhances the sparing of normal tissues. All patients also undergo daily image guidance, frequently performed with volumetric cone beam data acquisition, for assessment of soft-tissue deformation and bone positioning (a robust surrogate for limb position) during radiation therapy, since these may both have dosimetric implications.

Chemotherapy

The use of chemotherapy in the adjuvant setting to combat microscopic metastatic disease remains controversial. The standard of care for nearly all pediatric sarcomas involves chemotherapy. It is of proved benefit in patients with osteogenic sarcoma, Ewing sarcoma, and rhabdomyosarcoma. If chemotherapy is going to be adopted and have the same impact as radiation therapy and surgery in the management of soft-tissue sarcomas, more effective drugs have to be identified that clearly indicate efficacy in this disease. Unfortunately, the current status of this field remains disappointing. A large meta-analysis of 14 trials showed no effect of chemotherapy on survival. Additional data, including data from trials not included in the meta-analysis, appear to suggest some effect in that chemotherapy may be able to delay the development of metastases, but without actually preventing their eventual emergence (55). Therefore, at this time, routine use of chemotherapy is not the standard of care in most jurisdictions.

Conclusions

Optimal management of soft-tissue sarcomas requires a significant collaboration between radiologists, radiation oncologists, and surgical oncologists and often with medical oncologists for some subtypes of soft-tissue sarcomas. When this network is present, patients benefit from improvements in local control, function preservation, and limb preservation. As new techniques emerge for localization of soft-tissue sarcomas, functional characterization, molecular and physical targeting, and radiation delivery, the benefits to the patient of this collaboration continue to grow.

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Multidisciplinary Management of Soft-Tissue Sarcoma

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MR imaging is ideally suited to the imaging of soft-tissue masses (9,10) owing to its excellent soft-tissue contrast, multiplanar capabilities, and lack of ionizing radiation. It is invaluable for local staging and surgical planning and can play a role in diagnosis of soft-tissue sarcomas..

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Local evaluation of soft-tissue sarcomas is based on the location of the lesion, the lesion size, the amount of peritumoral edema, the compartmental extent of the mass, neurovascular involvement, and extension to the underlying bone or adjacent joint (13).

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The goal of surgery is a wide excisional margin, which is defined as 2 cm of skin, fat, or muscle, to resect the adjacent microscopic disease. Fascia is an excellent barrier to tumor spread, such that 1 mm of fascia can still be considered a wide margin.

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A planned positive margin is not associated with an increased risk of poor local control (42), as long as the remaining margins are adequate and adjuvant radiation therapy is included in the treatment regimen (Fig 17).

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Radiation therapy has an essential role in decreasing the need for amputation and improving functional outcome. With radiation therapy, the zone of microscopic disease around the gross tumor can be sterilized instead of resected, decreasing the size of the surgical margin required.