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THE ROLE OF RADIOLOGICAL METHODS IN THE DIFFERENTIAL DIAGNOSIS TUMORS OF SOFT TISSUE

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Abstract: Soft tissue sarcomas are rare and a heterogeneous group of neoplasms. Over the years imaging has played a crucial role in the initial staging, monitoring response to chemotherapy, and surveillance for recurrence. In the era of rapidly evolving individualized treatment due to evolving chemotherapies, increasing demand has been placed on the role of imaging in the management of this heterogeneous group. The rapidly evolving technologies in imaging are trying to keep up with the challenge, with development of newer strategies and hybrid imaging. However, many of these newer technologies are either not available or too costly, even in advanced countries, and hence their exact role remains uncertain. Due to this, and the vast diversity of sarcomas, the imaging appearance and management strategies vary and there is no universally accepted algorithm for the role of individual imaging technologies. The basic imaging techniques; however, remain the same, with these newer techniques and strategies vying for their roles in management. We review current imaging techniques and their role in the management of soft tissue sarcomas.
Keywords: Soft tissue sarcoma, computed tomography, magnetic resonance imaging, positron emission tomography.
Аннотация. Саркомы мягких тканей являются редкой и гетерогенной группой новообразований. Радиологические изображения с годами сыграл решающую роль в начальной стадии, мониторинге ответа на химиотерапию и наблюдении
для рецидива. В эпоху быстро развивающегося индивидуального лечения из-за развития химиотерапии, растущий спрос был возложен на роль визуализации в управлении этим образованиям. Быстро развивающиеся технологии обработки изображений стараются не отставать от вызовов.
Разработка новых стратегий и гибридных изображений. Однако многие из этих новых технологий либо недоступны, либо слишком дороги даже в развитых странах, и поэтому их точная роль остается неопределенной. В связи с этим, а также из-за огромного разнообразия сарком, внешний вид изображений и стратегии лечения различаются и не существует общепринятого алгоритма роли отдельных технологий визуализации. Базовый методы визуализации; тем не менее, остаются прежними, с этими новыми методами и стратегиями, соперничающими за их роли в управлении. Мы рассматриваем современные методы визуализации и их роль в лечении мягких тканей.
Ключевые слова: Мягкотканое образование, компьютерная томография, магнитно-резонансная томография, позитронно - эмисионная томография.
Долзарблиги. Юмшоқ тўқималар саркомаси кам учрайди ва ўсмаларнинг мухим гетероген гурухига кирувчи қисмидир. Йиллар давомида ўсмаларни тасвиралаш ўсманинг дастлабки босқчида, рецидив беришини ва даволаш эффектини кўрсати мухим саналган. Саркомаларни даволашда янги қатор дори воситалари чиққанлиги учун диагностика қилиш хам мухим ахамият касб этади. Tasvirlashda jadal rivojlanayotgan texnologiyalar yangi strategiyalar va gibrid tasvirni ishlab chiqish bilan qiyinchiliklarga dosh berishga harakat qilmoqda. Biroq, bu yangi texnologiyalarning aksariyati hatto ilg'or mamlakatlarda ham mavjud emas yoki juda qimmat va shuning uchun ularning aniq roli noaniqligicha qolmoqda. Shu sababli va sarkomalarning xilma-xilligi tufayli tasvirlashning ko'rinishi va davolash strategiyalari har xil va individual tasvirlash texnologiyalarining roli uchun umume'tirof etilgan algoritm mavjud

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emas. Asosiy tasvir texnikasi; ammo, bir xil bo'lib qoladi, bu yangi texnika va strategiyalar boshqaruvdagi rollari uchun kurashmoqda. Biz hozirgi tasvirlash usullarini va ularning yumshoq to'qimalar sarkomalarini boshqarishdagi rolini ko'rib chiqamiz.
Kalit so'zlar: Yumshoq to'qimalar sarkomasi, kompyuter tomografiyasi, magnit-rezonans tomografiya, pozitron emissiya tomografiyasi.

Soft tissue sarcomas are rare, accounting for approximately 1% of solid cancers in adults, and represent a heterogeneous group of disorders arising from mesenchymal tissue [1,2]. Imaging plays a crucial role in the initial staging, monitoring response to therapy, and surveillance for recurrence. Due to the large variety, distribution, and age range, the detailed imaging of each sarcoma is not possible to review and we will limit our discussion mainly to the extremity soft tissue sarcomas. We will highlight the common imaging modalities and their role in routine sarcoma imaging, and briefly review some of the newer imaging techniques that have potential further role in sarcoma imaging.

Computed tomography (CT) The current utility of CT in evaluation of soft tissue sarcoma is limited, due to concern for radiation, and less contrast resolution compared to magnetic resonance imaging (MRI). However, in the extremities, radiation is less of a concern compared to the trunk. Based on their ability to attenuate X-rays, the tissues can be broadly divided into fat, fluid, soft tissue, or calcification/ossification density. CT easily identifies fat in fat-containing lesions such as a simple lipoma. However, unless the lesion is composed entirely of homogeneous fat density with or without a few thin delicate septa that show no or mild enhancement, CT cannot reliably distinguish a lipoma/ lipoma variant from well differentiated liposarcoma. The latter commonly will contain nodular or globular nonfatty tissue and/or thick septations which often show enhancement [14]. It is better than plain radiographs and other modalities in detection of soft tissue mineralization and differentiating calcification from ossification [12]. One particular utility of this is to determine the pattern of mineralization which distinguishes myositis ossificans (zonal phenomena with dense peripheral rim of calcification) from a soft tissue sarcoma which lacks that pattern [6]. CT is better than plain radiographs in evaluation of cortical invasion but its accuracy in evaluating intramedullary invasion is less than that of MRI [15]. The majority of sarcomas have CT attenuation slightly less or similar to that of muscles. Contrast material may be used to detect lesions when they are isodense on a non-contrast study, distinguish a cystic from solid lesion, and evaluate internal vascularity and vascular invasion [12]. CT with contrast is the modality of choice for staging if MRI is contraindicated. CT angiography can provide an even more sensitive evaluation of vascular invasion . It is common modality to guide biopsy. Other advantages include three dimensional (3D) postprocessing techniques that can visually display the anatomy for surgeons. CT may overestimate the extent of soft tissue sarcoma, as it cannot distinguish the surrounding reactive inflammation and edema from the tumor itself [13]. One drawback of CT with contrast is the potential for allergic reaction. There was also concern regarding the potential nephrotoxicity of iodinated contrast material, but a recent meta-analysis showed no significant association of contrast enhanced CT with acute kidney injury [18]. When MRI is contraindicated or not available, CT is a useful modality for local surveillance [19]. It is comparable to MRI for detection of larger recurrence, greater than 15 cm3. But similar to static post-contrast MRI, it cannot distinguish granulation/fibrosis from residual or recurrent tumor [20]. CT is modality of choice for detection of lung metastasis [21]. Compared to plain radiographs, CT can detect lung metastasis earlier, and more accurately identify the number of lesions and segments of involvement for planning of metastasectomy [22]. CT perfusion is an emerging tool for the evaluation of tumor angiogenesis and can help monitor the therapy targeting tumor angiogenesis [23].

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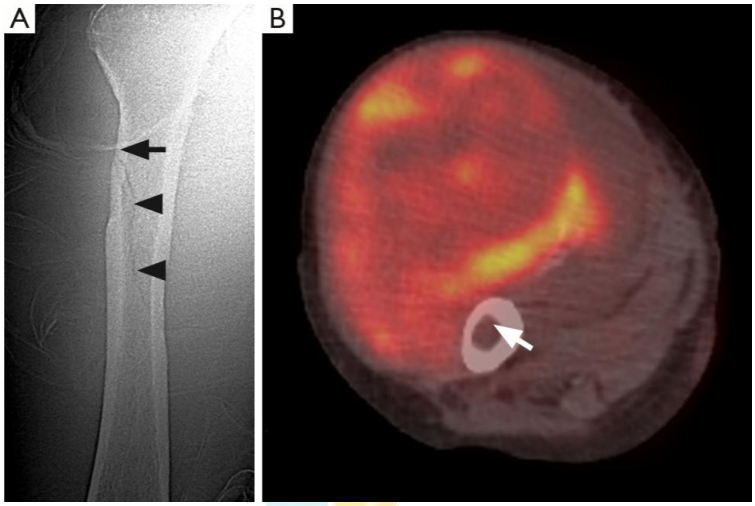


Figure 2. A 72-year-old female with right thigh mass. Plain radiograph (A) shows smooth pressure erosion and thinning of the lateral cortex (black arrow), with nondisplaced pathologic fracture (arrowheads). Fused 18F-FDG PET-CT image (B) shows a hypermetabolic mass (SUV max 25.1) with erosion and thinning of the cortex (white arrow). Previous biopsy at outside institute showed a high grade poorly differentiated spindle cell and epithelioid neoplasm.

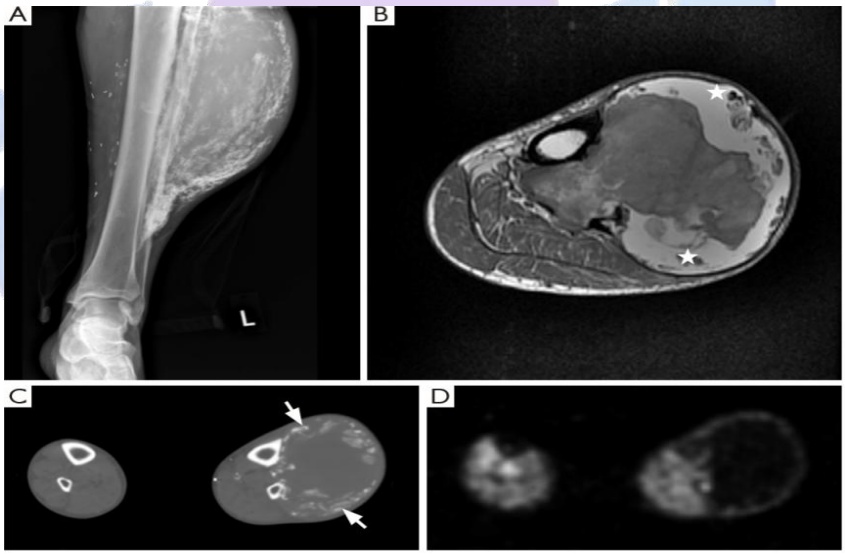


Figure 3 A 50-year-old man with left leg mass. Plain radiograph (A) of the leg shows a mass with peripheral mineralization. Axial T1 weighted (B) image shows heterogeneous mass, with areas of increased T1 signal (stars), which did not show enhancement (pre- and postcontrast T1 weighted with fat saturation (T1FS) images not shown). Due to concern for underlying neoplasm, 18F-FDG PET-CT (C and D) was performed which shows predominant peripheral calcification (arrows) seen with chronic hematoma or myositis ossificans. There was no hypermetabolism to suggest an underlying neoplasm. The mass was excised and confirmed to be organizing hematoma at histopathology.

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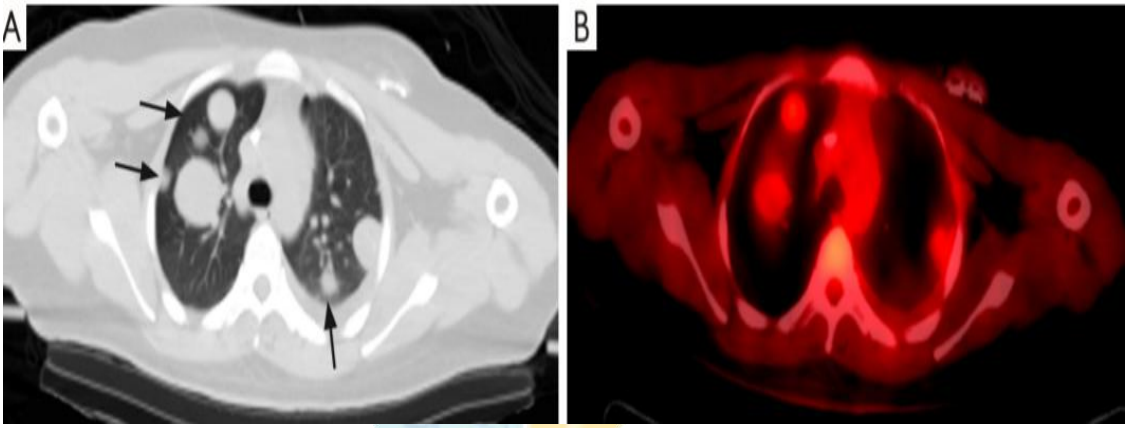
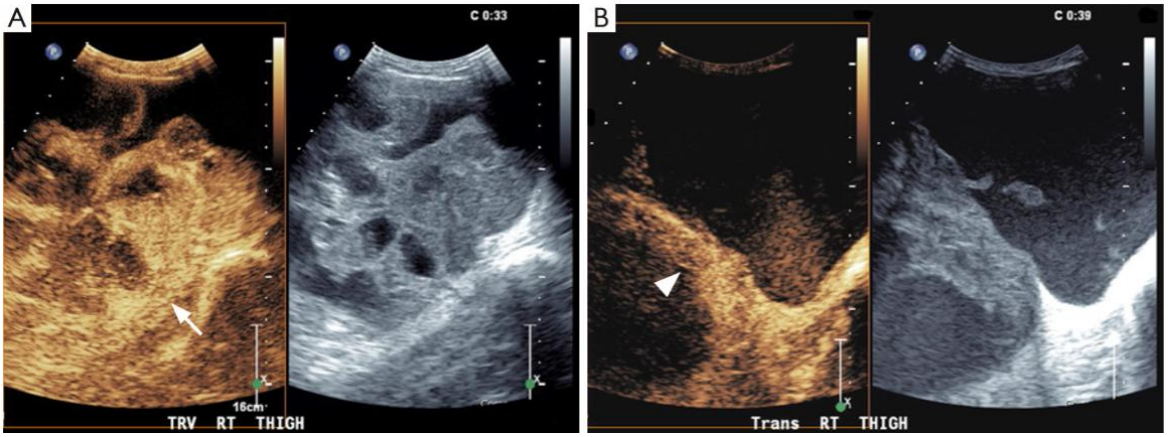


Figure 4 A 16-year-old female with synovial sarcoma of the leg. Axial CT portion of the 18F-FDG PET-CT (A) and fused 18F-FDG PETCT (B) images show multiple pulmonary metastases (SUVmax 1.7–2). Note multiple smaller metastases (arrows) that are not identified on the fused images.

Ultrasound (US). The main role of ultrasound is as an initial imaging study for evaluation of superficial soft tissue mass. Most superficial extremity soft tissue masses are benign with lipoma being the most common. US confirms the presence of the mass, measures its dimensions and depth, evaluates its internal echotexture and vascularity, and can differentiate a few typical benign tumors and other non-neoplastic lesions such as ganglion cysts from others which need further evaluation [24]. Ultrasound is widely available and cheap and does not have the side effects of radiation [25]. Color or power Doppler is essential to evaluate the presence of internal vascularity, and differentiate between a cyst and a cystic appearing solid mass [26]. Combination of grayscale and color Doppler studies can divide the tumors into cystic, solid, or mixed solid and cystic (complex). Simple cystic masses such as ganglion and synovial cysts are well defined, anechoic with posterior acoustic enhancement, and no internal vascularity on Doppler studies [27]. Solid and mixed solid and cystic masses have broad differential and include non-neoplastic lesions such as hematoma and abscess, benign neoplasms such as lipoma and nerve sheath tumor, and sarcoma [28]. In general, if the appearance does not conform to the well-recognized US appearance of a benign soft tissue mass such as lipoma or nerve sheath tumor, then it needs to be evaluated further with MRI or biopsied (Figure 5). Evaluation with US, however, can be limited in a large lesion, deep lesions, or when the lesion is behind bones which preclude penetration of the ultrasound waves. For superficial masses, the sensitivity and specificity of identifying malignancy is 94.1% and 99.7% respectively [29]. While the sensitivity and specificity of US in distinguishing benign from malignant soft tissue masses is high, the accuracy is dependent on pretest probability.

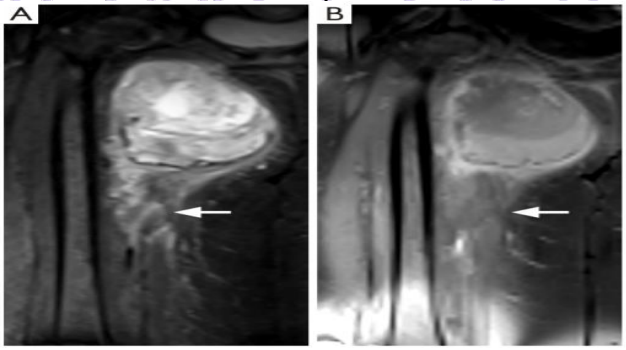


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Figure 6. A 55-year-old man with sarcoma of the right leg. Before starting neoadjuvant chemotherapy, CEUS image (A) at peak enhancement shows marked enhancement of the tumor (arrow) with a few small areas of necrosis. Following neoadjuvant chemotherapy (B) there is marked decrease in vascularized viable tissue (arrowhead) with large areas of cystic tumor necrosis.

The high accuracy has been attributed to the high pretest probability of the superficial mass as being benign, since benign masses far outnumber malignant masses. US is not only operator dependent but also needs a radiologist experienced in sonography to correctly interpret the findings [28-30]. US is the preferred modality to guide a biopsy (28). Other interventional use of US includes wire localization of a soft tissue mass prior to resection. US is a useful modality for detection of tumor recurrence, particularly when CT scan and MRI are limited due to metallic hardware [19]. As with MRI, it is limited in the early postoperative period. More recently, with wider availability of US contrast material, the role of US in the management of sarcoma has increased. Similar to dynamic contrast enhanced MRI (DCE-MRI), dynamic contrast enhanced US (CEUS) is used to evaluate the vascularity and perfusion of the lesion. Unlike DCE-MRI, the contrast remains in the intravascular compartment and does not diffuse into the interstitium. Microbubbles of an average size of 0.5– 10 micrometer are injected intravenously and its passage through the tumor vessels is monitored and plotted as a time intensity curve. As with DCE-MRI, in CEUS, viable tissue in malignant tumors showed earlier enhancement (time to peak enhancement) compared to benign lesions .

A classification system based on enhancement pattern (P1-nonenhancement or thin peripheral rim-like enhancement, P2-peripheral enhancement with confluent areas of nonenhancement, P3-inhomogeneous or patchy enhancement, and P4-homogeneous enhancement) has been proposed with P2 or P3 pattern seen with malignant lesions [33,34]. In a preliminary study, CEUS showed potential to monitor the response of neoadjuvant chemotherapy, as seen by decreased enhancement suggesting less viable tissue and increased central areas of nonenhancement suggesting necrosis (Figure 6) [35]. Advantages include less cost compared to contrast enhanced CT and contrast enhanced MRI. US elastography is being investigated for its role in the evaluation of soft tissue masses and sarcoma. It is a method of evaluating tissue stiffness. Ultrasound waves transiently compress and deform tissue and the degree of displacement is measured giving insight to its mechanical property. In general, malignant soft tissue tumors are harder and stiffer and have less elasticity compared to benign soft tissue tumors. One study looking at the strain ratio (ratio of elasticity of the lesion to reference tissue at the same depth) showed that the strain ratios of malignant soft tissue tumors were lower than those of benign tumors [36]. Another study looking at the role of strain elastography found it to be useful in differentiating malignant from benign masses with a sensitivity and specificity of 93.8% and 80.5% respectively [37]. However, another recent study with 105 masses looked at the role of shear wave elastography in evaluating musculoskeletal soft tissue masses and concluded that there was no statistically significant association between shear wave velocity and malignancy, and that there is no additional role for this technique over conventional US [38].



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Figure 7 A 64-year-old woman with right thigh mass biopsy proven to be undifferentiated pleomorphic sarcoma. Zoomed coronal STIR (A) and post-contrast T1FS (B) images of the right thigh show peritumoral edema without enhancement (arrows). Static post-contrast T1FS images may not be helpful in distinguishing peritumoral edema from tumor. Peritumoral edema is resected along with the mass as it may contain island of viable tumor cells. (Note the band of increased signal at the inferior aspect of image B which is an artefact due to inhomogeneous fat saturation often seen with frequency selective fat saturation technique).

Magnetic resonance imaging (MRI)

MRI is imaging modality of choice for evaluation of soft tissue sarcoma, particularly to determine the local extent of the lesion. Lack of ionizing radiation, multiplanar imaging capability, and excellent tissue contrast makes it particularly suitable for evaluation of characteristics and extent of the lesion [4]. MRI can not only distinguish between simple cystic lesions and solid masses but can further help narrow the differential and point towards sarcoma as the potential etiology. MRI can evaluate the size and extent of the tumor and identify invasion of the compartments and important structures such as nerves, vessels and joints. A combination of fat sensitive (T1 weighted) and fluid sensitive (proton density weighted/T2 weighted) sequences without and with frequency selective fat saturation are utilized for imaging. Short tau inversion-recovery (STIR) sequence may replace fat saturation fluid sensitive sequences, and has the advantage of more homogenous fat suppression but has lower signal-to-noise ratio and is susceptible to motion artifact. The T1 weighted sequences show fat, melanin and methemoglobin as high signal intensity. The signal from fat suppresses with frequency selective fat saturation, while that from melanin and methemoglobin does not [4]. On STIR, the signal from tissues with T1 relaxation times similar to that of fat such as melanin and hemorrhage can also suppress [39]. Most sarcomas have high signal on fluid sensitive sequences. Surrounding reactive peritumoral edema is also hyperintense but has normal or very little T1 signal abnormality (Figure 7) [40]. Despite this, the two are difficult to distinguish, and static post contrast imaging is also not helpful in this regard [41]. T2* gradient echo imaging, although rarely performed, can show hemosiderin as signal loss with blooming [42]. Evaluation of static T1 weighted images after intravenous administration of gadolinium-based contrast material, when the contrast is in equilibrium between the interstitium and plasma, is a standard practice for evaluation of a soft tissue mass. The use of contrast material may be contraindicated either due to allergy or risk of nephrogenic systemic fibrosis. Whether to use fat saturation or not depends on individual preference, but subtraction images, where the precontrast T1 weighted images are digitally subtracted from post-contrast images, are helpful when evaluating for subtle enhancement. For this, it is imperative to obtain a baseline precontrast T1 weighted sequence and use the same parameters for post-contrast imaging in the same plane. Contrast administration helps in identification of vessels and their direct invasion by tumor. It gives insight in to tumor vascularity [43]. The area with most intense enhancement is more likely to represent the most aggressive and highest grade of the tumor [44].

Dynamic contrast enhanced MRI (DCE-MRI). A dynamic contrast enhanced study, utilizing gradient echo sequence, is used for evaluation of enhancement pattern of the tumor over the initial 2–3 minutes following a rapid intravenous bolus injection of gadolinium based contrast material followed by a saline flush. Quantitative timeintensity curves are generated by operator dependent placement of region of interest (ROI) (Figure 8). DCE-MRI gives information of tissue perfusion, vascularization, capillary permeability and volume of interstitial space that is not available with static imaging [45]. It helps in assessment of viable tissue, and identifying the area of most rapid enhancement which is potentially the site of highest grade in the tumor and thus a preferable site of biopsy [44,46]. It differentiates between the tumor and the peritumoral edema (the latter enhances later) that is not possible with static post-contrast images [44]. Although there is significant overlap, it can help differentiate a malignant soft tissue tumor from a benign soft tissue tumor, or at least narrow the differential diagnosis [47].

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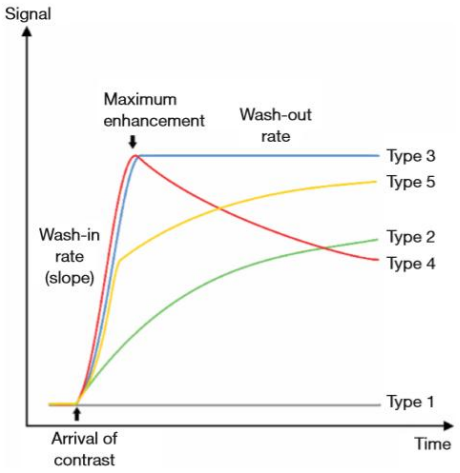


Figure 8 Dynamic contrast enhanced MRI-time-signal intensity curve. Time intensity curve shows the time when the enhancement begins, the enhancement rate during the first pass (slope), maximum enhancement, and the washout rate. A typical malignant lesion will have early, rapid and intense enhancement with washout of contrast (type 4), a typical benign lesion will show slow and gradual enhancement (type 2), while a cyst or hematoma will show no enhancement (type 1). Type 3 enhancement is seen in benign vascular tumors, desmoid tumors and some malignant tumors. Type 5 enhancement is seen in tumors after chemotherapy or radiation therapy, and myxoid tumors.

In one study, a combination of maximum relative enhancement in first minute, and in second minute, and steepest slope of enhancement had an overall accuracy of 95.5% in differentiating malignant from benign soft tissue tumors [48]. Malignant tumors show areas of necrosis, and peripheral or inhomogeneous dynamic contrast enhancement that is early, rapid and intense (within 6 seconds after arterial enhancement) followed by a plateau or washout [47,49,50].
Highly vascularized/perfused benign lesions such as nerve sheath tumors and desmoid-type fibromatosis may have characteristics similar to malignant tissue [48,50]. After starting neoadjuvant chemotherapy, DCE-MRI is useful in monitoring the tumor response identifying viable tumor tissue (Figure 9) [44,46]. A poor response may affect the feasibility of curative surgery, and necessitate a change of chemotherapy. Later, during surveillance after surgery, it can help identification of a residual or recurrent tumor, which commonly shows early, rapid and intense contrast enhancement, and differentiate it from inflammatory change and pseudotumor (Figure 10) [44,46]. Radiation-induced pseudotumor (also known as inflammatory pseudotumor or pseudomass) is an ovoid illdefined area of enhancement, without or with little mass effect. Caution should be exercised as early granulation tissue may mimic viable tumor.
Diffusion weighted imaging (DWI). It provides a qualitative and quantitative assessment of tissue cellularity and cell membrane integrity. DWI measures Brownian (random) motion of the water molecules in the tissue [51]. The three main tissue compartments include the extracellular compartment, intracellular compartment and the intravascular compartment (microcirculation-perfusion). In general, with increased cellularity and membrane integrity, there is decreased size of the extracellular compartment, and higher restriction of motion of the water molecules. On the other hand, necrosis leads to membrane breakdown leading to expansion of the extracellular space, and thus increasing the diffusion [52]. A map of apparent diffusion coefficient (ADC) is generated as a quantitative measure of diffusion at each pixel [51]. There is larger motion of the water molecules in the intravascular compartment, compared to the other compartments. Its contribution to the total diffusion depends on the degree of vascularization of the tissue. In highly vascularized tissues, as seen in malignancy, this increases the ADC values. Diffusion images corrected for perfusion eliminates or decreases the contribution of perfusion to the

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overall diffusion [51-53]. The DWI images and the ADC map images are read together with increased signal on DWI and decreased signal on ADC map images indicating restricted diffusion. Overall, DWI provides the measure of tissue cellularity and membrane integrity rather than whether the lesion is malignant or benign. Highly cellular tissues restrict diffusion more than less cellular tissue and have lower ADC values. This is reflected as higher signal on DWI map images but decreased signal on ADC map images. Malignant lesions, being more cellular and with relatively larger cell size, restrict diffusion more than benign lesions (particularly with myxoid component) and thus can potentially differentiate them from benign lesions (Figure 11) (51,54). However, as with dynamic contrast enhancement, there is considerable overlap between the two (55). DWI can help identify residual or recurrent tumor, and differentiate it from a radiation-induced pseudotumor or postoperative granulation tissue or scarring (56). In response to chemotherapy, there is increase in diffusion related to the tumor necrosis (51,57). Magnetic resonance spectroscopy (MRS) Proton (H1) MRS is not as frequently used in sarcoma imaging as that in brain tumors, and is still considered largely a research tool with only a few articles published evaluating its utility in differentiating benign from malignant lesion, monitoring treatment response, and postsurgical follow up (58,59).

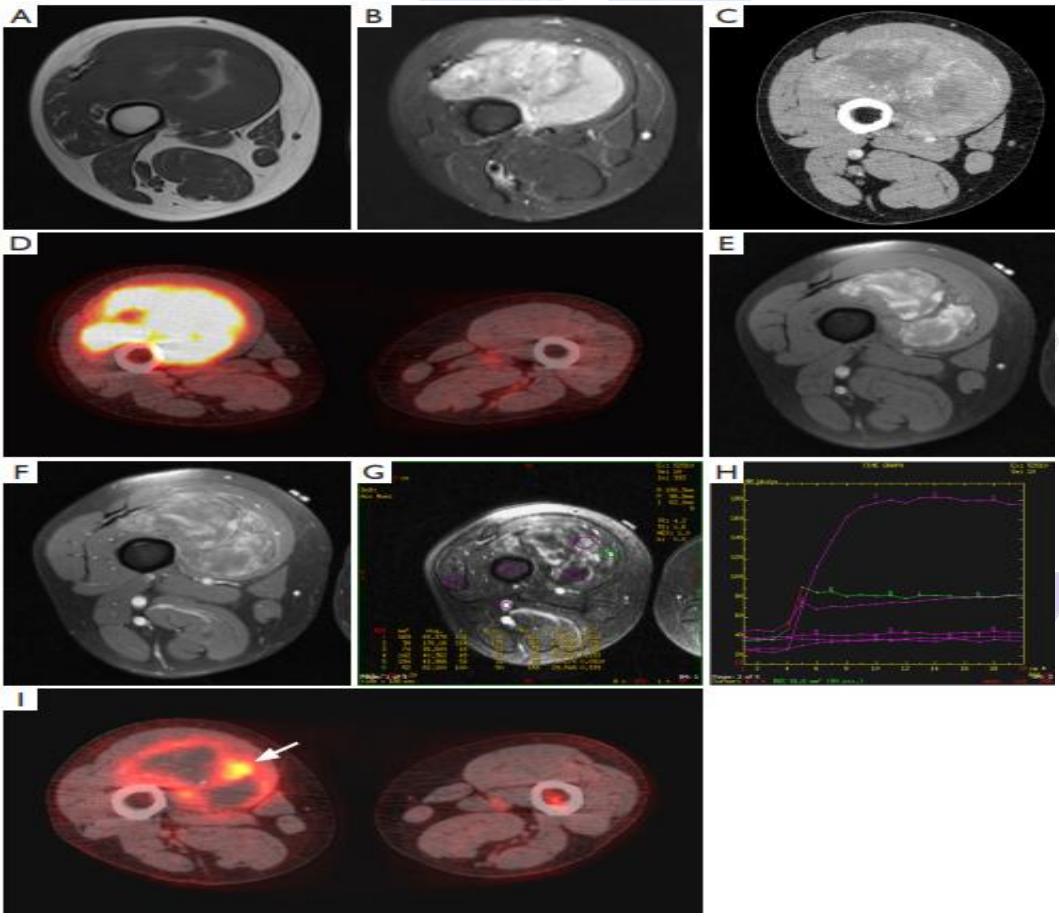


Figure 9 A 31-year-old man with right thigh mass proven to be synovial sarcoma. Axial T1 weighted (A) and STIR (B) MRI images of the initial study performed at an outside institute without administration of intravenous contrast shows mass in the anterior compartment of the right thigh. Frequency selective fat saturation sequence was not obtained which makes it difficult to distinguish fat from hemorrhage. Post contrast axial CT image (C) obtained close to the initial presentation shows heterogeneously enhancing mass and the fused 18F-FDG PET-CT image (D) shows intense hypermetabolic activity (SUVmax 8.2). Neoadjuvant chemotherapy was given. Subsequent axial T1FS (E) and post contrast T1FS (F) MRI images show areas of hemorrhage

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seen on precontrast image, and heterogeneous areas of enhancement after contrast. DCE-MRI images (G and H) show few viable areas of tumor with early moderate enhancement with plateau (green line). On fused 18F-FDG PET-CT image (I), there is decrease in metabolism (SUVmax 3.1) with central areas of hypo- absent metabolism suggesting favorable response. Note area of more active metabolism (arrow) indicating viable tumor. This corresponds to the region of viable tumor, thus providing complementary information as that with DCE.

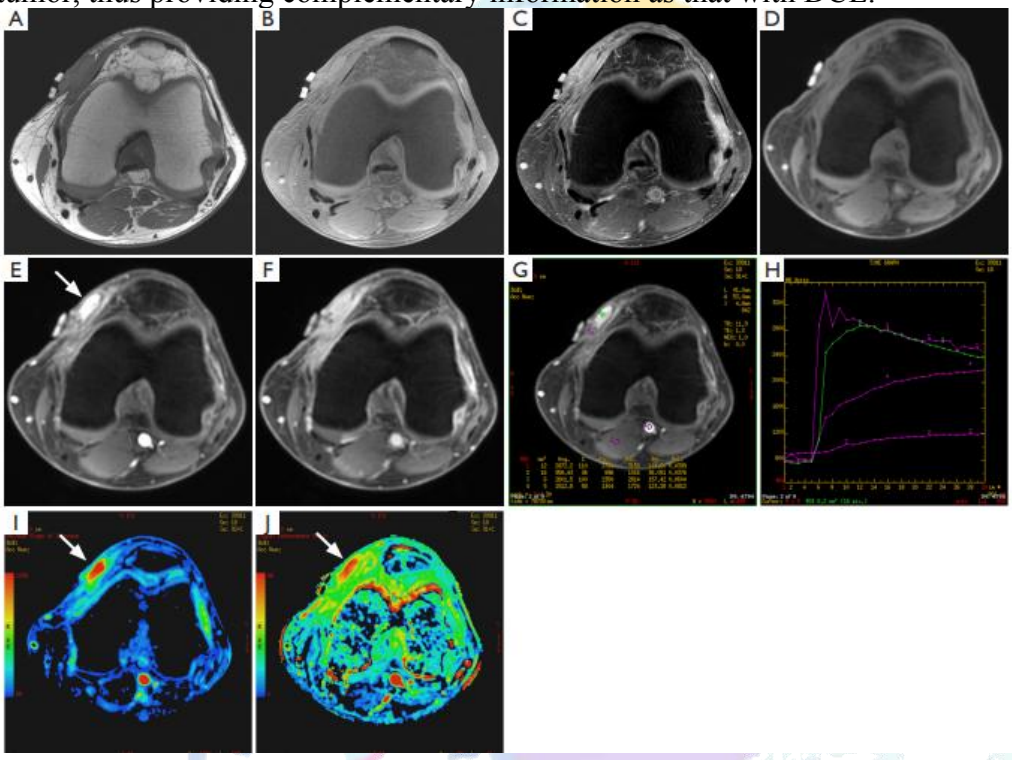


Figure 10 A 64-year-old man with history of marginal resection of an undifferentiated pleomorphic sarcoma at an outside institute. Axial T1 weighted (A), precontrast T1FS (B) and post-contrast T1FS (C) images show isointense region of abnormality on precontrast examination that enhances on post-contrast study. It is not possible to differentiate the residual tumor from surrounding post-surgical granulation and scarring. Three images from a dynamic sequence-before (D), during early enhancement phase (E), and in the delayed phase (F) show early intense enhancement of the residual tumor (arrow) compared to the surrounding granulation and scarring. On the delayed phase the enhancement of the two becomes similar to each other, with decrease in intensity of the residual tumor and increase in intensity of the granulation/scarring. The parametric maps are generated by manually operator dependent placement of regions of interest (G) (1: artery, 2: muscle, 3: tumor, 4: granulation tissue) and can be displayed as time-signal intensity curve (H), or as maximum slope of enhancement (I) and signal enhancement ratio (J) maps. Note early enhancement and wash-out of the tumor (green line in H)

However, the principles remain the same. There is increase in choline, a membrane phospholipid, in tissues with increased cell membrane turnover such as sarcoma (Figure 12) (59,60). Its concentration can be measured in absolute terms or relative to noise or creatine. Care is taken to avoid including areas of necrotic or hemorrhagic foci, gas, calcification, bone and muscle in the sample. A discrete elevated choline peak can diagnose malignancy with a sensitivity and specificity of 88% and 68% respectively, while a very low concentration (with known sarcoma with a symptomatic bone metastasis, it can identify additional areas of bone involvement that can be targeted for biopsy, if necessary.

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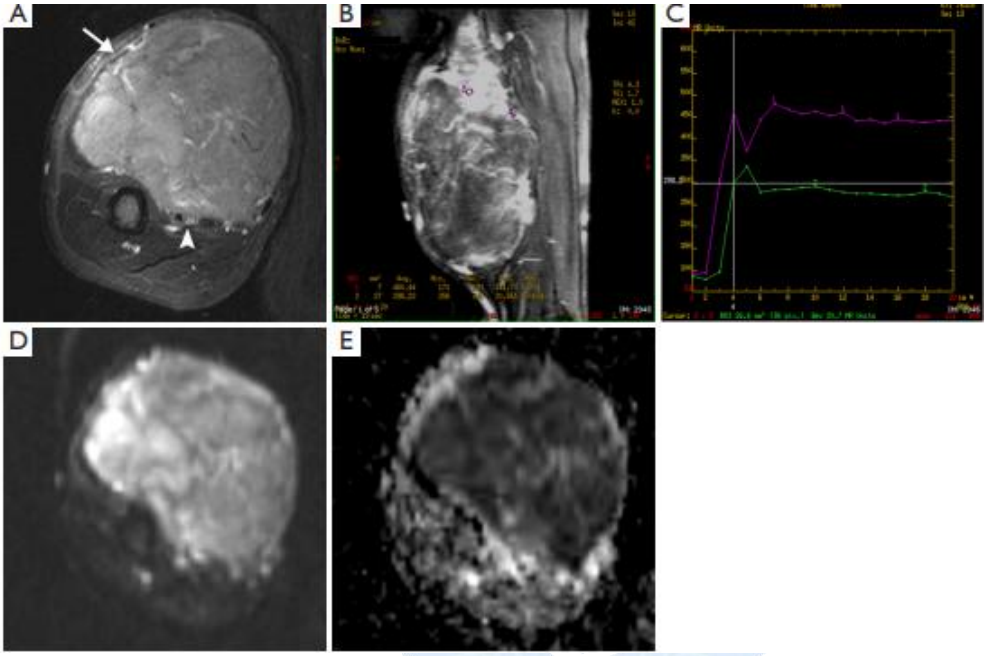


Figure 11 A 65-year-old man with high grade pleomorphic sarcoma of the right arm and extrapulmonary metastasis (not shown) was treated with chemotherapy. Axial post-contrast TIFS MRI image (A) shows enhancing mass (arrow) abutting the brachial neurovascular structures (arrowhead). On sagittal DCE-MRI (B and C), there is early moderately intense type-3 tumor enhancement (green curve). DWI (D) and ADC map (E) images show increased signal on DWI and decreased signal on ADC suggesting restricted diffusion. The relative lack of necrosis and the findings on DCE-MRI, and DWI and ADC map images are compatible with poor chemotherapy response

In addition, it can draw attention to an asymptomatic metastasis that has potential risk of pathologic fracture. 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET-CT) 18F 2-fluoro-2-deoxy-D-glucose (18F-FDG) positron e m i s s i o n t o m o g r a p h y h a s b e e n e v a l u a t e d f o r characterization and grading of soft tissue sarcoma. 18F-FDG, being a glucose analogue, is actively transported in to the tumor cells depending on their rate of metabolism, and standardized uptake value (SUV) acts as the measure of the degree of metabolism.

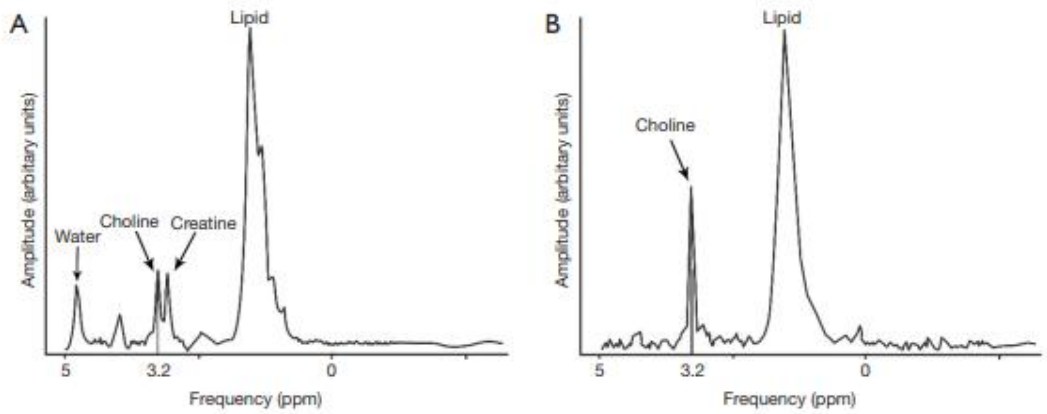


Figure 12 MR spectroscopy (MRS) of normal muscle (A) demonstrates various peaks of metabolites, which are separated by their resonance frequency in parts per million (ppm), with the amplitude dependent on concentration. MRS of a malignant tumor (B) shows elevation of the choline peak relative to background noise.

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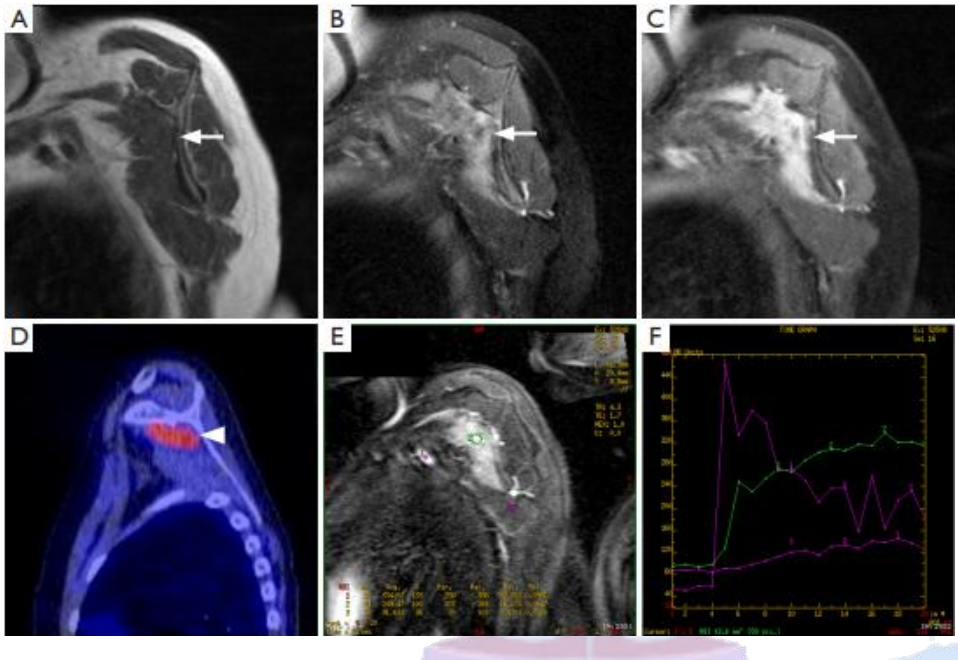


Figure 13 A 13-year-old boy with left shoulder pain. Sagittal T1 weighted (A), T2FS (B) and post contrast T1FS (C) images show isointense T1, heterogeneous slightly hyperintense T2 weighted with fat saturation (T2FS), enhancing mass (arrows) in the subscapularis fossa infiltrating the muscle. Sagittal fused 18F-FDG PET-CT image of the left shoulder (D) shows increased metabolism (arrowhead) with SUVmax of 2.7, raising a possibility of malignant lesion. However, time signal intensity-curve on DCE-MRI image (E and F) shows early moderate but progressive enhancement (green line). Open surgical biopsy was performed due to the location of the lesion which at pathology was desmoid-type fibromatosis.

18F-FDG uptake correlates with the histologic grade of the tumor, with intermediate to high grade tumors having higher uptake than low grade tumors (66). There is strong correlation between SUV and pathological grade, cellularity, cell proliferation as indicated by mitotic activity and MIB-1 labeling index, and p53 overexpression (67). The degree of uptake has also been used to discriminate between benign lesions and soft tissue sarcomas. In a meta-analysis by Ioannidis, using an SUV of 2.0 as a cutoff, and higher SUV indicating malignant lesion, the sensitivity and specificity of 18F-FDG PET are 87% and 79% respectively, while using the SUV of 3.0 they are 70% and 87% respectively (66).

There is however significant overlap between low grade sarcomas and inflammatory and benign highly cellular or metabolically active lesions (Figure 13) (66). Thus, in an individual case the utility of 18F-FDG PET may be limited, unless the SUV is significantly high. Pretreatment SUV has been shown to correlate with outcome, with high SUV associated with shorter disease-free interval and overall survival (68). SUV and heterogeneity of uptake were found to be independent predictor of survival, and disease progression and outcome respectively (69). Pretreatment tumor necrosis as determined by 18F-FDG PET-CT has also been shown to correlate with prognosis and mortality in sarcomas (70). The 18F-FDG PET-CT also helps staging by evaluating the extent of the disease. It can look for additional lesions and distant spread including that to lymph nodes, bones, and lungs (Figure 14). 18F-FDG PET-CT can identify increased metabolism in normal size lymph nodes [70]. It is necessary to emphasize, that metastasis to lymph nodes is extremely uncommon in sarcomas except for a few (e.g., rhabdomyosarcoma, angiosarcoma, clear cell sarcoma, epithelioid sarcoma, synovial sarcoma) [62,63]. In regard to lung metastases, 18F-FDG PET has lower sensitivity but higher specificity compared to CT alone (Figure 3). This is likely related to limited resolution of 18F-FDG PET

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and lack of good blood supply compared to the original tumor [64,65]. Overall, 18F-FDG PET-CT is a valuable tool in initial staging of the sarcoma, but according to the American College of Radiology appropriateness criteria, the role of 18F-FDG PET-CT in the evaluation of soft tissue sarcoma is not yet fully established and it is not typically used for initial assessment of soft tissue mass. It can be used to identify the target area of biopsy, detect metastasis, assess treatment response (Figure 15), and distinguish hemorrhagic tumor and hematoma (Figure 2) [16,66]. As with the dynamic contrast enhanced ultrasound and dynamic contrast enhanced MRI, 18F-FDG PET is useful in evaluation of response to chemotherapy [67,68]. It is an excellent modality for evaluation of local recurrence and metastasis, particularly the former when MRI and CT are limited by metal artifact. The main drawback of 18F-FDG PET-CT is related to the radiation exposure and availability. Its routine use however needs to be explored further with emphasis on cost benefit analysis and outcome measures, particularly with advances in other modalities with less or no radiation [70].

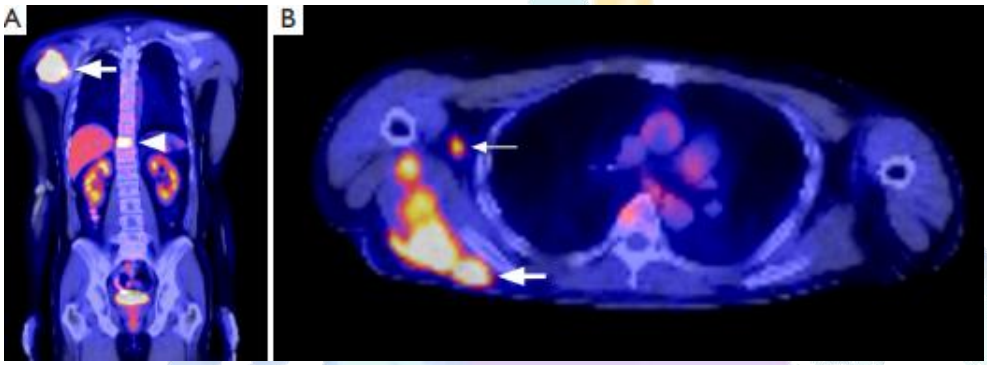
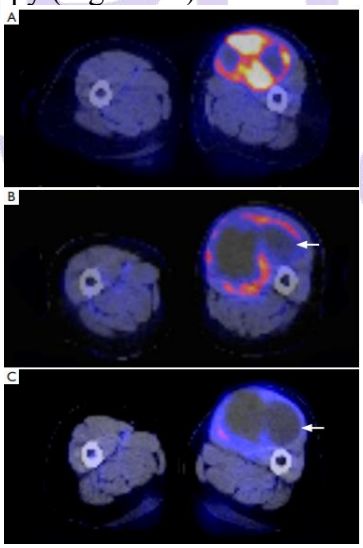


Figure 14 A 50-year-old man with parascapular rhabdomyosarcoma. Coronal (A) and axial (B) fused 18F-FDG PET-CT images show a hypermetabolic right shoulder mass (thick arrows, SUVmax 13.9) and spinal metastasis (arrowhead, SUVmax 7) and lymph node metastasis (thin arrow, SUVmax 5.7). 18F-FDG PET-CT upgraded the staging in this case.

18F-FDG PET-MRI, a newer imaging technique which promises to combine the best of 18F-FDG PET and MRI, is promising but further studies are needed to establish its role in evaluation and treatment of soft tissue sarcoma (60,61). Direct arteriography Direct arteriography currently has very limited role in evaluation of soft tissue sarcoma, having been replaced by other imaging modalities. It is performed as a part of vascular intervention procedure such as embolization or isolated limb perfusion chemotherapy (Figure 16).



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Figure 15 A 61-year-old woman with left thigh mass. Fused 18F-FDG PET-CT image (A) at the time of initial presentation shows areas of very high metabolism (SUVmax 14.9). Following neoadjuvant chemotherapy, on 18F-FDG PET-CT obtained approximately at 3 months (B) and 5 months (C) after the initial study, there is progressive decrease in metabolism with SUVmax of 10.2 and 3.2, respectively. Note enlargement of the mass. There may be paradoxical increase in size due to hemorrhage and necrosis, as in this case seen as large area of central photopenia (arrows).

Image guided biopsy Adequate tissue representing different components of the sarcoma is a must for complete pathologic evaluation which includes special techniques such as immunohistochemistry, and molecular testing. While necrosis is a feature of malignancy, biopsy sample comprising only or mostly of necrotic tissue is inadequate for complete evaluation. Although the debate is still going on as to whether core needle biopsy or open biopsy should be performed, fine needle aspiration (FNA) biopsy has limited role and its use is mostly limited to confirm local recurrence or metastasis that usually mimics the histology of original tumor.

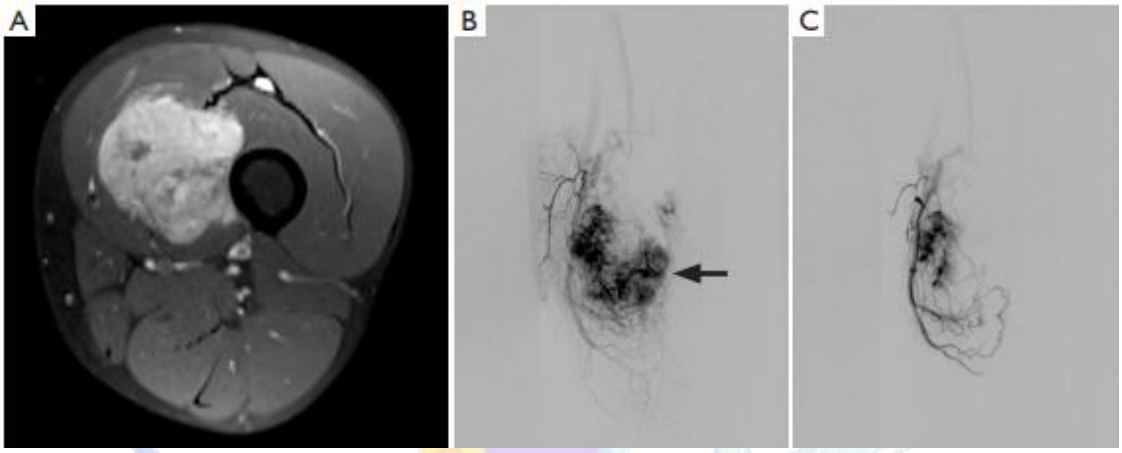


Figure 16 A 32-year-old man with alveolar soft part sarcoma. Post-contrast axial T1FS (A) image shows an intensely enhancing hypermetabolic mass. At open biopsy the mass bled excessively and preoperative embolization was performed. Initial angiographic image (B) shows the vascularity of the mass (arrow) which decreased as seen on post embolization image (C).

It yields only small amount of tissue, does not allow for the evaluation of tissue architecture, and specimen may not be adequate for additional studies such as molecular testing (21,63). Image guided core needle biopsy can be performed with less complications, morbidity and cost compared to open biopsy, giving good tissue sample. There is also less risk of contamination with coaxial technique and although the potential for inadequate sampling remains, it can be repeated with the accuracy after repeat biopsy as high as 94% (64). With large gauge biopsy needles, inadequate sampling is uncommon, particularly if a cytopathology technologist is immediately available to evaluate the sample.

Open biopsy is costly with complication rates up to 16%, but is more accurate in determining malignancy and exact diagnosis (grade and subtype) compared to core needle biopsy with accuracy close to 100% (45,66). The choice of needle type and gauge is dependent on the radiologist preference and location of the lesion in relation to vital structures. Both ultrasound and CT scan can be used for biopsy depending on the radiologists' preference, site of the mass, and location of the potential highest-grade component.

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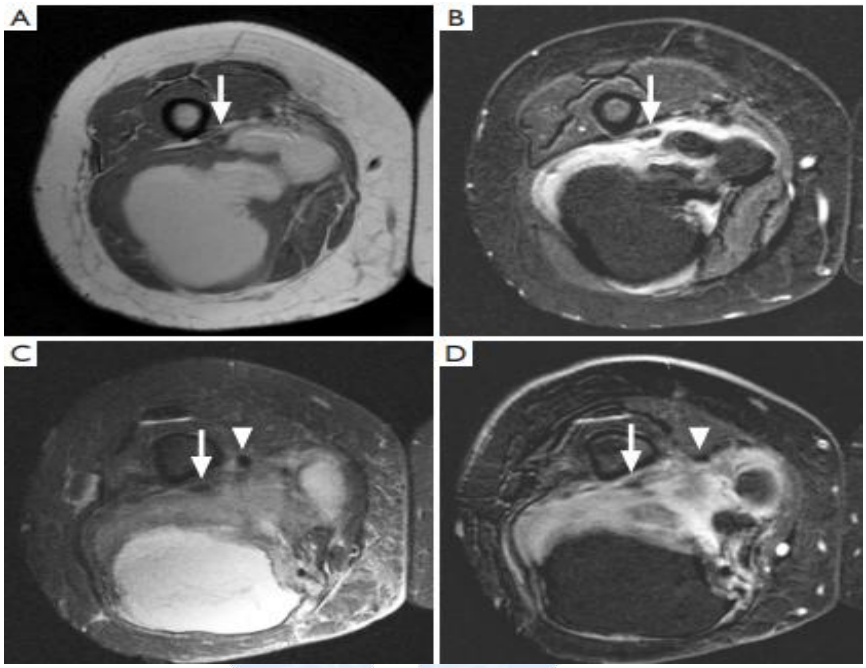
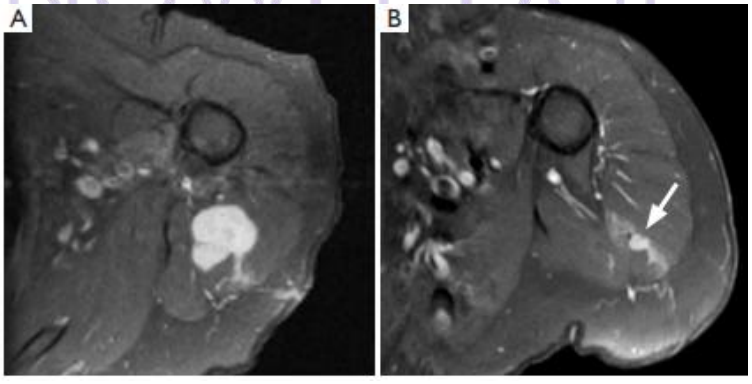


Figure 17 A 77-year-old woman with extraskeletal osteosarcoma. Axial T1 weighted (A) and post-contrast subtraction (B) images show the mass encircling the sciatic nerve (arrows). At a slightly different level, axial STIR (C) and post-contrast subtraction (D) images show edema and enhancement encircling the artery by greater than 180 degree (arrowheads). At surgery the nerve and artery were involved by the tumor at multiple sites and on frozen section of perivascular tissue, tumor cells were present.

The biopsy should be performed after imaging since hemorrhage and edema/inflammation associated with biopsy can alter the imaging appearance of the tumor (57). Prior imaging can identify the potential site of highest tumor grade which needs to be targeted. The biopsy of a suspected soft tissue sarcoma should only be performed after consultation with an orthopedic surgeon, to determine the best approach to biopsy. While the shortest path to the lesion is preferred, crossing an uninvolved compartment as well as important vessels, nerves, joint and vital structures should be avoided (57). The biopsy tract is resected en bloc along with the mass (53). Role of imaging Imaging establishes the presence and location of the soft tissue mass, identifies a definitely benign lesion and separates them from indeterminate or possibly malignant lesions, narrows the differential based on imaging characteristics of the tumor, and identifies the local extent (local staging) of the lesion and its relation to the compartment anatomy, vessels, nerves, bone and joint. Its role in biopsy has already been discussed. Once a diagnosis of soft tissue sarcoma is established by biopsy, imaging is used to identify distant metastasis and stage the tumor.



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Figure 18 Axial post-contrast image (A) at initial presentation shows a mass proven to be an undifferentiated pleomorphic sarcoma. On post contrast T1FS image of surveillance MRI (B) an enhancing nodule (arrow) was seen suggesting tumor recurrence. However, at open biopsy this showed reactive changes only with no residual or recurrent sarcoma

Imaging helps monitor response to neoadjuvant chemotherapy and once definitive surgery is performed, is used for monitoring for local recurrence and distant metastasis. Apart from the imaging appearance and local invasion, specialized imaging techniques such as DCE-MRI and DWI and in selected cases 18F-FDG PET-CT helps identify the potentially malignant lesions. As discussed, while no individual or a combination of features can categorize the lesion as benign or malignant, a combination of features can suggest the possibility of a lesion being malignant. Overall, in one study looking at the value of MRI for differentiating malignant from benign soft tissue masses, T1 signal heterogeneity, absence of low signal on T2, and mean diameter >33 mm showed highest sensitivity, while necrosis, bone or neurovascular involvement or metastases, and mean diameter >66 mm showed highest specificity (48). Liposarcomas, leiomyosarcomas, undifferentiated pleomorphic sarcomas, synovial sarcomas, myxofibrosarcomas and fibrosarcomas are the most common sarcomas and make up about two thirds of the soft tissue sarcomas. There is considerable overlap of imaging characteristics of benign and malignant lesions and they cannot be reliably differentiated (47). In general, benign soft tissue tumors far outnumber malignant soft tissue tumors (49). Imaging evaluation and characterization of mass While characterizing tissue type is and will remain the domain of pathology, which is the gold standard, a small list of differential diagnosis needs to be provided depending on the imaging features. Based on signal characteristics, lesions can be classified into four broad categories. The first group has signal characteristics consistent with fat (high signal on T1 weighted sequence), where the tissue follows the signal of subcutaneous fat or yellow marrow on all pulse sequences, and the signal suppresses equally to fat with frequency selective fat saturation and STIR imaging. In sarcoma imaging, this is consistent with liposarcoma when benign fat containing lesions such as lipoma, lipoma variants and hemangioma are excluded. Well differentiated liposarcomas are predominantly fat with presence of thick (>2 mm) enhancing septations and nonfatty tissue. Dedifferentiated liposarcomas also have variable amount of nonfatty tissue. Myxoid liposarcomas have typical appearance of myxoid tissue (see later). Areas of round cell component within them have lower signal than the myxoid component on fluid sensitive sequences. Pleomorphic liposarcomas are high grade liposarcomas with imaging appearance similar to other sarcomas but the presence of identifiable fat still helps narrow the differential. However, some higher grade liposarcomas may not have visible fat (5). The second group also has high signal on T1 weighted sequence but also has high or intermediate signal on T2 weighted sequence. This group represents tissue such as subacute blood as seen in hemorrhagic tumors, proteinaceous fluid as seen in lymphangioma/slow flow vascular malformation, or melanin as seen in melanoma and clear cell sarcoma (4). The third group has relatively low signal on both T1 weighted sequence and T2 weighted sequence. This corresponds to fibrous tissue, hemosiderin or calcification (4). Plain radiographs are helpful to evaluate calcification. Highly cellular malignancy and lymphomas have relatively lower signal on fluid sensitive sequences. Additional MRI features seen in muscle lymphoma include involvement of more than one muscle compartment, direct involvement of the adjacent subcutaneous tissue and spread along the neurovascular bundle (10). The last group, where most of the sarcomas fall, has intermediate signal on T1 weighted sequence and high signal on T2 weighted sequence (31). In this group cystic appearing lesions with very high T2 signal, but those that enhance with contrast, form a distinct group and mainly comprise of tumors with myxoid component such as myxoma, myxoid liposarcoma, and other myxoid sarcomas. Some articles have further described clues that can further narrow the differential or suggest a possible etiology of sarcoma. For example, a deep lesion with fluid-like signal and enhancing fascial tail can suggest myxofibrosarcoma and undifferentiated sarcomas as possible diagnosis (22,23).

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Staging Soft tissue sarcoma should ideally be managed by a multidisciplinary team with expertise in sarcoma (21). Staging of a lesion provides basis of management and prognosis. Staging is important for surgical planning as wide resection remains the mainstay of treatment of soft tissue sarcoma with or without adjuvant/neoadjuvant chemotherapy and/or radiation therapy. A biopsy proven soft tissue sarcoma, is usually staged further with CT scan of the chest (21). Due to their high probability for extrapulmonary metastasis, CT scan or MRI of the abdomen and pelvis may be obtained when an extremity myxoid liposarcoma is diagnosed, and CT (or MRI) of the brain may be obtained for extremity alveolar soft part sarcoma, clear cell sarcoma and angiosarcoma (21). Multiple staging systems are available and imaging plays an important role in its assessment. While the choice of which staging system to follow depends on the local institute, knowledge about these staging systems in necessary so that attention is paid to the various components of the system while reporting an imaging study. Of importance are the tumor size (both, the largest dimension, and three-dimensional measurement), location of the tumor in relation to the deep fascia, relationship to the other components that form a compartment such as bones and joints, invasion/encasement of the vessels and nerves, satellite nodule, lymph node metastasis, and distant metastasis. The extent of the peripheral reactive zone, and "fascial tail" if present, should also be clearly identified as it may contain tumor cells and has to be removed at surgery (62,67). When the tumor contacts more than 180 degree of a vessels or nerve, encasement is suggested, with sensitivity for arterial, vein and nerve encasement of 84.6%, 84.6%, and 77.8–72.2% respectively; and specificities of greater than 90% (68). Thrombus in a vessel near the soft tissue sarcoma can be due to direct invasion. Despite involvement of the vessels, a limb sparing surgery can still be performed but may need arterial and/or venous reconstruction (69). When the tumor abuts the vessels, it may lead to marginal resection and may necessitate post-operative radiation. Complete encasement of a major nerve, however, usually ends in amputation (Figure 17). Invasion of the bone is seen in 5.5% of soft tissue sarcoma, seen as microscopic tumor invasion of the cortex or penetration into the medullary cavity, but is more common in synovial sarcoma (60). Whether the tumor is abutting the bone or invading the bone is important and MR images must be scrutinized to assess this. Signal alteration in the cortex on T1 weighted and T2 weighted sequences, and medullary cavity on T1 weighted sequence suggests invasion of cortex and medullary cavity respectively, if the tumor abuts the bone on T1 weighted sequence (50). The extent of marrow involvement however, can be better determined on T1 weighted sequence without fat saturation. If the tumor is abutting the bone, the periosteum is resected en bloc with tumor but with deeper invasion the bone must be resected (51). Joint involvement is uncommon occurring in about 2–3% (38). Monitoring of response to treatment The aim of monitoring the response to neoadjuvant chemotherapy is to identify nonresponders in whom the chemotherapy can be changed or stopped. Thus, the potential toxicity of the chemotherapy can be avoided. Imaging response to chemotherapy has traditionally been based on size as in Response Evaluation Criteria in Solid Tumors (RECIST) criteria. However, it may not truly predict the treatment response, and in this regard decreased attenuation on CT (as in Choi criteria) or decrease in tumor enhancement may be better (42). Functional changes at cellular level (metabolism, and tumor perfusion and permeability) occur earlier than anatomical change of decrease in size. In a patient on neoadjuvant chemotherapy, it is important to distinguish the increase in tumor size related to intralesional hemorrhage and necrosis from progressive disease (Figure 15). In addition, enhancement of granulation tissue and fibrosis that form as result of treatment response limits utility of traditional noncontrast and static post-contrast sequences for evaluation of treatment response. Multiple imaging techniques including DCE-MRI, DWI and 18F-FDG PET-CT have been used to monitor the early response to chemotherapy. Overall, with favorable tumor response, there is decrease in metabolism (decrease in SUV on 18F-FDG PET) and perfusion (decrease in slope and delayed enhancement on DCE-MRI). In addition, there is increase in ADC values with decrease in tumor size (52)

Postoperative follow up

About 5–35% of soft tissue sarcoma show local recurrence with increased risk with high grade, deep location, and positive or close surgical margins. Most local recurrences appear within the first 2–3 years after initial surgery (21). There is no evidence based universally accepted guidelines for follow up of soft tissue sarcoma following resection. In general, a baseline study is performed 3–6 months postoperatively, followed by imaging every 3–6 months up to 5 years, and then annually up to 10 years (19). Longer intervals are suggested for low grade tumors (21). MRI is the imaging modality of choice for follow up of local resection site. Postoperative evaluation may be limited by the presence of artifact from metallic hardware or micrometallic debris in which case CT or US can be an alternative. The knowledge of previous clinical, surgical and therapeutic history including radiation therapy is essential for a more comprehensive assessment since soft tissue reconstruction such as a myocutaneous flap, vascular reconstruction, and prior radiation can create confusing appearance. Initial pretreatment imaging should be reviewed as the recurrence frequently has a similar appearance. In addition, previous postoperative surveillance images should also be reviewed and compared to, as immediate postoperative changes such as inflammation and granulation is expected to decrease over time. Changes related to the treatment are expected to diminish in a time related manner. The recurrent tumor needs to be differentiated from areas of granulation, hemorrhage, seromas and radiation induced changes (Figure 18). Typical tumor recurrence is seen as discrete nodular region of increased fluid sensitive signal that enhances and has similar signal characteristics as original tumor. Exceptions do occur to this pattern, such as in myxofibrosarcoma where the recurrence can be infiltrative or occur in a superficial spreading manner with a tapering tail-like margin. On static post-contrast images granulation tissue and fibrosis can mimic tumor recurrence, but DCE-MRI and DWI significant increases the specificity of differentiating tumor recurrence from postsurgical scarring. 18F-FDG PET-CT can be used as problem solving tool and has comparable sensitivity and specificity as MRI for detecting local recurrence. It can evaluate for local and distant metastasis at the same time. However, biopsy may be needed to exclude a recurrence. The possibility of developing the rare radiation induced soft tissue sarcoma (most commonly undifferentiated pleomorphic sarcoma) after mean interval of 8–12 years should also be kept in mind. Conclusions We reviewed the various imaging modalities used in the diagnosis, initial staging, monitoring response to therapy, and subsequent postsurgical surveillance of soft tissue sarcoma. A multidisciplinary approach of management by a team with expertise and experience in soft tissue sarcomas cannot be overemphasized.

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