Update in Imaging Evaluation of Bone and Soft Tissue Sarcomas

Atualização na avaliação por imagens dos sarcomas ósseos e das partes moles

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Abstract

The evolution in imaging evaluation of musculoskeletal sarcomas contributed to a significant improvement in the prognosis and survival of patients with these neoplasms. The precise characterization of these lesions, using the most appropriate imaging modalities to each clinical condition presented, is of paramount importance in the design of the therapeutic approach to be instituted, with a direct impact on clinical outcomes. The present article seeks to update the reader regarding imaging methodologies in the context of local and systemic evaluation of bone sarcomas and soft tissues.

Keywords

- diagnostic imaging
- multimodal imaging
- neoplasms, connective tissue
- neoplasms, bone tissue
- radiology
- sarcoma

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Resumo

Palavras-chave

- diagnóstico por imagem
- imagem multimodal
- neoplasias de tecido conjuntivo
- neoplasias de tecido ósseo

A evolução na avaliação por imagens dos sarcomas musculoesqueléticos contribuiu para melhora significativa no prognóstico e na sobrevida dos portadores destas neoplasias. A caracterização precisa destas lesões, mediante utilização das modalidades de imagem mais adequadas a cada condição clínica apresentada, é de suma importância no delineamento da abordagem terapêutica a ser instituída, com impacto direto sobre os desfechos clínicos. O presente artigo busca atualizar o leitor a propósito das metodologias de imagem no contexto da avaliação local e sistêmica dos sarcomas ósseos e das partes moles.

Introduction

Since the beginning of the 20th century, the diagnostic approach of musculoskeletal sarcomas (MSSs) has been evolving, contributing to progressive and substantial improvement in clinical outcomes, prognosis, and survival.[1,2] In recent decades, we have observed a significant change in the conduction of these neoplasms as a result of the progress made in the various stages of their management,[1] especially in imaging.

When evaluating MSS, diagnostic accuracy depends on the correlation between clinic, bioimaging and pathology – the multidisciplinary review of these aspects will define the appropriate planning of the instituted treatment.[3–6]

Bone sarcomas (BSs) are painful and soft tissue sarcomas (STSs) are not – but there are exceptions to this general rule. Patients often have a tumor that grows progressively. At first, constitutional symptoms are rare, but fever, malaise, and weight loss can be observed, especially in Ewing sarcoma. Diagnostic delay is common, especially if the tumor is paucissymptomatic – there is usually no search for medical attention until the lesion becomes evident.[4]

After the initial clinical evaluation, radiographs are requested to confirm the presence of neoplasia or to provide an alternative explanation for the symptoms presented by the patient.[3,7]

Following the investigation, in view of suspected MSS, other imaging methodologies are required to characterize the lesions, informing about size, margins, enhancement, and homogeneity versus heterogeneity of the matrix, establishing its biological behavior. This anatomical and morphological evaluation has been recently improved, including metabolic and functional characterization,[1,3,8] and expanding the ability to detect these neoplasms,[9] allowing their evaluation in the context of follow-up and therapeutic response.[2,9]

On the other hand, recent studies[10,11] have identified a high percentage of inappropriate indications of imaging tests requested to evaluate musculoskeletal neoplasms, justifying the need to disseminate knowledge in this context.

The objective of the present work is to update the reader on the image methodologies used in the context of local and systemic evaluation of BS and STS.

Image Evaluation of Musculoskeletal Sarcomas

Image evaluation is fundamental in the approach of MSSs.[3] Recent advances provide accurate information on the composition of the skin, anatomical relationships, and metabolic and functional profiles of these lesions.[1,3] However, consecrated methodologies have not lost value over time and should not be set aside in this task.

This evaluation should precede biopsy[6] because: (a) it allows precise collection planning in the topography of the definitive surgical access and the most representative area of the lesion; (b) it facilitates the differential diagnosis, allowing histopathological correlation; (c) it avoids previous manipulation that affects images, generating edema and artifacts, especially magnetic resonance imaging (MRI).[12]

Local Assessment (►Table 1)

Radiographic Examination

The radiographic examination of the affected segment, in at least two orthogonal incidences, establishes the basis of the imaging evaluation,[1–3,5–7,9,13–17] and is the method of choice in the initial evaluation of primary bone tumors according to the Appropriateness Criteria of the American College of Radiology (ACR).[7,13,18] Failure to obtain radiographs has been associated with significant delay in the diagnosis of BS.[19]

Guidelines from the Musculoskeletal Tumor Society (MSTS)[20] and the American Academy of Orthopaedic Surgeons (AAOS)[21] indicate that, in the initial assessment of suspected bone tumor, the use of radiographs is supported by moderate evidence.

Radiography is the most frequently performed imaging exam,[22] presenting advantages such as speed, low cost,[4,5,13] and great availability. Specific characteristics provide information that allows narrowing the differential diagnosis.[23] It presents superior spatial resolution of the bone trabeculate,[13,16] regardless of age,[14] enabling a definitive diagnosis for most benign bone tumors and pseudotumor lesions, by determining the topography[1,2,4–6,13–17] and biological activity,[3,5–7,9,13,14,16,17] defined by appearance (matrix, pattern

Table 1 Imaging methodologies used in the local evaluation of musculoskeletal sarcomas. Advantages and disadvantages.

Mode	Advantages	Disadvantages
Conventional radiographs	• Accessible and available; • Basis of image evaluation – screening for other methodologies; • Provides the entire anatomical image of the region of interest; • Superior spatial resolution of the bone trabeculate; • Bone sarcomas: size, shape and biological behavior; • Soft tissue sarcomas: mineralization, density and bone involvement; • Definitive diagnosis in 80% of bone tumors.	• Limited evaluation of soft tissue tumors, especially small and superficial tumors; • Poor contrast resolution; • Low sensitivity in osteolytic lesions; • Variable ionizing radiation.
Computed tomography	• Accessible and available; • Multiplanar evaluation – imaging of extensive anatomical regions; • Detects very small differences in the density of the seam; • Rapid acquisition, short scan time, temporal resolution higher than MRI; • Spatial resolution, definition of matrix mineralization and cortical involvement superior to MRI; • Well-established role as a guide for bone biopsies; • Amputation planning – customization of prostheses; • Simulation and planning of radiotherapy treatments.	• Lower contrast resolution compared with MRI; • Small lesions may not be incorporated into the cuts; • Variable ionizing radiation; • Allergic reactions to iodated contrast, which may be mild (uncommon) or severe (rare). Contraindicated use of contrast in patients allergic to iode;
Magnetic resonance imaging	• Available • Direct multiplanar imaging; • Devoid of ionizing radiation; • Higher resolution of soft tissue contrast, higher than on CT; • More sensitive in determining the extent of musculoskeletal sarcomas.	• Cost; • Small confined space (claustrophobia, difficulties in the examinations of obese patients); • MRI contraindications related to the generated magnetic field; • Time for image acquisition may require sedation; • Allergic reactions to gadolinium (very rare).
Ultrasound	• Accessible and available; • Real-time image; • Devoid of ionizing radiation; • Differentiates solid tumors from cystic tumors and determines their vascularization (Doppler); • Better at evaluating small and superficial soft tissue tumors. • Guide soft tissue biopsies, preventing neurovascular lesions and avoiding necrotic portions of tumors; • Use in conditions where MRI and/or CT are contraindicated.	• Examiner-dependent methodology; • The appearance of solid tumors is usually nonspecific; • Lower resolution and contrast to CT and MRI; • Bone tumors cannot be evaluated; • Tumors of larger and deeper soft tissues do not allow adequate evaluation by this modality.

of destruction, and periosteal reaction), size, extension (intra and extraosseous) and interface with the affected bone.[1,3–7,13–17,24]

In general, BS is characterized by rapid growth, presenting a wide transition area with the host bone, imprecise limits, permeative aspect, cortical destruction and/or interrupted periosteal reaction, in sunrays, lamelar or amorphous.[1,3,5,14,16,17,25]

Radiographs are less valuable in the evaluation of STS,[1–5,13,16,17] particularly when the tumor is small and superficial,[3] due to the weak contrast resolution compared with computed tomography (CT) and MRI. [3] In the absence of reliable evidence,[20,21] radiographic examination is a reasonable method in the initial evaluation, allowing to detect and define the pattern of mineralization, assist in the specific and differential diagnosis (ossifying myositis, tumor calcinosis, vascular malformations, gout, extraskeletal mesenchymal chondrossarcoma, extraskeletal osteosarcoma, liposarcoma, and synovial sarcoma) and inform about density (radiolucence in lesions rich in fat) and bone involvement (deformation, erosion, destruction).[1–6,9,16,17,25,26]

This methodology has low sensitivity in the evaluation of osteolytic lesions, detectable only after loss of between 30 and 50% of bone mass.[5,13,27,28] Faced with high suspicion, the

investigation should be continued, even when the appearance is normal.[7,13,26]

Clinical history, physical examination and radiographs allow establishing the diagnosis of a bone tumor in > 80% of cases.[17] When dealing with MSS, the images usually suggest local aggressiveness or the findings are normal/indeterminate despite the symptomatology, demanding additional modalities to assist in the evaluation.[6,7,13]

Ultrasound

Ultrasonography is a methodology for the initial evaluation of superficial soft tissue tumors,[25] identified by acoustic impedance and distortion of local anatomy.

Although ultrasound is safe,[1,2,25] easily available,[1,25] and provides an excellent cost-effectiveness ratio[1,25] and real-time images,[2] it is examiner-dependent,[25] differently from cross-sectional imaging methodologies (CT and MRI),[1,2] higher in the evaluation of MSS.

The Doppler effect is useful in accessing the vascularization of tumors[2,25] and in differentiating between cystic and solid lesions with cystic areas,[25] which is important in the diagnosis and preoperative planning.[2]

Soft tissue sarcomas are usually hypoecoic and hypervascular and the appearance of solid tumors is usually nonspecific.[1] Bone sarcomas cannot be evaluated by the inability of cortical penetration by sonic waves.[2,7] Moderate evidence supports that this method helps distinguishing between benign and malignant soft tissue tumors.[20,21] There is consensus regarding the indication in the evaluation of small (< 5 cm) and superficial tumors, distinguishing lipomas, vascular malformations, cystic structures, and solid tumors.[20,21,25] Major and deep lesions do not allow adequate evaluation by this modality.[20,21,25]

The indications of ultrasound are: (a) differentiation between cystic and solid tumors[1,2]; (b) to guide biopsies, avoiding neurovascular lesions and necrotic portions of tumors[1,2] (CT is usually used for this, especially in complex anatomical sites)[2]; (c) to detect recurrences where there are metal implants that prevent the use of other methodologies,[2] due to the generation of image artifacts; (d) to diagnose collections in the postoperative period;[1] (e) conditions under which MRI and/or CT are contraindicated.

Cross-sectional Imaging Techniques

Cross-sectional imaging is the basis for the diagnosis, therapeutic planning, and follow-up of MSS. The tests requested from radiographic findings[20,21] are MRI (by multiplanar evaluation and superior tissue contrast) or CT, if MRI is unavailable,[1,6,16,20,21] contraindicated,[1,2,5,6,13,16] or when the patient is claustrophobic.[1]

The choice between MRI or CT depends on the clinical question to be answered.[3,5] Some cases benefit from different but complementary information provided by both.[3,5–7] Computed tomography provides better spatial resolution, matrix mineralization definition and cortical involvement.[1,3,5–7,13] The higher contrast provided by MRI allows the distinguishing of intrinsic elements, enabling more specific differential diagnosis.[3,5–7,13]

Computed Tomography

Computed tomography offers better spatial resolution than MRI,[16] detecting very small differences in the tissular density. It has greater sensitivity than radiographs, identifying lesions that affect < 40% of the bone stock.[5] It is superior in the evaluation of the axial skeleton, the waist and the short bones of the hand or foot.[7] It provides detailed information about the tumor (extension, size, location, joint involvement, discontinuous lesions, and relationship with neurovascular structures), facilitating therapeutic planning.[1,6,16]

The role of CT to guide bone biopsies is well-established – yield, accuracy, and low rates of false-negative results corroborate this statement. It is also indicated in the planning of amputations, guiding the customization of prostheses, and is essential in the simulation and planning of radiotherapy.[1]

The introduction of spiral/helical CT and then multidetector CT allowed an increase in scan speed (reducing problems related to movements during the examination),[1,2,16] besides allowing three-dimensional reconstruction and generating quality multiplanar images, using a lower radiation dose.[1,16] Multislice CT, when introduced, provided even higher resolution and scan speed, in addition to mapping larger anatomical segments.[1]

The increased availability of MRI and the concern about radiation limited the use of CT in clinical practice. Technological advances resulted in a "return" by declining exposure, through clear guidelines and dose limits for clinical use. Currently, the tests are frequently performed and last a few seconds, being little more irradiating than radiographs.[29]

Magnetic Resonance Imaging

Magnetic resonance imaging is more sensitive in determining the extent of MSS. High-resolution, multiplanar images allow for additional characterization (highlight pattern, location, and signal potential).[1–3,5–9,13,24] It better evaluates the elements contained in sarcomas (that is, lipomatous, myxomatous, or fibrous),[3] discriminating between water, fat and blood, revealing physiological information about a dynamic process in the same way as bone scintigraphy (BSC).[5] It should include the entire affected segment,[3,6] seeking to identify discontinuous bone tumors (skip metastasis).

Contrast is essential in the evaluation of musculoskeletal tumors,[30] allowing the perfusion study of some of them. Gadolinium, whose paramagnetic properties alter the signal of tissues, provides an enhancement that determines the biological potential of the lesions.[20,21,25] In addition, it avoids unnecessary waste of time by recalling the patient to complement the examination and presents an excellent safety profile, being well tolerated by most patients.[30,31] Gadolinium-based contrasts should be used with caution in chronic renal patients, due to the risk of systemic nephrogenic fibrosis (SNF); however, recent studies[30,31] have shown that, when updated guidelines related to the use of these agents are followed,[30] their use is safe. In a recent systematic review[31] that evaluated 4,931patients with advanced chronic kidney disease (clearance < 30, stages 4, 5 and 5D) there was a risk of SNF equal to zero with gadolinium

use. As with any other procedure, one should always pay attention to the risk-benefit of performing the examination.

Magnetic resonance imaging allows to infer characteristics that help in the differential diagnosis of soft tissue tumors. Benign lesions are usually small, homogeneous, and superficial, while STSs are larger ($>$ 4 cm), heterogeneous, and deeply rooted. Malignant lesions often show enhancement, presenting areas of necrosis and hemorrhage that determine a heterogeneous pattern. Hypointense pseudocapsule or hyperintense peritumoral edema on T2-weighted recovery images or short-time inversion recovery (STIR) images are often observed in STS.[3]

Magnetic resonance imaging is routinely used to assess therapeutic response. Adequate results are translated by decreased tumor volume or, when neurovascular structures are involved or contiguous, by beam release, facilitating the surgical approach. There may be an increase in tumor volume due to necrosis and hemorrhage, while viable neoplasia decreases in response to treatment.[3]

The disadvantages of MRI include restricted space, affecting obese and claustrophobic patients, high time for imaging (may require sedation), in addition to contraindications related to the generated magnetic field (metal implants).[16]

Advanced MRI Techniques

Advanced MRI techniques, when contextualized by history, physical examination, and radiographs, are important tools in the diagnosis and follow-up of patients with musculoskeletal neoplasms, avoiding unnecessary biopsies, increasing diagnostic accuracy and treatment efficacy, and improving prognosis and survival.[9,12,32] The dynamic contrast study (DCS) and diffusion sequences (DWI) and magnetic susceptibility (SWI) are examples of these techniques.

Dynamic contrast study (DCS) reports on vascularization, tissue perfusion, capillary permeability, and volume of tissue interstitial space.[9,12,32] It is performed with volumetric sequences weighted in T1 gradient-echo, acquired consecutively for 5 minutes, after gadolinium administration. After acquisition, qualitative and quantitative evaluations are obtained. The qualitative analysis translates the *time intensity curve* (TIC), evaluating the speed of gadolinium enhancement over time, and quantitative analysis uses the numerical value as a parameter. This technique allows greater precision in the identification of areas of viable neoplastic tissue, guiding biopsies and avoiding inconclusive results, besides increasing sensitivity in the differentiation between residual lesion/tumor recurrence and fibrosis (lesions that present early and intense enhancement tend to have neoplastic nature). In the evaluation of the response to chemotherapy, lesions that present an increase in the pattern of the TIC curve, unchanged curves or with slight reduction, are indicative of little tumor necrosis, suggesting a worse prognosis, while lesions with at least 60% decrease in the quantitative value of the perfusion curve indicate $>$ 90% of tumor necrosis and better prognosis (►**Figure 1**).[33,34]

Diffusion study (DWI) is extremely useful in the clinical practice, providing functional information of tumors and assisting in their detection and characterization, including staging and follow-up.[9,12,35,36] The technique translates the intravoxel incoherent movement of water molecules in the

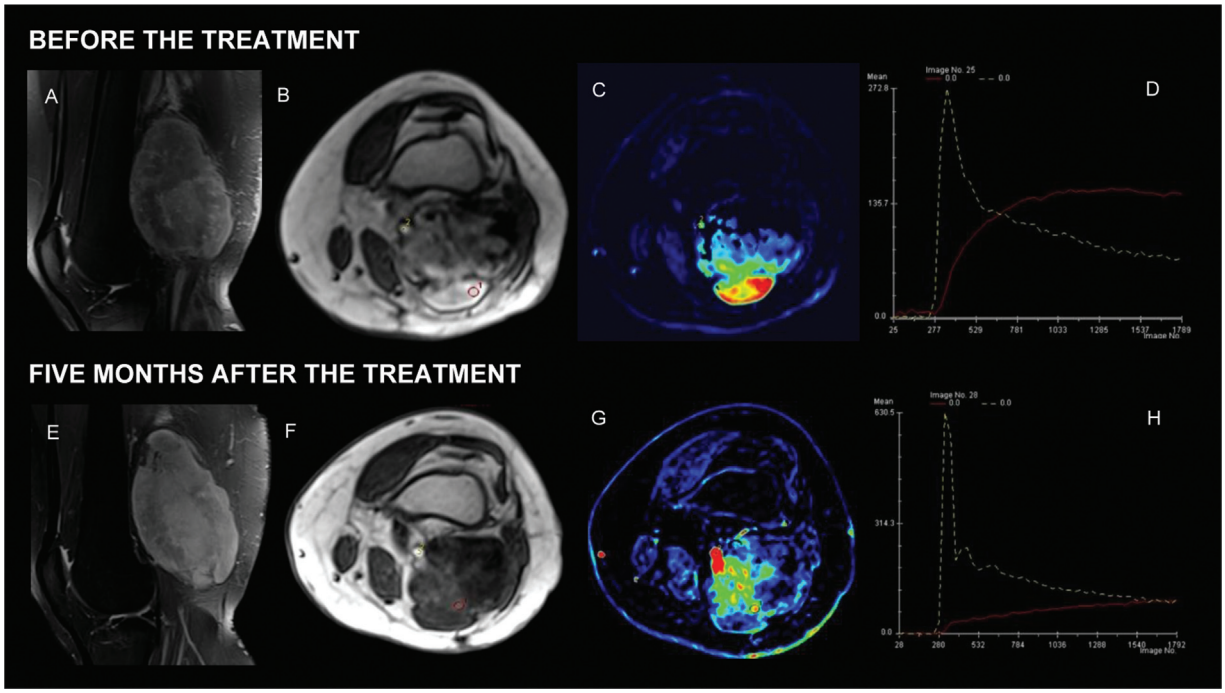

Fig. 1 Male, 29 years old, high-grade sarcoma in the right knee. Sequences in prosthetic density with fat suppression in the sagittal plane before treatment (A) demonstrating heterogeneous lesion in the posterior compartment. Axial dynamic study (B) and color map (C) demonstrating early enhancement in the posterior and superficial part of the lesion with type III TIC (red line in D). Five months after treatment, conventional resonance does not show a significant change in the signal intensity of the lesion (E). However, the axial dynamic study (F) and color map (G) show a change in the enhancement pattern, with type V TIC (red line in H), indicating good response to treatment. Histological analysis showed more than 90% of tumor necrosis.

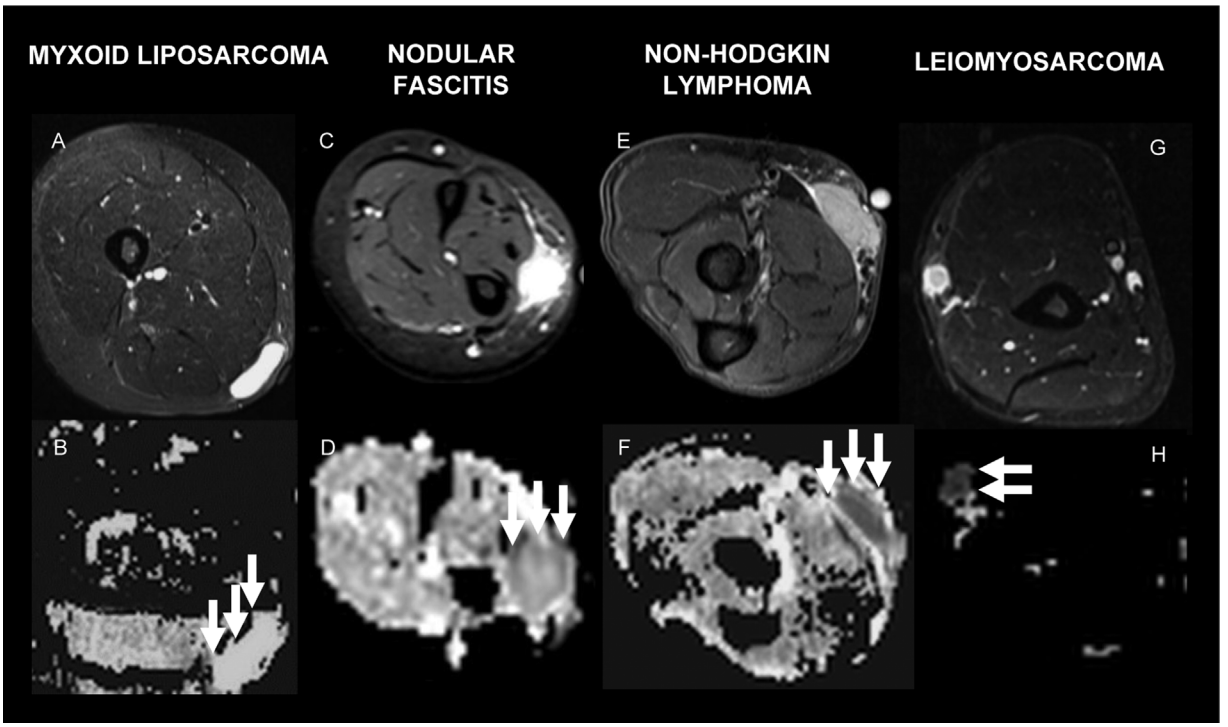

Fig. 2 Tissue characterization of soft tissue lesions. Myxoid liposarcoma in the thigh at T1 with contrast suppression after gadolinium administration (A) and ADC map (B) demonstrating ADC = 2.6×10^3 mm^2/s. Nodular fasciitis of the forearm in T1 with contrast suppression after gadolinium administration (C) and ADC map (D) demonstrating ADC = 1.4×10^3 mm^2/s. Non-Hodgkin lymphoma of the forearm at T1 with contrast suppression after gadolinium administration (E) and ADC (F) map demonstrating ADC = 0.6×10^3 mm^2/s. Leiomyosarcoma of the arm on T1-day with contrast suppression after gadolinium administration (C) and ADC map (D) demonstrating ADC = 0.97×10^3 mm^2/s.

intra- and extracellular spaces (diffusion) and microcirculation (perfusion). It can be analyzed qualitatively and quantitatively, measuring the apparent diffusion coefficient (ADC), which reflects the density of tumor cells and the integrity of the cell membrane. Most malignant tumors have low ADC values due to high cellularity.[37] Some authors have reported overlap in ADC values in benign and malignant soft tissue tumors, making it difficult to differentiate;[12,37,38] this overlap is probably due to the fact that these values are affected not only by cellularity, but also by the characteristic of the extracellular matrix. Soft tissue tumors with myxoid matrix present ample interstitial space and greater movement of water molecules, influencing ADC values. As a result, myxoid tumors have higher ADC values than nonmyxoid tumors, regardless of whether they are benign or malignant. Another applicability of DWI is the monitoring of therapeutic response. With effective treatment, tissue necrosis occurs with changes in the tumor microenvironment, resulting in increased diffusion of water molecules and ADC value (►**Figure 2**).[12,33]

Magnetic susceptibility weighted images (SWI) are used to identify tissues with these characteristics (hemosiderin, melanin, and calcification), assisting in the characterization of some neoplasms (►**Figure 3**).[38]

Systemic Assessment (►Table 2)

The preferred diffusion pathway of MSS is hematogenous, which makes the lungs and the skeleton the most common sites of metastatic dissemination.

Although uncommon, lymphatic dissemination through regional lymphadenopathy, abdominal, and pelvic metastases may occur in synovial sarcoma, myxoid liposarcoma, epithelioid sarcoma, clear cell sarcoma, leiomyosarcoma, and angiosarcoma.[3,6,39–41]

X-rays (Chest) and CT (Thorax, Abdomen and Pelvis)

Guidelines[20,21] indicate that, in the absence of reliable evidence, it is not necessary to x-ray the chest for staging of suspected MSS. In this condition,[42] high-resolution CT is used, which is more sensitive in detecting metastases.[2,3,6,13,19,43,44]

The National Comprehensive Cancer Network (NCCN) recommends CT of the abdomen and pelvis in the evaluation of STS prone to dissemination to these sites.[3,6,39,40,44]

Bone Scintigraphy

Bone scintigraphy is sensitive, inexpensive, available, with low radiation exposure, devoid of contraindications and side effects, and allows evaluation of the entire skeleton at the same imaging time.[45] It uses radioactive markers with short half-life and high affinity for osteoblastic activity,[5] reflecting physiological events more than anatomical ones.

The most used radiopharmaceutical is methylene-diphosphonate marked with technecium-99m (MDP-99mTc), which binds to the inorganic bone matrix where there is proliferative activity.[46] Other radiopharmaceuticals used for specificity gain[45,46] are metaiodobenzylguanidine (MIBG) marked with iodine-123 or iodine-131in neuroblastoma metastases;[46] galium-67, which binds to transferrin,

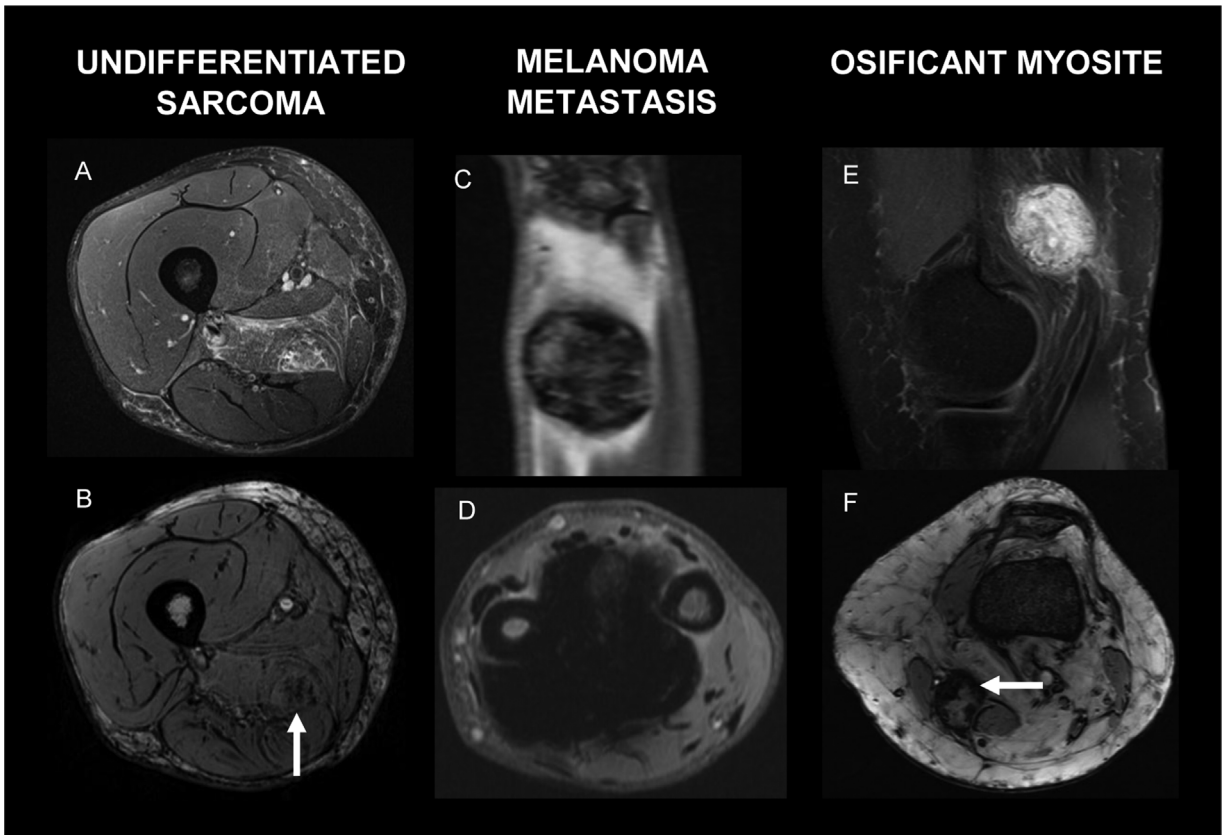

Fig. 3 Different applicability of magnetic susceptibility sequences (SWI). Undifferentiated sarcoma of the left thigh in prosthetic density with suppression of fat in the axial plane (A) and axial SWI (B) demonstrating hemorrhagic foci inside the lesion. Melanoma metastasis in the right forearm in prosthetic density with coronal (C) and axial SWI (D) fat suppression, demonstrating areas of melanin inside the tumor. Ossifying myositis of the left knee in prosthetic density with fat suppression in the sagittal (E) and axial SWI (F) planes demonstrating peripheral calcification.

accumulating in tissues rich in receptors of this protein,[46] in lymphoma staging; and radioactive colloides, in the evaluation of the bone marrow.[45]

The uses of two methodologies: (a) 3-phase – early images evaluate the vascularization profile of a given segment (flow and pool steps), followed by late images of the whole body, between 3 and 4 hours after radiopharmaceutical injection; and (b) late images of the whole body, seeking to identify osteoblastic changes in the skeleton. It identifies metabolic changes as a result of local events – cellular activity occurs rapidly, but structural changes occur slowly. It may detect infection or avascular necrosis 24 hours after its onset; in hyperparathyroidism or metastatic bone disease, lesions are detected long before radiography is visible.[5]

Bone scintigraphy is used in the staging of BS, identifying similar lesions or bone metastases (BMs), because most induce bone matrix proliferation, enabling its uptake.[4,19,42] It has lower accuracy in the staging of STS, captured only in the early stages (flow and balance).[42] It is a pillar in the diagnosis and evaluation of BMs.[45,47] It is useful in the follow-up of neoplasms with a high recurrence rate or metastatic potential[45] and allows early diagnosis of skip metastasis.[47] Its sensitivity is between 79 and 85%, with erratic specificity.[45,48]

Pathologies associated with increased bone metabolism alter the examination – this, in addition to limited spatial resolution, make its role in the diagnosis of BS controversial. The most frequent findings are an increase in blood flow and pool and capture in late images, proportional to the biological behavior of the lesion.[46] Purely lytic-destructive lesions, without reactive sclerosis, such as multiple myeloma (MM) and renal BM or thyroid carcinoma, do not usually demonstrate hyperuptake.[5] It is essential to correlate clinical data with those obtained through other methodologies to approach the diagnosis.[45,46] The association of BSC with CT with fusion of images (SPECT/CT) has addressed these limitations, bringing significant gains in diagnostic accuracy.

Osteoblastic metastatic lesions are hypercapturing, and their prevalence in the face of the evaluated pathology should be considered.[45,48] The presence of BM at diagnosis is more frequent in Ewing tumor than in osteosarcoma (10 versus 2%), making BSC in the staging of the former fundamental.[47]

Suspicions of BM (especially single lesions) should be confirmed before labeling patients as having advanced disease, depriving them of treatment with curative intent.[47] When the suspected lesion is solitary, asymptomatic or located in a location not conducive to biopsy, BSC is indicated to detect lesions more accessible to the procedure.[45]

This method also allows evaluating the differentiation of benign lesions, such as osteosarcoma secondary to Paget disease, where a hypocaptant area arises in the hypercaptant bone, a characteristic finding of this condition.[46]

Table 2 Imaging methodologies used in the systemic evaluation of musculoskeletal sarcomas. Advantages and disadvantages

mode	Advantages	Disadvantages
CT (thorax, abdomen, and pelvis)	• Accessible and available; • Chest CT: increased sensitivity in the detection of pulmonary metastasis; • CT of abdomen and pelvis: staging of synovial sarcoma, epithelioid, clear cells, leiomyosarcoma, angiosarcoma and myxoid liposarcoma.	• Ionizing radiation [a]
Bone mapping	• Accessible and available; • Evaluation of the entire skeletal system in a single exam; • Sensitive; detects physiological changes before structural changes; • Pillar in the diagnosis and evaluation of bone metastasis; • Follow-up of lesions with high recurrence rate or metastatic potential; • Early diagnosis of *skip metastasis.*	• Ionizing radiation [a]; • Lesions not involved by reactive or very anaplastic bone may not capture (e.g., multiple myeloma, thyroid or kidney CA metastasis); • Inadequate in the evaluation of therapeutic response - *flare phenomenon;* • Not very specific.
FBMRI	• Differentiation between therapeutic response and disease advancement; • Superior resolution of contrast in soft parts, good spatial resolution; • Acquisition of images faster than PET/CT; • Devoid of ionizing radiation or need to use contrast; • Early diagnosis of bone metastases; • Prediction of imminent risk of fracture. • High accuracy in bone marrow study.	• Cost; • Accessibility and availability; • Time for image acquisition may require sedation; • MRI contraindications.
PET/CT	• Earlier diagnosis; • More precise staging of bone metastases than scintigraphy; • Evaluates tumor/tissue viability, access to metabolic activity; • Distinguishes residual disease from scar injuries; • Facilitates the evaluation of the therapeutic response; • Detects small pulmonary nodules; • Allows you to guide biopsies to metabolically active areas of the tumor. • Exams performed in 30 minutes;	• High cost; • Low availability; • Ionizing radiation [b]; • Limited contrast in soft parts; • Overlap in metabolic activity of benign and malignant lesions; • Infections and granulomatous processes have high glucose consumption; • CT acquisition time makes it impossible to make extra time for PET acquisition.
PET/MRI	• Earlier diagnosis; • More precise staging of bone metastases than scintigraphy; • Evaluates tumor/tissue viability, access to metabolic activity; • Allows to distinguish residual disease from scar injuries; • Facilitates the evaluation of the therapeutic response; • Allows to guide biopsies to metabolically active areas of the tumor. • Better anatomical location of lesions; • Higher than PET/CT in the CNS, liver, and spinal cord.	• High cost; • Very low availability; • Ionizing radiation [a]; • Protocols, indications and quantitative accuracy still under evaluation; • Time for image acquisition can exceed 1 hour; • Limited evaluation of pulmonary parenchyma.

Abbreviations: CNS, central nervous system; CT, computed tomography; FBMRI, full-body magnetic resonance imaging; PET, positron emission tomography; PET/CT, positros emission tomography computed tomography; PET/MRI, positron emission tomography magnetic resonance imaging.
[a] Estimated effective dose for adults 1–10 mSv; estimated effective dose for children 0.3–3 mSv.
[b] Estimated effective dose for adults 10–30 mSv; estimated effective dose for children 3–10 mSv.
(Source: Jordan DW, Becker M, Brady S, Feng JC, Jafari ME, Johnson LM et al. American College of Radiology ACR. Appropriateness Criteria®. Radiation Dose Assessment Introduction (revised 2020). Reston, VA: American College of Radiology. https://www.acr.org/-/media/ACR/Files/Appropriateness-Criteria/RadiationDoseAssessmentIntro.pdf).

Despite the proven role of BSC in the detection of BM, robust evidence supports the superiority of whole-body MRI, regardless of the primary tumor.[49] Bone scintighrahy remains an option in staging, especially when MRI is contraindicated and when the costs and low availability of MRI are considered.[7]

Bone scintighrahy is inadequate in the evaluation of the therapeutic response, due to the flare phenomenon (greater induction to bone repair by the treatment instituted, causing an increase in uptake and false impression of worsening); megaprostheses can induce bone proliferation up to 2 years after implantation.[46]

Full-Body Magnetic Resonance, Positron Emission Tomography – Computed Tomography, and Positron Emission Tomography – Magnetic Resonance Imaging

The routine indication of MRI,[19,49] positron emission tomography computed tomography (PET/CT)[19,42,49] or positron emission tomography magnetic resonance imaging (-PET/MRI)[19,49] is still under evaluation in the staging of MSS. Their use is justified in the evaluation of suspicious sites as demanded – precise staging has an impact on treatment and on the clinical outcome.[21]

Full-body Magnetic Resonance

MRI has excellent spatial resolution and contrast in soft tissues, being devoid of ionizing radiation.[50] These characteristics, together with the high accuracy in the study of the bone marrow,[51] allowed greater applicability in the evaluation of BMs, MMs, lymphomas, and of the response to the treatment instituted.[52,53] More recently, it has been used in the screening of carriers of genetic mutations (for example, germ mutation TP53), which predispose to the development of tumors more frequently and at an earlier age than the general population.[25] Full-body magnetic resonance imaging may also be useful in monitoring STSs that metastatize to the bones, such as myxoid liposarcoma.[25]

Although BSC and CT are established in international guidelines, they are limited in the staging and follow-up of BMs (mainly breast and prostate) and are ineffective in therapeutic targeting in this era of precision medicine. The bone marrow is formed by a mineralized component and a cellular component – only MRI can evaluate the latter, which presents extremely dynamic changes. This method allows detecting purely lytic lesions, at an early stage, little vascularized, being superior in the post-treatment follow-up. Full-body magnetic resonance imaging has greater efficacy in the detection and evaluation of the therapeutic response (for example, MMs, BMs),[49,50,53] allowing better differentiation between the last and advancement of the disease, which is difficult to characterize by BSC due to the flare phenomenon. Its sensitivity is similar to that of PET/CT in the medullary evaluation and characterization of focal alterations, differentiating inactive lesions treated from those in activity.[55]

Because it is a very sensitive methodology, FBMRI can induce unnecessary performance of subcutaneous examinations and biopsies. It is important to mention that results attributed to the methodology are directly related to the use of the appropriate protocol, the correct sequences, and the experience of those who interpret the exams.

Compared with PET/CT, MRI has higher sensitivity (68 versus 59%), specificity (83 versus 75%), and positive predictive value (88 versus 75%), being superior in the detection of small lesions and diffuse disease.[50]

Full-body magnetic resonance imaging is fast, devoid of ionizing radiation or of need for contrast, as well as economical and well tolerated,[43,47,53,54] and its prognostic value should be highlighted, by predicting the risk of fracture, enabling prophylactic treatment, with impact on survival.[45,55,56]

Positron Emission Tomography – Computed Tomography

The introduction of the positron emission imaging methodology[16,45,55,56] provided much more accurate staging, demonstrating tumor metabolic activity, and facilitating the evaluation of therapeutic response.[7,46]

Positron emission tomography uses radioisotopes submitted to the decomposition of positron emissions; a sophisticated detector ring identifies coincident photons, recording the interaction through images. The most used radiopharmaceutical is fluordeoxyglucose marked with Fluor-18 (FDG-F18), which is analogous to glucose. Its metabolite does not constitute a substrate for glycolytic enzymes, making it possible to quantify its metabolism, similar to that of glucose in tissues, which presents high consumption in numerous neoplasms. Fluoride-F18 enables the mapping of bone matrix proliferations as well as MDP-99mTc in BSC – a fluoride ion is incorporated into hydroxyapatite, forming fluoroapatite. This method allows the detection of primary and secondary lesions in lymph nodes, viscera and/or solid organs (except the central nervous system, which presents high glucose consumption). More anaplastic tumors usually present increased rates of glycolysis and FDG-F18 uptake in comparison with benign or low-grade malignant neoplasms – there is a strong correlation between FDG-F18 uptake and histological degree, with prognostic implications.[9]

The method is more sensitive in the detection of lytic lesions than blasts. Sensitivity is 91%,[48] with significant variability: 100% in osteosarcoma, 85.7% in relapses, and 95% in OM.[55–57] Fluor-18-PET is 95% sensitive and 75% specific in the diagnosis of STS.[9] However, some benign tumors (histiocytic or giant cell-rich lesions) may present greater accumulation of FDG.[9]

The sensitivity of PET/CT is higher than that of BSC, enabling earlier and more accurate diagnosis of BM, mainly by spatial resolution (0.4 cm in PET and between 1 and 1.5 cm

in BSC),[9,55,58] with excellent performance in the evaluation of lymph node involvement and soft tissue lesions.[55,58]

Positron emission tomography CT can be used in staging, restaging, and monitoring of therapeutic response (significant decrease in uptake in good responders, strongly correlated with histological responses).[55,56,58] It also allows to distinguish residual disease from scar injuries, impacting on clinical management.

Although PET/CT or PET/MRI with FDG-F18 capture MSS proportionally to biological activity, they have limited specificity – infectious and granulomatous processes also present high glucose consumption. In addition, PET/CT has limited contrast in the soft tissues.[59]

A meta-analysis[57] evaluated the performance of PET or PET/CT in the staging of musculoskeletal neoplasms, demonstrating sensitivity, specificity, accuracy, and positive and negative predictive values, respectively, of 96, 77, 88, 86 and 90%. False-positive results occurred in villonodular synoviritis, tenosynovial giant cell tumor, hibernoma, sarcoidosis, ossifying myositis, abscesses, and inflammatory processes; false-negative results occurred in myxoid liposarcomas, fibromyxoid sarcomas, well-differentiated liposarcomas, and spindle cell tumors.

Positron emission tomography CT allows guiding biopsies to metabolically active areas of tumors, ensuring accurate diagnosis[9,16] and defining more assertive therapy, particularly in heterogeneous lesions (chondrosarcomas or lesions with higher glycolytic metabolism), which present rapid change in the imaging pattern in response to treatment.

As PET/CT is expensive and less available, it should be selected in exceptional scenarios, confirming lesions in a noninvasive manner, particularly when it can modify the therapeutic approach.

Positron Emission Tomography – Magnetic Resonance Imaging

Positron emission tomography magnetic resonance imaging associates PET with MRI, usually using FDG-F18. It is restricted, for cost and availability. In the PET component, it presents the already described characteristics, associated with MRI findings, with reduced radiation exposure.[60] It allows better local and systemic evaluation than other methodologies, being superior to PET/CT in the evaluation of the central nervous system, of the liver and of the spinal cord, but is limited in the study of the pulmonary parenchyma.[59]

The role of PET/MRI in osteosarcoma has not been fully defined.[55,59] A study[60] demonstrated a better definition of the location of lesions by this method. As Ewing sarcoma most often affects children, PET/MRI is preferable to PET/CT in evaluation.

Positron emission tomography MRI seems very promising, adding information about the metabolic profile (PET) to the excellent resolution (MRI). Further cost-effectiveness studies and changes in outcomes are needed to define it in the routine investigation of MS.[59]

Final Considerations

Knowledge about the indications of imaging methodologies available for the evaluation of MSS is fundamental to avoid unnecessary prescription of tests and to define the most appropriate therapeutic planning for each clinical situation presented.

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Conflict of Interests
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