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Seminars in
NUCLEAR
MEDICINE

PET/CT Variants and Pitfalls in Bone and Soft Tissue Sarcoma

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Sarcomas are rare tumors of mesenchymal origin and comprise only around 1% of adult cancers. The abundance of sarcoma histiotypes, with distinct imaging characteristics, biology, clinical behavior and treatment strategy, result in a complex disease presentation, requiring management by multidisciplinary specialized sarcoma centers. Oncologic and musculoskeletal radiology guidelines provide minimal guidance and only fragmentary information on the indications of ^{18}F-FDG PET/CT in sarcoma. Therefore, knowledge of various phenotypes with preference for bone and lymph node metastases or higher incidence of local and distant recurrence is essential to select the appropriate diagnostic imaging tests and its interpretation. Benign and malignant soft tissue and bone tumors often share common radiographic and metabolic imaging characteristics. In addition, metastases of various histiotypes might exhibit a spectrum of atypical imaging appearances. Therefore, imaging specialists need to be aware of these variants and associated pitfalls of sarcoma imaging.
Semin Nucl Med 51:584-592

Introduction

Sarcomas are a rare and diverse group of cancers of mesenchymal origin. Although soft tissue and bone cancers comprise only around 1% of adult cancers,[1] soft tissue sarcomas (STS) constitute a family of about 50 different subtypes and bone sarcomas are categorized in more than 20 different diagnoses. They differ histologically and biologically, exhibit variable imaging characteristics, have different disease courses and often require specific therapeutic approaches.

The most common STS histiotype in adults are liposarcomas, followed by leiomyosarcomas, and undifferentiated pleomorphic sarcomas.[2] Osteosarcoma (35%), chondrosarcoma (30%), and Ewing sarcoma (16%) are the three most common forms of primary bone cancer.[3]

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The low incidence of sarcoma together with their heterogeneous phenotypes requires management by a multidisciplinary team at specialized sarcoma centers. This team should include surgical and medical oncologists, radiation-oncologists, musculoskeletal pathologists, and musculoskeletal imaging specialists.[4]

According to the 2015 consensus paper of the European Society of Musculoskeletal Radiology (ESSR) on guidelines for diagnostic imaging of soft tissue tumors, the following criteria in a patient with soft tissue tumor should result in referral to a sarcoma treatment center[4]:

- Any patient with a ≥ 5cm superficial tumor or with a deep-seated tumor regardless of size[5]
- Indeterminate ultrasound (US) or indeterminate magnetic resonance imaging (MRI) findings, or clinical suspicion of malignancy
- Patients should be referred before biopsy or surgery

Likewise, the 2017 ESSR consensus document for tumors and tumorlike lesions of bone[6] provides a referral pathway:

- For symptomatic patients with pain/swelling or incidental detection of a bone tumor, a non-linear pathway, essentially based on patient age (<40 vs. >40 years), number

 https://doi.org/10.1053/j.semnuclmed.2021.06.009
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of bone lesions (single vs. multiple), and the radiographic assessment of aggressiveness is utilized to guide referral to dedicated sarcoma treatment centers.

When to perform ^{18}F-FDG PET/CT?

The role of ^{18}F-FDG PET/CT in the initial diagnostic work-up of soft tissue and bone tumors is still not well established. ^{18}F-FDG PET/CT is not recommended in the imaging algorithm for initial local work-up of soft tissue tumors[4] and bone tumors.[6] In other words, it is not recommended for diagnosing sarcoma.

However, in patients with histopathological proven sarcoma, guidelines by the ESSR,[4] the National Comprehensive Cancer Network (NCCN)[7,8] and the European Society of Medical Oncology (ESMO)[9,10] provide some recommendations and considerations on the appropriateness of ^{18}F-FDG PET/CT. Key statements of these guidelines are summarized in Table 1 and 2.

Soft tissue sarcoma

^{18}F-FDG PET/CT in STS is still regarded as controversial. General comments in current guidelines state that ^{18}F-FDG PET/CT "may be useful" in staging and response assessment of STS. However, each guideline only provides fragmentary or no information on specific sarcoma histiotypes. The appropriateness to perform an ^{18}F-FDG PET/CT scan in STS can be derived from the increased incidence of osseous or nodal metastases in specific histiotypes.

Metastatic spread in STS is mainly hematogenous, and the lungs account for approximately 75 to 80% of metastases.[4] Therefore, chest CT is of upmost importance in staging, restaging, and surveillance alongside local staging.

Osseous metastases are reported in approximately 10% of STS patients.[14] Alveolar soft part sarcoma,[11,12] angiosarcoma,[12] leiomyosarcoma,[13] undifferentiated pleomorphic sarcoma,[14] and dedifferentiated liposarcoma[12] are histiotypes with increased incidence of bone metastases, which is acknowledged in the ESSR consensus paper,[4] with ^{18}F-FDG PET/CT stated as "may be useful" in these specific subtypes (Table 1 and 3). In addition, a high incidence of bone metastases (17% of patients / 56% of metastatic events) has been reported for myxoid liposarcoma.[17] Due to the low glycolytic phenotype of myxoid liposarcomas, (whole-body / spine) MRI remains the best imaging technique to detect osseous metastases and should be considered[18] (Fig. 1). Table 4

Lymph node involvement is rare and accounts for approximately 3% of STS metastases[4]. In several histiotypes, ^{18}F-FDG-PET positive lymph nodes therefore have a high likelihood of being false positive for metastatic disease. Lymph node involvement however is more frequently observed in high-grade rhabdomyosarcoma, clear cell sarcomas, epithelioid sarcoma, angiosarcoma, and synovial sarcoma[19-21] (Table 3). This is in part acknowledged in the NCCN STS guidelines (Table 1),[8] with ^{18}F-FDG PET/CT stated as "may be useful" in rhabdomyosarcoma.

Bone sarcoma

The use of ^{18}F-FDG PET/CT in osteosarcoma and Ewing sarcoma is less controversial in comparison to STS.

The NCCN guidelines for bone tumors recommend to include PET/CT (or bone scan) for the workup of symptomatic bone lesions with abnormal radiograph in patients ≥40 years of age.

Pulmonary metastases are the most frequent site of metastatic spread for all bone sarcomas. Extrapulmonary metastases are rare and include secondary bone metastases. Regional lymph node metastases from primary bone sarcomas are also rare.

However, besides chest CT and appropriate imaging of the primary site, the NCCN guideline[7] recommend ^{18}F-FDG PET/CT (and/or bone scan) for initial staging of osteosarcoma and Ewing sarcoma. In addition, ^{18}F-FDG PET/CT imaging should be considered for restaging and surveillance (Table 2).

Local staging and histiotypes

Knowledge of tumor location in relation to vessels and nerves is essential in the preoperative workup to determine surgical resectability. Therefore, MRI with its high soft tissue contrast is recommended for local staging of soft tissue and bone sarcoma (in bone sarcomas with or without additional plain radiographs and / or CT when appropriate). MRI can also be helpful to distinguish between lipomatous, myxoid, chondrogenic and neurogenic features of the tumor.

The information obtained by ^{18}F-FDG PET/CT for local staging in STS and bone sarcomas is less relevant in comparison to MRI. A higher glycolytic phenotype has been reported in patients with more aggressive STS and less favorable outcome,[22,23] such as malignant peripheral nerve sheath tumor (MPNST). However, the broad range of ^{18}F-FDG uptake within each histiotype not allows for an accurate prediction of the STS subtype.[22]

Approximately 75% of STS are considered grade 2 and 3, whereas 25% are considered grade 1.[2] The distinction is relevant because of different biology, clinical behavior, and treatment approaches. The glycolytic phenotype has been shown to correlate significantly with the histologic grade, with high-grade tumors having on average higher standardized uptake values (SUV) in comparison to low-grade tumors. However, low SUVs are observed in grade 1 - 3 tumors, therefore low tumor SUV does not rule out high grade sarcoma. Nonetheless, high ^{18}F-FDG uptake likely represents high grade sarcoma.[22]

Well-differentiated and myxoid liposarcomas have been shown to represent histiotypes with a low to absent glycolytic phenotype[15,22,24] (Fig. 1). In these histiotypes staging, response assessment, and surveillance with ^{18}F-FDG PET/CT can therefore not be recommended, but should be managed with MRI.

The NCCN guidelines suggest PET/CT to be considered to differentiate between well-differentiated and dedifferentiated liposarcomas, and to help to determine the site for biopsy.[8] However, because of the mostly distinct MRI imaging characteristics of a well-differentiated in comparison to a de-differentiated liposarcoma (Fig. 2), ^{18}F-FDG PET/CT does often not provide significant local tumor information in addition to MRI.

Table 1 Key statements for the use of ^{18}F-FDG PET/CT in soft tissue sarcoma

	ESSR[4]	NCCN[8]	ESMO[10]
General	Staging: The role of PET/CT and PET/MR for initial staging, therapy control, and follow-up is still regarded as controversial. It may lead to upstaging in only a minority of patients and is currently not recommended for routine use Follow up: In case of large metallic hardware, US, dual-energy CT or CT using modern iterative reconstruction algorithms of raw data sets, or PET/CT can be considered as alternative or additive to MRI Biopsy: It is essential to target viable tumor areas, identified by color doppler US, contrast-enhanced MRI, or PET/CT	General: PET/CT may be useful in staging, prognostication, grading, and determining response to systemic therapy	Diagnosis and pathology: When preoperative treatment is an option, radiological imaging [including PET] may be useful, in addition to pathology, in providing the clinician with information that helps to estimate the malignancy grade (e.g. necrosis) Staging and risk assessment: Bone scan, whole-body MRI and PET scan are optional Management of advanced/metastatic disease: When surgery of lung metastases is selected, an abdominal CT scan and a bone scan or a FDG-PET are mandatory to confirm that lung metastases are 'isolated'
Specific	PET/CT may be useful for detection of osseous metastases in: - Alveolar soft part sarcoma[11,12] - Angiosarcoma[12] - Leiomyosarcoma[13] - Undifferentiated pleomorphic sarcoma[14] - Dedifferentiated liposarcoma[12]	Retroperitoneal/intra-abdominal: Consider PET/CT as a tool to help differentiate between well-differentiated and dedifferentiated liposarcoma and to help determine site for biopsy[15] Rhabdomyosarcoma: PET or PET/CT may be useful for initial staging because of the possibility of nodal metastases and the appearance of unusual sites of initial metastatic disease in adult patients	

Table 2 Key statements for the use of ^{18}F FDG-PET/CT in bone sarcoma

	ESSR[6]	NCCN[7]	ESMO[9]
General	Initial work-up of bone tumor: FDG PET is not indicated for initial work-up of bone tumors	Work-up of symptomatic bone lesions: Bone scan or PET/CT recommended for the workup of symptomatic bone lesions with abnormal radiograph in patients $\geq$40 years	Staging and risk assessment: General staging should be carried out to assess the extent of distant disease, including bone scintigraphy, chest radiographs and CT, whole-body MRI and PET/CT or PET/MRI
	PET/CT does not yet have a role in the initial differentiation of benign from malignant bone tumors but may aid in problem solving in a suspected local recurrence Staging: Advanced imaging modalities such as MRI, scintigraphy, and PET/CT are useful for subsequent local and distant staging, respectively, of the disease rather than the initial diagnosis	The standard staging workup for a suspected primary bone cancer should include chest imaging, appropriate imaging of the primary site, and bone scan or PET/CT	Follow-up, long-term implications and survivorship: More modern techniques (e.g. PET or whole-body MRI) are increasingly being adopted into routine practice but require further evaluation in clinical trials
Specific		Osteosarcoma: Initial staging: PET/CT and/or bone scan recommended Restaging: Consider PET/CT or bone scan Surveillance: Consider PET/CT and/or bone scan Ewing sarcoma: Initial staging: PET/CT and/or bone scan recommended Restaging: Consider PET/CT or bone scan Surveillance: Consider PET/CT or bone scan Chordoma: Consider PET/CT	Osteosarcoma: PET/CT scanning may be advantageous for response assessment in high-grade craniofacial osteosarcoma Ewing sarcoma: Bone marrow biopsies and aspirates (from sites distant to the primary or known metastatic lesions) may be considered in the staging, but several experts underline that there is a very low incidence of bone marrow metastases in localized disease if the PET scan is negative[16]

Table 3 Histiotypes with higher incidence of bone and lymph node metastases

Bone metastases	Lymph node metastases[19-21]
- Alveolar soft tissue sarcoma[11,12] - Angiosarcoma[12] - Leiomyosarcoma[13] - Undifferentiated pleomorphic sarcoma[14] - Dedifferentiated liposarcoma[12] - Myxoid liposarcoma[17]	- High-grade rhabdomyosarcoma - Clear cell sarcoma - Epithelioid sarcoma - Angiosarcoma - Synovial sarcoma

PET as a predictive and prognostic imaging biomarker

A meta-analysis of 6 studies comprising 514 patients with STS and bone sarcoma evaluated the prognostic significance of ^{18}F-FDG PET/CT at diagnosis.[25] The meta-analysis indicated that a high glycolytic phenotype at baseline is significantly correlated with poor prognosis.

Changes in ^{18}F-FDG uptake after the initial cycle and after completion of neoadjuvant therapy have been shown to be predictive and prognostic imaging biomarkers of histopathologic tumor response (histopathological tumor necrosis $\geq$ 90% - 95%) and survival in STS[26-28] and bone sarcoma.[29] However, strong decreases in ^{18}F-FDG uptake have also been observed in treatment non-responders.[27,30]

Tumor size changes might not accurately reflect tumor response, e.g. due to post-treatment hemorrhage in STS or varying degrees of calcification in metastases of osteosarcomas with corresponding absence of tumor size reduction (Fig. 3).

In a predominantly calcified osteosarcoma metastasis ^{18}F-FDG uptake is low / absent which complicates treatment response assessment due to low baseline ^{18}F-FDG uptake. In concordance, tumor size reduction of a predominantly calcified metastasis is not expected, even after complete tumor response, which hinders differentiation between viable and non-viable tumor.

Local recurrence

Reported local recurrence rates (LRR) of STS range from approximately 6% to 25%; higher reported LRR predate the widespread use of (neo)adjuvant chemoradiation treatment.[31] Several intrinsic and extrinsic factors have been described that determine the LRR for extremity, retroperitoneal, and visceral STS.[31,32]

Histiotypes with increased risk of local recurrence are angiosarcoma,[33,34] leiomyosarcoma,[35] myxofibrosarcoma[36,37] and undifferentiated pleomorphic sarcoma.[38]

Post-surgical or post-radiation inflammatory changes might persist for several months to years following treatment and need to be considered when the operative bed is evaluated. In addition, metal artifacts due to tumor prosthesis can impact lesion detectability and reader confidence.

Specific examples of variants and pitfalls of distant metastases

Osteosarcoma

Osteosarcoma metastases are often characterized by calcifications. The degree of calcification can vary from in part to entirely calcified. ^{18}F-FDG uptake in osteosarcoma metastases depends on the degree of calcification and can be false negative in an entirely calcified lesion. In this case the ^{18}F-FDG PET should not be misread as negative for viable tumor.

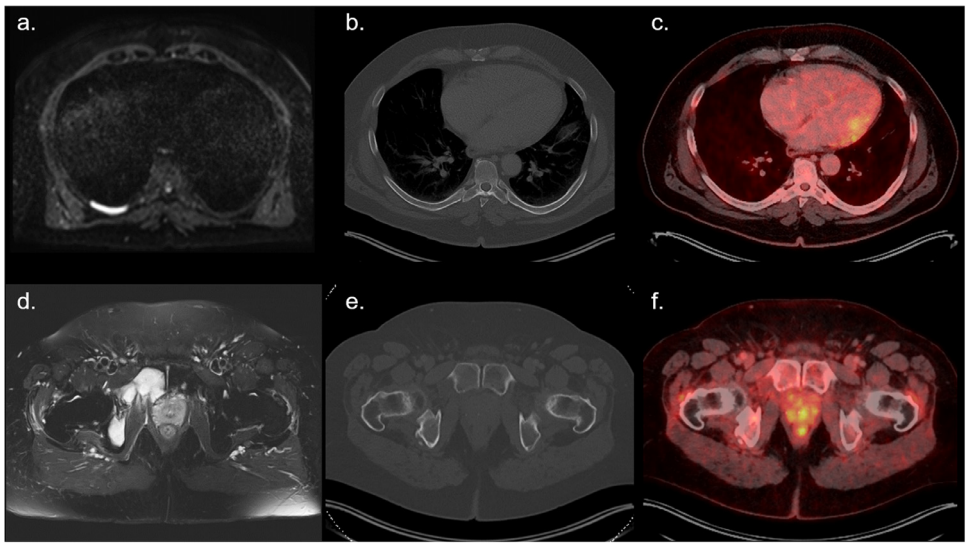

Figure 1 Myxoid liposarcoma. (A - F) 57 y/o male with myxoid liposarcoma metastases. (A) DWI and (D) T2 fs show increased signal intensity of osseous metastases in the right 8th rib and the right ischiopubic ramus. (B, E) CT and (C, F) fused ^{18}F-FDG PET/CT without corresponding imaging changes.

Table 4 Summary of variants and pitfalls

General
- The appropriateness to perform an ^{18}F-FDG PET/CT scan in STS can be derived from the increased incidence of osseous or nodal metastases in specific histiotypes.
- The broad range of ^{18}F-FDG uptake within each histiotype does not allow for an accurate prediction of the STS subtype.
- Low SUVs are observed in grade 1 - 3 tumors, therefore low tumor SUV does not rule out high grade sarcoma.
- Strong decreases in ^{18}F-FDG uptake during neoadjuvant therapy have also been observed in treatment non-responders.
- Post-surgical or post-radiation inflammatory changes might persist for several months to years following treatment and need to be considered when the operative bed is evaluated.
- Although benign bone and soft tissue lesions typically have a low glycolytic phenotype, both can display a wide spectrum of ^{18}F-FDG uptake.
Specific
- Well-differentiated and myxoid liposarcomas have been shown to represent histiotypes with a low to absent glycolytic phenotype.
- Osteosarcoma metastases are often characterized by calcifications. ^{18}F-FDG uptake in osteosarcoma metastases depends on the degree of calcification and can be false negative in an entirely calcified lesion.
- Angiosarcoma metastases might present as hemorrhagic or cystic, accordingly the ^{18}F-FDG uptake in these lesions is variable.

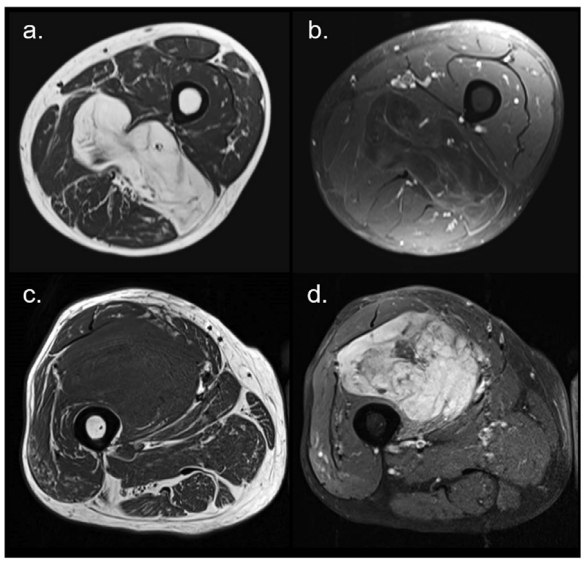

Figure 2 Well-differentiated and dedifferentiated liposarcoma. (A, B) 69 y/o male with well-differentiated liposarcoma of the left thigh. (A) T1 shows a large fatty mass with septa. (B) T1 fs post-contrast shows the majority of the fatty mass to suppress in signal intensity and only linear contrast media enhancement of the septa. (C, D) 94 y/o male with dedifferentiated liposarcoma of the right thigh. (C) T1 shows a solid tumor without detection of macroscopic fat. (D) T1 fs post-contrast shows significant contrast media enhancement of the majority of the lesion.

Figure 3 shows a patient with an ^{18}F-FDG negative entirely calcified metastasis to the pancreatic tail with interval increase of the pancreatic lesion, and the occurrence of new, in part calcified mediastinal lymph node metastases (not shown) on follow up imaging.

Angiosarcoma

Angiosarcoma metastases have been reported to exhibit a variety of radiograph features.[39,40] Hemorrhagic or thin-walled cysts are

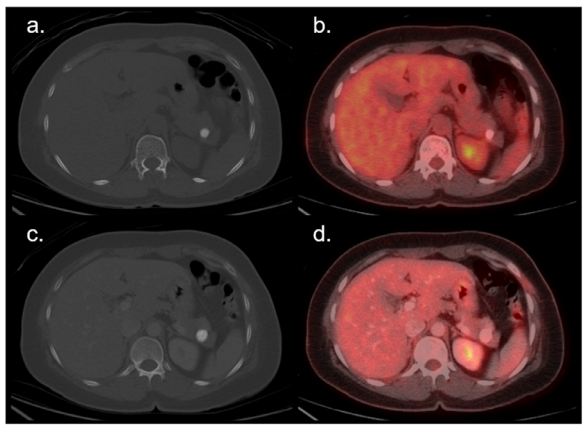

Figure 3 Osteosarcoma metastasis. (A - D) 51 y/o female with osteosarcoma metastasis. At baseline (A) CT and (B) fused ^{18}F-FDG PET/CT show an entirely calcified metastasis in the pancreatic tail without corresponding ^{18}F-FDG uptake. At follow up (C) CT and (D) fused ^{18}F-FDG PET/CT show increase in size without corresponding ^{18}F-FDG uptake.

reported to be present in around 20% - 25% of pulmonary angiosarcoma metastases.[39] Hemorrhagic metastases are characterized by a ground-glass component surrounding the solid nodule ("halo sign") and should not be dismissed as infectious disease (fungi, septic emboli, mycobacterial) in known primary neoplasms with high vascularity. The ground glass is thought to represent peritumoral alveolar hemorrhage, secondary to the fragility of neovascular tissue (Fig. 4).

In concordance to pulmonary angiosarcoma metastases, hemorrhagic and cystic changes can also be present in hepatic metastases.[40]

Synovial sarcoma

Synovial sarcoma shows an atypical imaging appearance of the pulmonary metastatic distribution in comparison to other

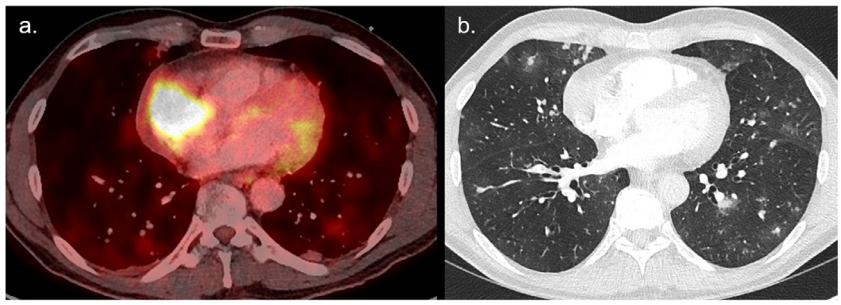

Figure 4 Angiosarcoma with hemorrhagic pulmonary metastases. (A, B) 62 y/o male with cardiac angiosarcoma (A) Fused ^{18}F-FDG PET/CT shows primary tumor in the right atrium with increased ^{18}F-FDG uptake. (B) Chest CT shows bipulmonary hemorrhagic metastases (ground glass attenuation surrounding solid nodules) in random distribution.

histiotypes with pleuropulmonary metastases being the most common site of metastatic spread.[41]

Benign versus malignant soft tissue and bone lesions

Clear tumor delineation, absence of a perifocal edema, and absence of local tumor infiltration on cross sectional imaging (CT and MRI) are imaging features shared by benign and malignant soft tissue tumors, and cannot reliably be applied to assess the benign or malignant nature of the tumor.

Tumor size, tumor location, tumor depth, localization in relation to the fascia, and to a certain extent tumor necrosis are local tumor characteristics that can be assessed by imaging and impact tumor staging[42] and / or prognostication.[43]

Although benign bone and soft tissue lesions typically have a low glycolytic phenotype, both can display a wide spectrum of ^{18}F-FDG uptake.

In benign soft tissue lesions, avid ^{18}F-FDG uptake has been observed in e.g. infectious disease, sterile inflammatory process,[44,45] neurofibroma,[46] schwannoma,[47,48] elastofibroma dorsi,[49] pigmented villonodular synovitis (PVNS) and tenosynovial giant cell tumor (TGCT).[50]

Common benign bone findings, such as hemangiomas, bone infarcts, and bone islands, mostly exhibit low SUVs.[51] On the other hand increased ^{18}F-FDG uptake can be observed in e.g. activated red bone marrow, fracture, osteoarthritis, osteomyelitis, fibrous dysplasia,[52] or Paget's disease[53] limiting the use of metabolic tumor information by ^{18}F-FDG PET/CT in differentiating between benign and malignant.

In contrary, the low glycolytic phenotype and the predominance of fat impairs differentiation between well-differentiated liposarcoma and lipoma due to shared imaging characteristics on ^{18}F-FDG PET/CT and MRI.

Although the metabolic information might be imperfect to discriminate between benign and malignant tumors, additional features such as patient's age, tumor location, and further imaging characteristics are helpful to narrow down the differential diagnosis (Fig. 5).

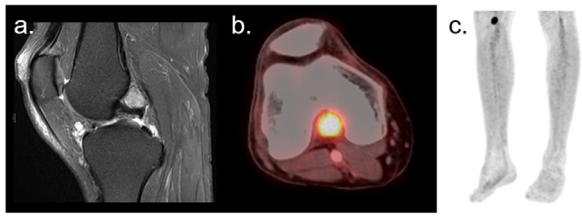

Figure 5 Tenosynovial giant cell tumor (localized type). (A - C) 43 y/o female with TGCT of the right knee. (A) T1 post-contrast shows significant contrast media enhancement in a well-circumscribed soft tissue nodule within the posterior joint space. (B) Fused ^{18}F-FDG PET/CT and (C) ^{18}F-FDG PET MIP show corresponding intense ^{18}F-FDG uptake.

Other radiotracers

3′-deoxy-3'-fluorothymidine (^{18}F-FLT)

^{18}F-FLT uptake has been studied as a surrogate of cell proliferation. Proliferative activity dependent accumulation of ^{18}F-FLT has been demonstrated for a variety of neoplasms. An avid ^{18}F-FLT phenotype in various STS histiotypes has been reported.[54] Changes in ^{18}F-FLT uptake before and after neoadjuvant therapy however did not reliably predict tumor response, and post-neoadjuvant ^{18}F-FLT uptake was unrelated to thymidine kinase 1 (TK1) and Ki-67 expression.[54]

^{68}Ga-fibroblast activation protein (^{68}Ga-FAPI)

^{68}Ga-FAPI targets the fibroblast activation protein (FAP). FAP is highly expressed in cancer-associated fibroblasts in the stroma of several tumor entities, including sarcoma.[55] The extent of ^{68}Ga-FAPI expression and the accuracy of ^{68}Ga-FAPI to differentiate between benign and malignant soft tissue and bone lesions warrants further studies.

Conflicts of interest

The authors declare no conflict of interest in regards to this work.

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