

Spectrum of Flurodeoxyglucose Positron Emission Tomography/Computerized Tomography Findings in Tumors and Tumor-Like Conditions of the Musculoskeletal System

Abstract

Bone and soft-tissue tumors display a wide range of metabolic activity on flurodeoxyglucose positron emission tomography/computerized tomography (FDG PET/CT) imaging due to their varying histopathological features. Several benign tumors show high FDG uptake similar to that seen in malignant lesions and their metabolic characteristics can overlap. Certain benign tumors can potentially undergo malignant transformation and FDG PET/CT can play an important role in detecting malignant change. The intensity of metabolic activity on FDG PET/CT correlates with histological grade of malignant tumors and also acts as a valuable prognostic factor. FDG PET/CT plays an important role in the staging work up of bone and soft-tissue malignancies. It has been found to be superior to conventional imaging techniques primarily for detecting distant metastatic disease. Because of its ability to detect metabolic changes, FDG PET/CT is a very useful in assessing response to treatment. Metabolic response seen on FDG PET is a powerful surrogate marker of histopathological response to chemotherapy. The purpose of this article is to study the variable patterns of FDG uptake in tumors of the musculoskeletal system, describe the clinical utility of FDG PET/CT in predicting malignant change in benign tumors and discuss its role in staging, response assessment, and prognostication of malignant lesions.

Keywords: Bone, flurodeoxyglucose positron emission tomography/computerized tomography, musculoskeletal, soft-tissue, tumors

Introduction

Tumors of the bone and soft-tissue encompass a wide range of benign and malignant pathologies. Imaging modalities such as plain radiographs, computerized tomography (CT) scan, and magnetic resonance imaging (MRI) are routinely used to evaluate these tumors. Majority of the tumors of the musculoskeletal (msk) system have well-documented morphological imaging features that help in diagnosis, characterization, staging, and treatment planning. Flurodeoxyglucose positron emission tomography (FDG PET) and PET/CT is an established imaging modality in evaluation of several malignancies. Both benign and malignant msk tumors display variable metabolic characteristics on FDG PET/CT imaging owing to their unique histopathological features. In the context of bone and soft-tissue tumors, the role of FDG PET/CT in establishing diagnosis, staging, response evaluation,

prognostication, and predicting histological grade is still evolving unlike its established role in several other cancers. With the ever increasing use of FDG PET/CT across a variety of clinical conditions, it is important to get familiarized with its role and scope in msk tumors and also learn about the common diagnostic dilemmas and pitfalls likely to be encountered in routine clinical practice.

Benign Bone Lesions and Flurodeoxyglucose Uptake [Table 1]

Lesions with high flurodeoxyglucose uptake

Benign tumors show a wide range of metabolic activity on FDG PET/CT studies based on their varied histologies. A few mechanisms have been proposed and believed to be the cause of intense FDG concentration in certain benign tumors. The cellular composition of many benign bone tumors contains histiocytes and

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giant cells which belong to the monocyte-macrophage lineage.^[1,2] Energy for these cells is predominantly provided by intracellular glucose mechanism^[3,4] which is the cause of high intratumoral concentration of FDG on PET studies. Tumors which have abundance of histiocytes and giant cells and show high FDG avidity include chondroblastomas [Figure 1], osteoblastomas [Figure 2], giant cell tumors [Figure 3], and aneurysmal bone cysts.^[5-7] Brown tumors which are not true tumors are lytic bone lesions formed due to increased osteoclastic activity caused by excess secretion of parathyroid hormone in end stages of primary and secondary hyperparathyroidism. Brown tumors are histologically similar to giant cell tumors and show FDG uptake due to the presence of giant cells and macrophages [Figure 4]. Reduction of FDG uptake in brown tumors is noted after treatment for hyperparathyroidism.^[8]

Osteoid osteomas are benign lesions that can show intense FDG uptake.^[9] The nidus of painful osteoid osteomas show

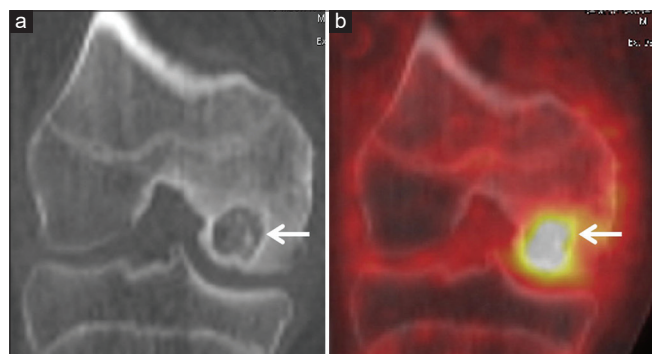


Figure 1: Chondroblastoma in a 24 year old man with complaints of pain around the knee. (a) Coronal reformatted CT image shows a well defined lytic lesion with a narrow zone of transition and a sclerotic rim in the epiphyseal region of the lower end of the tibia with specks of calcification (arrow). (b) Axial FDG PET/CT shows intense FDG uptake in the chondroblastoma (arrow) with a SUVmax of 12.5. Chondroblastomas are known to concentrate FDG

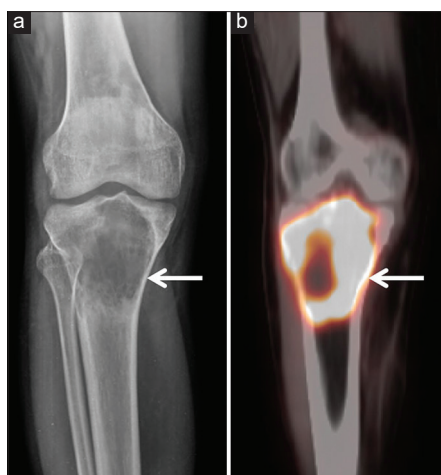


Figure 3: GCT of the tibia in a 28 year old man who presented with pain around the knee. (a) Plain radiograph (antero-posterior view) shows a well defined sub-articular lytic lesion in the upper end of the tibia (arrow). (b) Coronal FDG PET/CT shows intense FDG uptake in the lesion (arrow) with SUVmax of 22.2. GCT's are FDG avid benign bone tumors

increased cyclooxygenase-2 expression.^[10] Pain associated with osteoid osteomas is due to release of prostaglandins as a direct result of high levels of cyclooxygenase-2. Increased levels of prostaglandins cause vasodilation in the vascular nidus, this increased blood supply causes increased recruitment of inflammatory cells, which are known to utilize glucose for their energy requirements. This could be one of the mechanisms explaining high FDG uptake in painful osteoid osteomas [Figure 5].^[11] Percutaneous radiofrequency ablation (RFA) has become a preferred treatment modality for many of the benign tumors such as osteoid osteoma, chondroblastoma, and osteoblastoma to relieve pain and to prevent further growth.^[12-14] High concentration of FDG in these benign lesions can form the

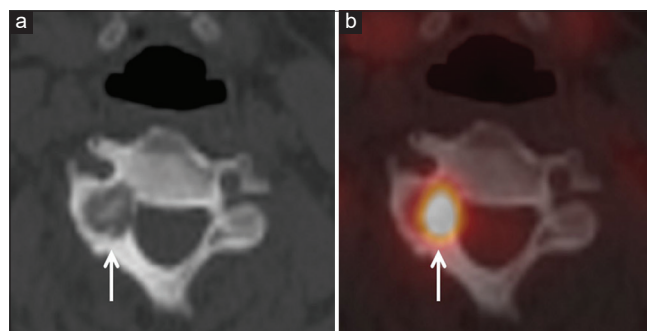


Figure 2: Osteoblastoma in a cervical vertebra of a 21 year old lady with neck pain. (a) Axial CT image shows a well defined lytic lesion in the articular process (arrow) with central calcification. (b) Axial FDG PET/CT shows intense FDG uptake in the osteoblastoma (arrow) with SUVmax of 11. Osteoblastomas are FDG avid benign bone tumors

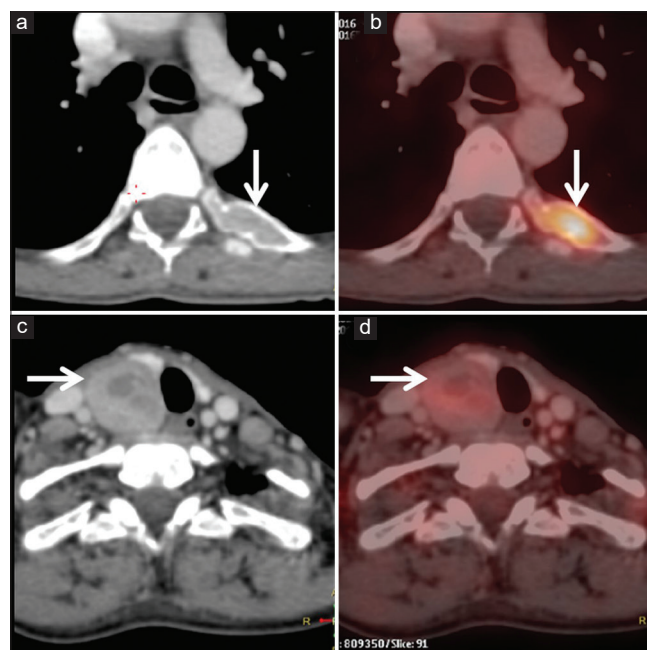


Figure 4: Brown tumor in a 34 year old female with primary hyperparathyroidism who presented with neck swelling and bone pains. (a) CT shows an expansile lytic lesion in the posterior aspect of the rib (arrow). (b) FDG PET/CT shows high FDG uptake in the lytic brown tumor. (c) CT shows a well defined enhancing parathyroid adenoma (arrow). (d) FDG PET/CT shows low grade FDG uptake in the parathyroid adenoma

basis of using FDG PET/CT as an imaging tool to monitor response to RFA. RFA causes coagulation necrosis in the ablated lesion and destruction of its metabolic pathways. Resolution of FDG uptake after RFA can thus be used as a surrogate marker of completeness of ablation.^[11]

In lesions, such as fibrous dysplasia [Figure 6] and other fibrous tumors such as cortical desmoid, desmoplastic fibroma, nonossifying fibroma/fibrous cortical defect [Figure 7], and osteofibrous dysplasia fibroblasts are the predominant proliferating cells. Although giant cells are present in some amounts around degenerative foci in these lesions, it is the actively proliferating fibroblasts that are responsible for high concentration of FDG.^[6,15,16] Variation in the intensity of FDG uptake in various fibrous lesions and also among the tumors belonging to the same histology can be attributed to the difference in the amount of actively proliferating fibroblasts.

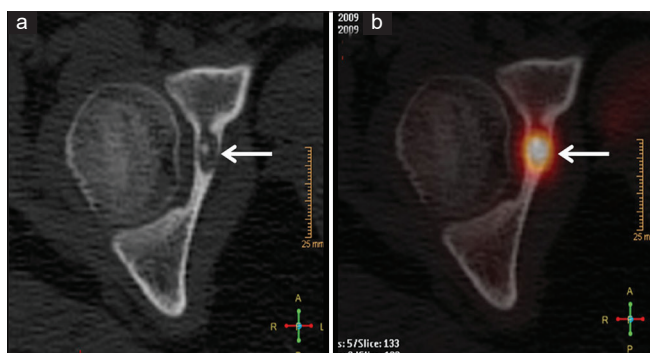


Figure 5: Osteoid Osteoma of the ischio-pubic ramus in a 14 year old girl who presented with right hip pain. (a) Axial CT image shows a well defined lucency with a central sclerotic nidus (arrow). (b) Axial FDG PET/CT shows intense FDG uptake in the nidus of the OO with SUVmax of 10.5. Nidus of painful OO concentrates FDG

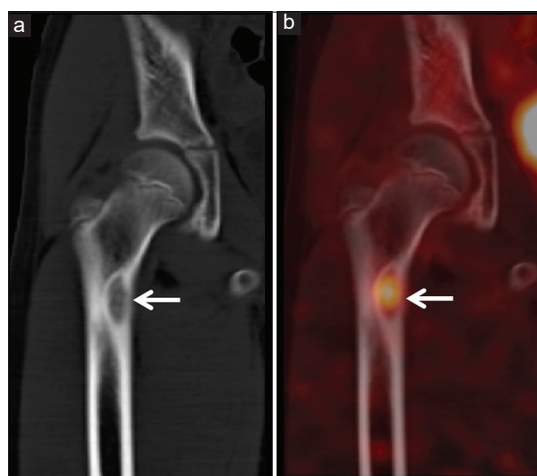


Figure 7: Incidentally detected non-ossifying fibroma in a 12 year old boy with Ewings sarcoma of the clavicle. (a) Coronal reformatted CT shows a well defined cortical based lytic lesion with a sclerotic rim in the proximal femoral shaft (arrow) with a SUVmax of 2.6. (b) Coronal FDG PET/CT shows focal FDG uptake in the lesion (arrow) with a SUVmax of 2.6. NOF's are known to concentrate FDG

It should be borne in mind that many benign bone lesions whether slow growing and indolent or aggressive can show higher tracer uptake compared to certain malignant bone tumors. Thus, the intensity of metabolic activity should not be considered as a pointer toward malignancy while evaluating such lesions and emphasis should be given to the radiographic and CT features to look for signs of aggressive malignant traits.^[17]

Lesions with low flurodeoxyglucose uptake

Benign cartilaginous tumors such as enchondroma and osteochondroma [Figure 8] show low concentration of FDG in most instances.^[5,6,18,19] Studies have shown that as compared to other benign tumors, cartilaginous tumors both benign as well as their malignant counterparts show a surprising paucity of FDG uptake. The primary reason for this can be attributed to the histological nature and cell type of these tumors. Cartilage tumors show relative hypovascularity, have a matrix which is gelatinous^[19] and are hypocellular with high water content. These factors contribute to poor FDG uptake in majority of cartilage tumors, though occasionally one could come across a lesion

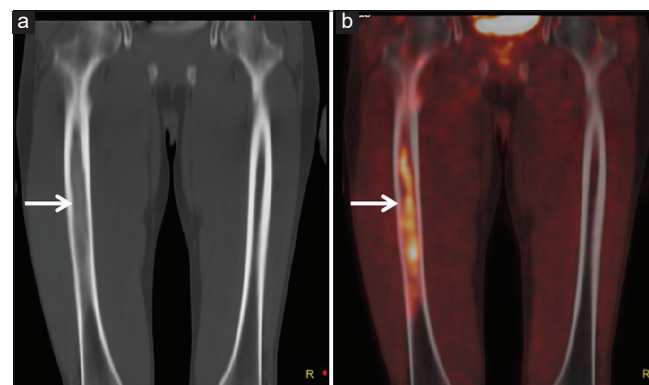


Figure 6: Incidentally detected FD in a 42 year old man with malignancy of the oral cavity. (a) Coronal reformatted CT image shows ground glass change in the expanded marrow of the right femoral shaft (arrow). (b) Coronal FDG PET/CT shows FDG avidity in the ground glass changes of FD (arrow) with SUVmax of 6.7. Actively proliferating fibroblasts of FD concentrate FDG

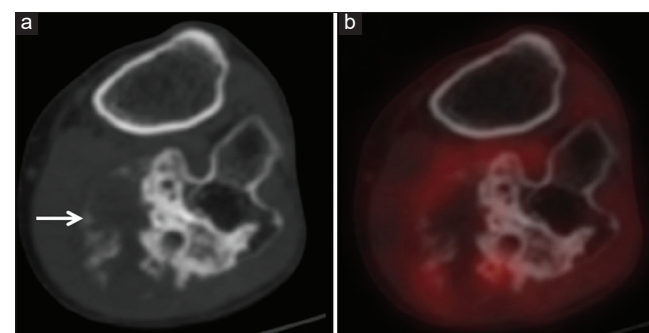


Figure 8: Osteochondroma in a 28 year old man who presented with swelling in the leg. (a) Axial CT shows an exophytic osteochondral lesion arising from the fibula (arrow). (b) Axial FDG PET/CT show no significant FDG uptake within the lesion, SUVmax 2.0. Osteochondromas show poor FDG concentration

with relatively higher metabolism [Figure 9]. Intraosseous lipomas and hemangiomas [Figure 10] are other benign lesions which show poor FDG uptake which could be attributed to their indolent, nonaggressive nature with low cellularity and metabolism.

Benign Soft-Tissue Lesions and Fluorodeoxyglucose Uptake [Table 1]

FDG is known to concentrate in certain benign soft tissue tumors and tumor like conditions. Hibernoma is a benign tumor of brown fat origin that has morphological imaging characteristics similar to other fat containing tumors such as lipoma and liposarcoma. Brown fat is a producer of heat and contains large quantities of mitochondria and hence is highly metabolic, the primary reason for high FDG avidity of hibernomas [Figure 11].^[20,21] Differentiating hibernoma from liposarcomas can be tricky with overlapping features

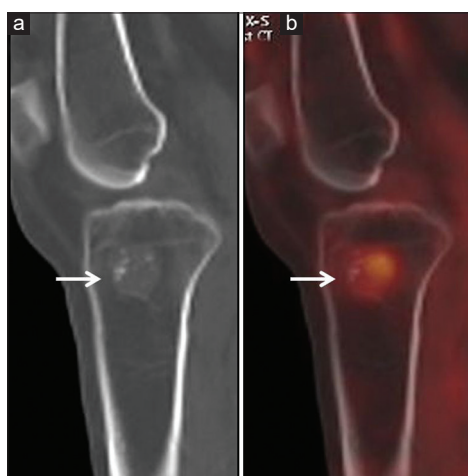


Figure 9: Enchondroma in a 44 year old lady with pain around the knee. (a) Sagittal reformatted CT image shows a lesion in the femur with characteristic chondroid calcification (arrow). (b) Sagittal FDG PET/CT show moderate grade FDG uptake in the enchondroma (arrow), SUVmax3.2. Majority of enchondromas show poor FDG concentration with occasional lesion showing moderate to high uptake

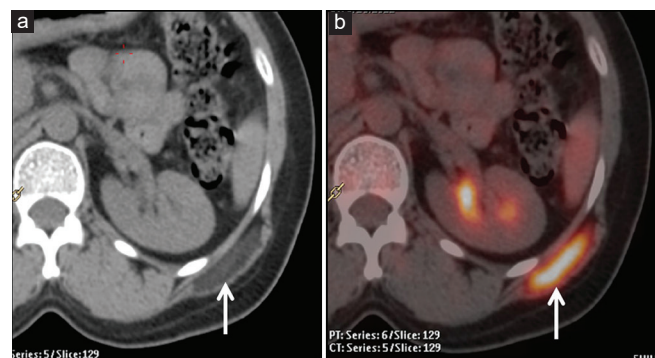


Figure 11: Incidentally detected hibernoma in a 37 year old lady with breast cancer. (a) Axial CT image shows a well defined subcutaneous fat density lesion in the lumbar lesion, with areas of soft tissue attenuation within (arrow). (b) Axial FDG PET/CT shows intense FDG uptake in the hibernoma with a SUV maxof 22. Hibernomas are tumors of brown adipose tissue and highly metabolic in nature

on CT, MRI as well as on FDG PET since liposarcomas show high FDG uptake. Variations and fluctuations in the standardized uptake value (SUV) of FDG concentration over time in hibernomas can be useful in differentiating them from malignant fat containing tumors.^[21]

Elastofibroma dorsi (EFD) is a benign soft-tissue tumor located in the inferior scapular region. EFD can be bilateral or unilateral, majority are asymptomatic and incidentally detected on imaging, though occasionally they can present as painful lumps.^[22] EFD are known to concentrate FDG and are often seen as hypermetabolic soft-tissue lesions in the inferior scapular region [Figure 12] when PET/CT scans are performed for other indications.^[23,24] The mechanism of FDG uptake in EFD is uncertain, one of the possible mechanisms could be the accumulation and proliferation of abnormal elastic fibers,^[25] high vascularity, and increased metabolic activity. Due to their hypermetabolic nature, EFD can be erroneously interpreted as metastatic soft tissue deposits during an oncologic PET/CT examination. Typical location in the inferior scapular region, CT appearance of a lenticular shaped lesion isoattenuating to the surrounding musculature with hypodense fatty striations^[26] and stability of FDG avidity over serial PET scans^[27] can be useful in differentiating EFD from malignant lesions and prevent unnecessary biopsies.

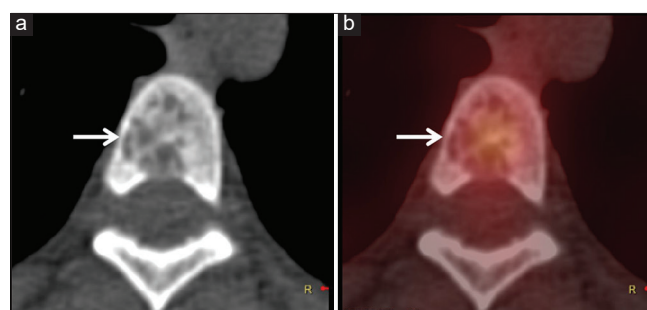


Figure 10: Incidentally detected vertebral hemangioma in 20 yearoldman with ewing's sarcoma. (a) Axial CT image shows a well definedtrabaculated lesion in the vertebral body. (b) Axial FDG PET/CT image shows low grade FDG uptake in the hemangioma with SUVmax of 1.2. Hemangiomas show poor or low FDG uptake

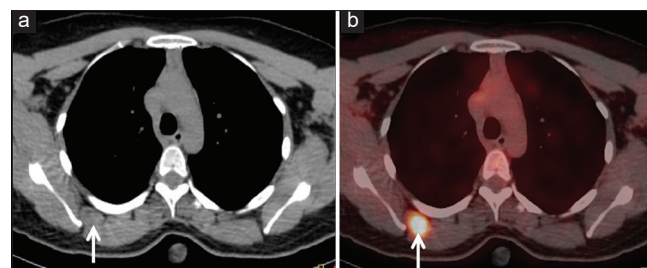


Figure 12: Incidentally detected elastofibroma dorsi in a 23 year old lady with ewingssarcoma of the thumb. (a) Axial CT image shows a soft tissue nodule adjacent to the medial scapular margin (arrow). (b) Axial FDG PET/CT image shows intense FDG uptake in the nodule (arrow) with SUVmax of 9.2. Biopsy confirmed diagnosis of EFD. EFD's are benign tumors that concentrate FDG

Tumors of the nerve sheath such as schwannoma and neurofibroma are not infrequently seen during whole body PET/CT examination either as incidental findings or when the study is performed to evaluate hereditary conditions such as neurofibromatosis-1 (NF-1). Both schwannoma and neurofibroma whether sporadic or as a part of a hereditary syndrome can show varying degrees of FDG uptake. Schwannomas are benign, slow growing tumors arising from the nerve sheath usually in the extremities or the head-neck region^[28] and less commonly in the chest and abdomen. The exact reason for high FDG uptake in schwannomas is unclear: Overexpression of glucose transporter protein-type 3 (GLUT 3) which is one of the major glucose transporters on neuronal surface could provide an explanation,^[29] but this is yet to be conclusively proven. FDG uptake in schwannomas can be variable ranging from low grade to highly FDG avid tumors [Figure 13]. This wide range of FDG uptake can be explained by tumor cellularity, hypercellular tumors showing high SUV compared to hypocellular tumors.^[29] Heterogeneity of uptake is also a feature seen in schwannomas particularly in larger tumors which frequently exhibit cystic and necrotic changes. FDG uptake in smaller lesions tends to be more homogeneous. Neurofibromas are also benign tumors arising from the nerve sheath and can be sporadic in nature or as a part of a neurocutaneous syndrome like NF-1. They show a more homogeneous pattern of FDG uptake [Figure 14] which is uniformly low compared to that observed in schwannomas.^[30] Multiple nerve sheath tumors located in regions such as neck, mediastinum, and retroperitoneum can mimic more sinister pathology like lymph nodes or soft tissue deposits in patients with a known malignancy. This diagnostic pitfall should be borne in mind during PET/CT interpretation.

Langerhans cell histiocytosis (LCH) is a multisystem disorder in which lesions demonstrate increased FDG

uptake [Figure 15] as they contain abundance of histiocytes and giant cells. Since treatment decisions are dictated by the presence of solitary versus multiple bone lesions, FDG

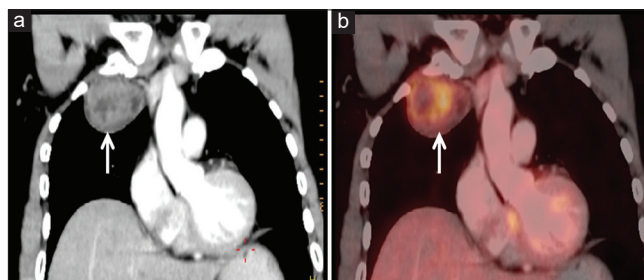


Figure 13: Schwannoma in a 47 year old man with complaints of right sided chest pain.(a) Coronal reformatted CT image shows a well demarcated heterogeneously enhancing extrapleural mass in the region of the lung apex with cystic areas within (arrow). (b) Coronal FDG PET/CT image shows high but heterogeneous FDG uptake in the mass with SUVmax of 7.0. Biopsy confirmed the diagnosis of schwannoma.Heterogeneity of FDG uptake can be seen in schwannomas due to cystic changes

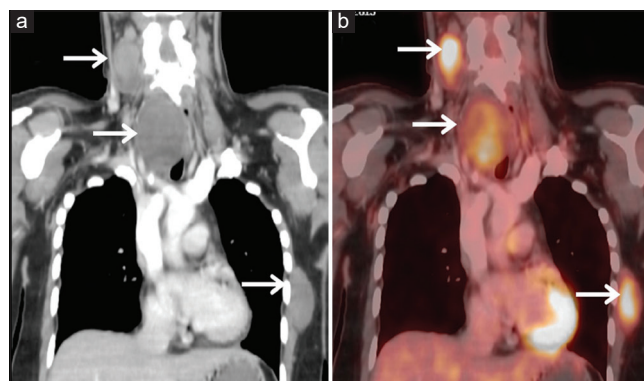


Figure 14: Multiple neurofibromas in a 36 year old lady with NF-1. (a) Coronal reformatted CT image shows well defined enhancing soft tissue masses in the neck and the thoracic wall (arrows). (b) Coronal FDG PET/CT image shows high and fairly homogenous FDG uptake in the masses with average SUVmax of 6.5 (arrows).Neurofibromas are known to concentrate FDG

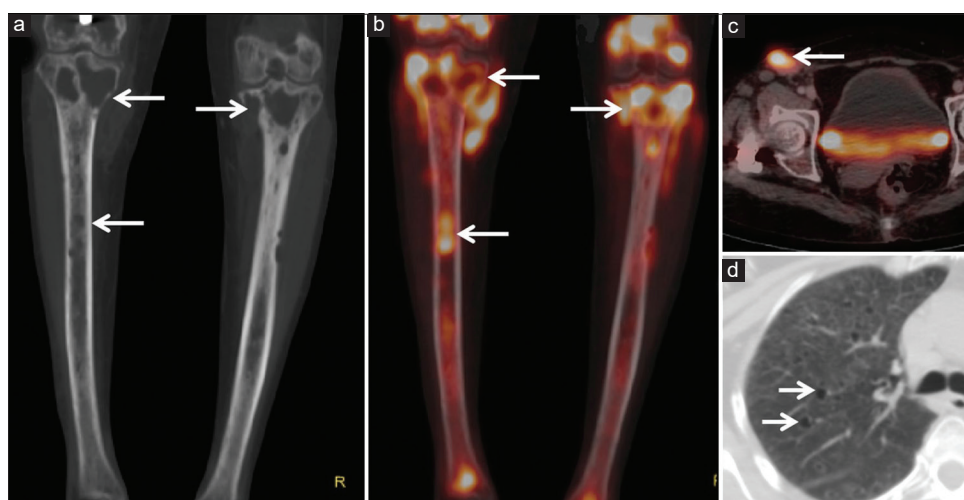


Figure 15: Multisystem involvement in a 36 year old lady with LCH. (a) Coronal reformatted CT image shows multiple lytic lesions in tibia bilaterally (arrows). (b) Coronal FDG PET/CT shows FDG avidity in the tibial lesions (arrows). (c) Axial PET/CT shows a FDG avid inguinal node involved by disease (arrow). (d) Axial CT in lung window settings shows cystic areas in the lungs(arrows). FDG PET/CT can demonstrate multisystem involvement in LCH

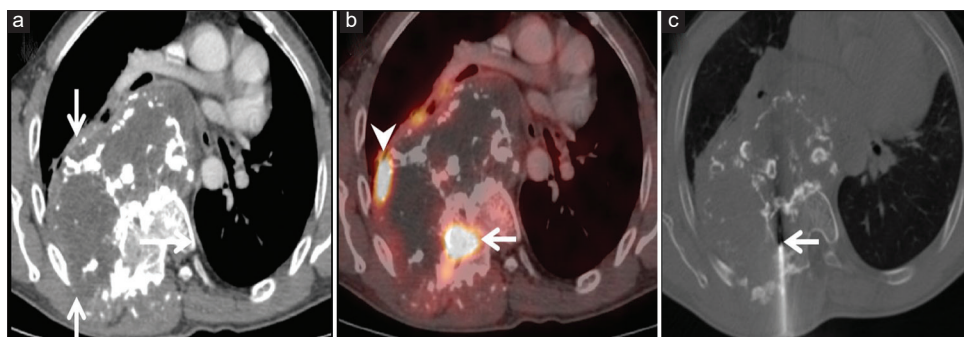


Figure 16: 34 year old man with known osteochondroma of the rib with complaints of recent onset chest pain. (a) CT shows a osteochondral lesion arising from the costovertebral region with an associated soft tissue mass (arrows). (b) FDG PET/CT shows an intense focus of uptake within the mass suggesting a malignant change (arrow). Arrowhead shows FDG avidity in the atelectatic component of the lung. (c) CT guided biopsy from the FDG avid focus (arrow) confirmed the diagnosis of grade II chondrosarcoma

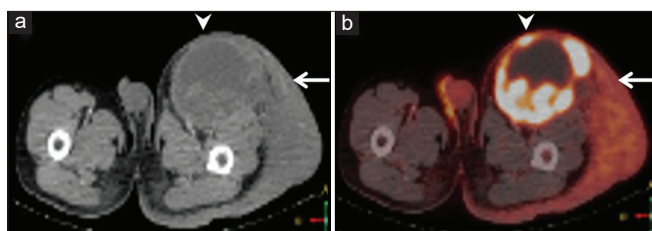


Figure 17: 30 year old man with NF-1 presented with gradually increasing upper thigh swelling. (a) Axial CT shows infiltrative subcutaneous soft tissue thickening consistent with plexiform neurofibroma (arrow). Necrotic soft tissue is seen within the neurofibroma (arrowhead). (b) Axial FDG PET/CT shows diffuse and uniform low grade FDG uptake in the plexiform neurofibroma (arrow) and intense uptake (SUVmax 15.2) in the necrotic mass, biopsy from which confirmed malignant peripheral nerve sheath tumor

PET can impact management by identifying multifocal skeletal disease more effectively compared to conventional imaging.^[31] In addition, it can act as a prognostic marker by detecting disease in high risk organs such as liver, spleen, and lungs. FDG PET/CT can monitor response to systemic therapy in LCH by demonstrating reduction in metabolic activity in patients who are good responders.

Prediction of Malignant Change by Positron Emission Tomography/Computerized Tomography

FDG PET/CT has the potential to detect malignant change in certain benign bone and soft-tissue tumors. Although many benign tumors show high degree of FDG uptake there are certain chondroid lesions such as enchondroma and osteochondroma which show a relative paucity of FDG uptake. These benign chondroid tumors can undergo malignant or sarcomatous transformation, which can be seen as foci of high FDG uptake within a relatively hypometabolic background [Figure 16]. FDG PET/CT is a promising tool to predict malignant change and to differentiate benign from malignant osteochondromas.^[32,33] The differentiation between a benign osteochondroma and a grade I chondrosarcoma is often difficult because both lesions often display lower relative paucity of FDG uptake. Lesions which show a malignant change to grade

II/grade III or de-differentiated chondrosarcoma show a significantly higher FDG uptake as compared to benign lesions. In patients with multiple hereditary exostoses who are clinically symptomatic for malignant change, PET can detect early malignant change at other clinically asymptomatic sites in addition to confirming sarcomatous transformation at the suspected site. FDG PET/CT by directing percutaneous biopsy from the metabolically avid part of the lesion can be used to obtain the most biologically representative sample for histological analysis. This approach can avoid biopsies from nonrepresentative areas and the possibility of incorrect or missed diagnosis [Figure 16].

Detecting malignant transformation in benign nerve sheath tumors is clinically challenging and morphologic imaging cannot reliably differentiate benign lesions from the malignant transformed ones. FDG PET/CT has been found to be useful in detecting early malignant transformation in benign peripheral nerve sheath tumors particularly in patients with neurocutaneous syndromes like NF-1. A nerve sheath tumor that shows focal FDG uptake that is much intense compared to rest of the lesions is likely to have undergone a sarcomatous change [Figure 17]. Both visual qualitative PET assessment and use of semi-quantitative SUV cutoff have shown good diagnostic accuracy.^[34-36] However, due to the lack of set criteria for visual interpretation and variability of SUV cut offs, its use is somewhat restricted in clinical practice.

Paget's disease is characterized by abnormal and excessive remodeling of the bone.^[37] Plain radiographs are the main stay of diagnosis and classical findings are described depending on the phase of the disease. Due to increased vascularity and remodeling the bone lesions show increased radionuclide uptake on bone scintigraphy. Paget's disease is not associated with increased FDG uptake in majority of patients though rarely hypermetabolism can be seen in more active cases.^[38] Sarcomatous transformation is one of the rare but dreaded complications seen in long standing disease. The relative paucity of FDG uptake in pagetoid lesions can aid in localizing the site of malignant

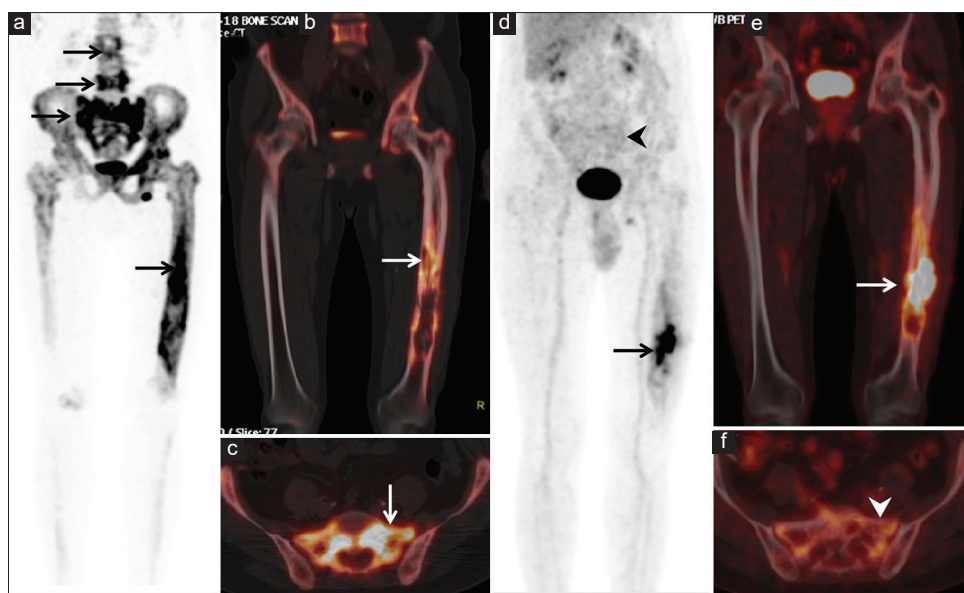


Figure 18: 70 year old man with Pagets disease presented with complaints of pain in the left thigh. (a) Maximum intensity projection (MIP) image of a ^{18}F Sodium fluoride (NaF) PET/CT scan shows increased tracer uptake in several skeletal sites (arrows) representing increased bone turnover of Pagets disease. (b) and (c) Coronal and axial NaF PET/CT images show increased tracer uptake in the left femur and the sacrum (arrows). 70 year old man with Pagets disease presented with complaints of pain in the left thigh. (d) and (e), MIP and coronal FDG PET/CT images of the same patient shows increased FDG uptake in the left femur corresponding to the site of sarcomatous transformation (arrows) with a SUVmax of 15.8. (f) Axial FDG PET/CT shows the absence of FDG uptake in rest of the pagetoid lesions (arrowheads in d and f).

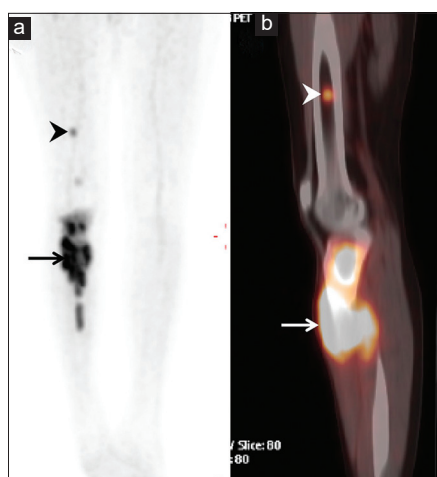


Figure 19: 17 year old girl with Ewing's sarcoma of the tibia referred for baseline staging with FDG PET/CT. (a) Coronal MIP image shows FDG avid lesion in the right tibia (arrow) with a SUVmax of 10.9 and another smaller focus of FDG uptake in the right femur (arrowhead). (b) Sagittal FDG PET/CT image confirms the disease at the primary site in the tibia (arrow) and a marrow metastasis in the femur (arrowhead).

transformation which will demonstrate high FDG uptake associated with sarcomas [Figure 18].

Fluorodeoxyglucose Positron Emission Tomography/Computerized Tomography in Staging Malignant Tumors

Bone sarcomas such as Ewing's sarcoma (EWS) and osteogenic sarcoma (OS) show high rate of glycolysis and thereby high FDG uptake. FDG PET/CT is included in the

standard metastatic work-up of EWS patients due to its high accuracy in detecting skeletal metastases [Figure 19]. Its sensitivity is significantly higher compared to bone scintigraphy for skeletal metastases.^[39,40] If no evidence of metastatic disease is seen on FDG PET/CT additional imaging investigations or procedures like bone marrow aspiration/biopsy can be avoided.^[41] Thus, inclusion of FDG PET/CT in the metastatic work up of EWS has strong implications for staging and subsequent therapy planning.

OS is FDG avid tumors and PET/CT has been used for initial staging work up. Studies have shown that FDG PET/CT has a better sensitivity compared to bone scan in detecting skeletal lesions of OS.^[42,43] FDG PET/CT scores over bone scintigraphy by detecting more metastatic lesions in the region of the growth plate in young adults [Figure 20], where the high physiological tracer uptake can mask metastatic disease on bone scans.^[42] The incremental benefit of FDG PET/CT over bone scintigraphy observed in OS is not as pronounced as that seen in EWS.^[39] This could be due to the different nature of metastases produced by the two sarcomas. Metastases of OS are bone forming or osteoblastic and are easily detected by bone scintigraphy, which has a high sensitivity for new bone/osteoid formation, whereas metastases of EWS predominantly infiltrate the marrow and characterized by osteoclastic activity. Owing to this the impact of FDG PET/CT on staging and therapy planning in OS is limited as compared to EWS.

Soft-tissue sarcomas (STS) are histologically a heterogeneous group of malignant tumors. Majority of

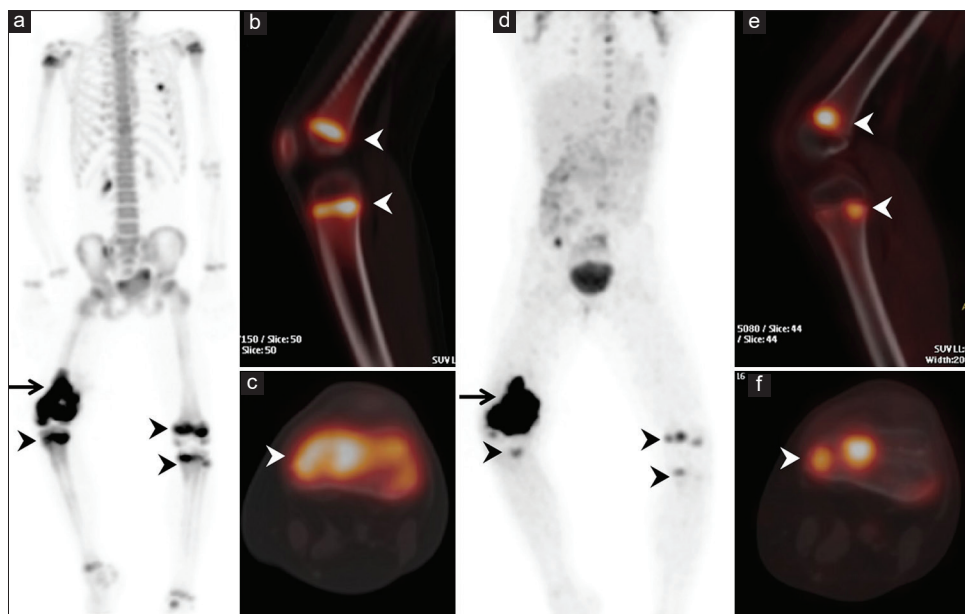


Figure 20: 8 year old boy with osteogenic sarcoma of the femur referred for metastatic staging. (a) MIP image of a ^{18}F NaF PET/CT scan shows increased tracer uptake at the primary site in the femur (arrow) and also linear uptake in the region of the growth plates in the distal femur and proximal tibia (arrowheads). (b) and (c) Sagittal and axial sodium fluoride PET/CT images confirms the location of uptake to be in the physal plates (arrowheads) 8 year old boy with osteogenic sarcoma of the femur referred for metastatic staging. (d) MIP image of FDG PET/CT in the same patient shows increased FDG uptake at the primary site (arrow) and focal uptake in the region of the growth plates in the distal femur and proximal tibia (arrowheads). (e) and (f) Saggital and axial FDG PET/CT confirms the focal nature of uptake in the physal plates (arrowheads).

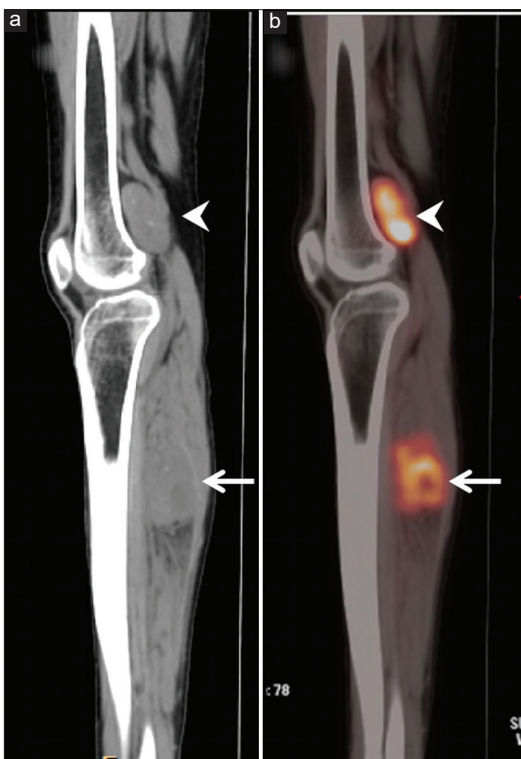


Figure 21: 15 year old girl with synovial sarcoma of the calf referred for baseline staging with FDG PET/CT. (a) Sagittal reformatted CT image shows an illdefined soft tissue in the calf (arrow) and an enlarged popliteal node (arrowhead). (b) Sagittal FDG PET/CT shows increased FDG uptake in the primary mass (SUVmax 14.9) (arrow) as well as the popliteal node (arrowhead). FDG PET/CT detects nodal and distant metastases in high grade soft tissue sarcoma

histological subtypes (98%) show FDG avidity which can vary in intensity based on their histopathological grade.^[44] Since more than 75% of metastases in adult STS occur in the lungs, the role for metastatic work up beyond CT chest is questionable. Hence, FDG PET/CT is not routinely used in metastatic staging of adult STS. However, certain high-grade sarcomas have a higher propensity for nodal and skeletal metastases [Figure 21]. On such occasions, FDG PET/CT can be used for initial staging as it can potentially change management decisions by detecting distant metastases.

Pediatric tumors like rhabdomyosarcomas have a high risk of regional nodal metastases and regional nodal sampling is recommended during surgery.^[45] FDG PET/CT is superior to conventional imaging in detection of regional nodal disease in RMS^[39,46] and identifies more diseased nodes with less indeterminate results. It also provides a better overall initial staging accuracy by identifying unsuspected distant metastases.^[47]

Plasmacytoma and multiple myeloma (MM) are malignancies characterized by clonal proliferation of plasma cells. Both conditions demonstrate FDG avidity and PET/CT has been used for initial staging and assessing therapeutic response. Plasmacytoma can be confined to bone or occur in extramedullary locations. PET/CT due to its ability to scan the entire body is able to screen for additional lesions in patients who are presumed to have solitary plasmacytoma [Figure 22].

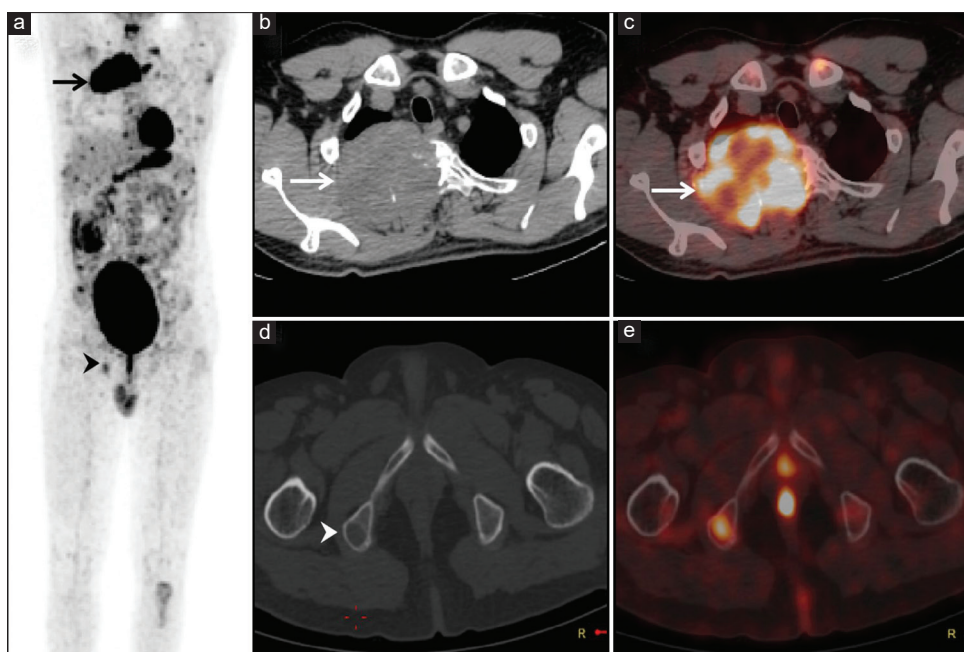


Figure 22: 43 year old man with a rib lesion diagnosed as plasmacytoma, underwent FDG PET/CT. (a) MIP image shows intense FDG uptake in the right hemithorax along with multiple avid foci in the skeleton (arrows). (b,c) CT reveals a soft tissue mass causing lytic destruction of the adjacent rib (arrow) showing intense FDG uptake on PET (arrows). (d,e) CT shows a lytic lesion in the right ischial tuberosity showing FDG avidity on PET (arrowheads). Biochemical and marrow work up suggested multiple myeloma

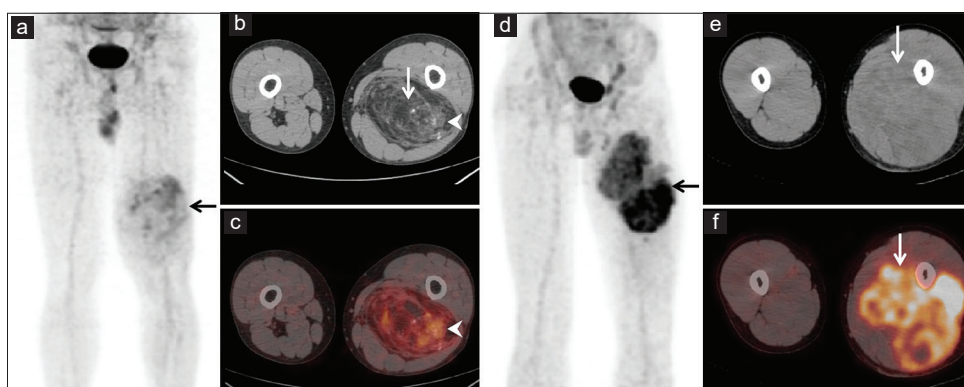


Figure 23: 61 man with liposarcoma of the thigh, underwent staging FDG PET/CT. (a) Coronal MIP image shows low grade uptake in the left thigh (arrow). (b) Axial CT shows a mass lesion in the posterior compartment of the thigh predominantly containing fatty tissue (arrow) interspersed with nodular and linear areas of soft tissue attenuation (arrowhead). (c) PET/CT shows low grade FDG uptake in the areas of soft tissue attenuation. Histopathological diagnosis was low grade, well differentiated liposarcoma. 32yr old man with synovial sarcoma of the thigh, underwent staging with FDG PET/CT. (d) MIP image shows intense FDG uptake in the left thigh (arrow). (e) Axial CT shows a soft tissue mass in the posterior compartment of the thigh (arrow). (f) PET/CT image shows intense FDG uptake in lesion. Histopathology revealed high grade synovial sarcoma. FDG uptake correlates with pathological tumor grade with high grade tumors displaying higher tracer concentration and SUV compared to low grade ones

Such patients are also at higher risk for evolution to MM and thus PET/CT can potentially have an impact on clinical management by changing treatment to systemic therapy rather than localized surgery or radiation.^[48,49] In a patient presumed to have a clinical diagnosis of solitary plasmacytoma, when FDG PET/CT shows several FDG avid lytic lesions along with multiple foci of FDG uptake in the marrow, the findings are more likely to represent MM. In MM, FDG PET/CT is useful in initial staging as it can detect multiplicity of lesions, diffuse marrow involvement, as well as

extramedullary disease. PET/CT is also used to image cases of smouldering MM, which is a mid-clinical stage, where it can predict rate of progression to established MM, which could be either slow and gradual or rapid and symptomatic.^[50,51]

Fluorodeoxyglucose Positron Emission Tomography/Computerized Tomography in Predicting Histological Grade and Prognosis

Bone and STS are heterogeneous tumors with the histology ranging from low grade to high grade. Within the same

Table 1: Flurodeoxyglucose uptake in commonly encountered benign bone and soft-tissue lesions

Nature of FDG uptake	Lesion	
High	Bone	
	Giant cell tumor	
	Chondroblastoma	
	Osteoblastoma	
	Aneurysmal bone cyst	
	Langerhans cell histiocytosis	
	Soft tissue	Elastofibroma dorsi
		Hibernoma
	Variable	Bone
Osteoid osteoma		
Nonossifying fibroma		
Fibrous dysplasia		
Paget's disease		
Cortical desmoid		
Soft tissue		
Neurofibroma		
Schwannoma		
Low		Bone
		Osteochondroma
		Enchondroma
		Hemangioma
		Intraosseous lipoma
		Soft tissue
	Hemangioma	
	Vascular malformation	
	Lipoma	

FDG: Flurodeoxyglucose

tumor, there could be separate foci of high and low grade as well as areas of necrosis. Hence, the histological grading is highly dependent on obtaining an adequate biopsy from the most biologically representative portion of the tumor. Metabolic activity on PET/CT has been correlated with histopathological characteristics of bone and STS and there appears to be a linear relationship with rising grades showing progressively higher SUV^[52] [Figure 23]. Chondrosarcomas which show a relatively poor concentration of FDG as compared to other bone and STS also demonstrate increasing metabolism with higher tumor grade.^[53] Tumors with myxoid component also tend to show on an average lower SUV values,^[54] due to the inability of FDG to access metabolically active cells as they are trapped within a myxoid stroma.^[55] Due to the presence of varying tumor features such as poor cellularity, myxoid stroma, necrosis, and hemorrhage, it is important to target the biopsy from the biologically most representative portion of the mass. Biopsy can be directed from the metabolically active component of the tumor seen on PET to obtain a

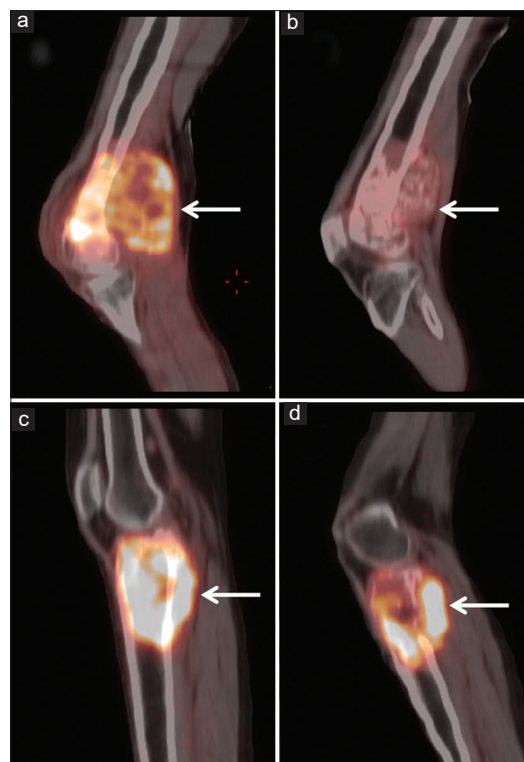


Figure 24: a-b: 21/M with OGS of the femur evaluated with FDG PET/CT at baseline and after 3 cycles of neoadjuvant chemotherapy show significant reduction in FDG uptake at the primary site suggesting metabolic response. Histopathological necrosis of 90% was seen after surgery. c-d: 18/F with tibial OGS evaluated with FDG PET/CT at baseline and after neoadjuvant chemotherapy show no significant change in FDG uptake suggesting metabolic non-responder. Histopathological necrosis of 20 % was seen after surgery

representative tissue sample that shows the correct tumor grade.

In sarcomas of the bone and soft tissue, the intensity of FDG uptake as measured by the SUV is associated with disease outcome. Tumors with higher SUV are generally high grade and have poorer overall survival compared to those with lower SUV.^[56] Thus, FDG PET/CT at diagnosis acts as a very useful predictive tool in these tumors.

Flurodeoxyglucose Positron Emission Tomography/Computerized Tomography in Evaluation of Treatment Response

Bone sarcomas are treated with multimodality treatment that includes chemotherapy, surgery, and radiation. Neoadjuvant chemotherapy downsizes the primary tumor to achieve better local control and also treats micrometastases. Tumor necrosis induced by neoadjuvant chemotherapy is the most important prognostic indicator of survival in patients with localized disease.^[57,58] Histopathological response assessment can only be done on the specimen obtained after surgery. Imaging techniques can act as noninvasive surrogate markers to predict pathological response. Size-based morphologic assessment evaluated

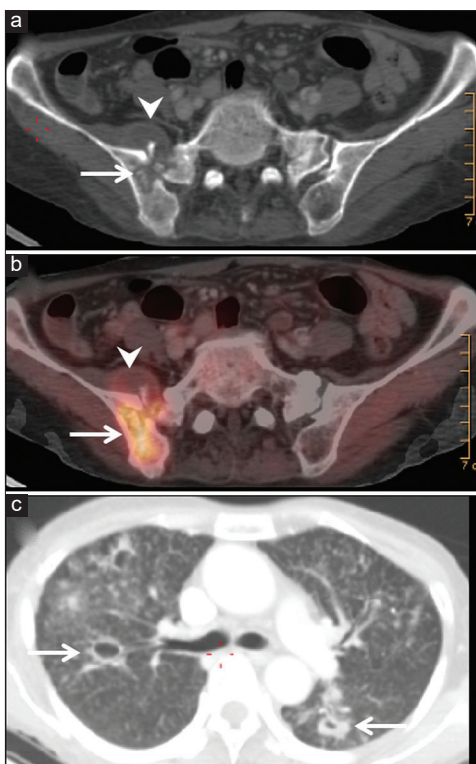


Figure 25: 64 yr old lady with backache, cough and weight loss underwent FDG PET/CT (a) CT shows an lytic lesion in the right iliac bone (arrow) with an associated collection (arrowhead). (b) FDG PET/CT shows increased FDG uptake in the lytic area (arrow) and low grade uptake in the walls of the collection (arrowhead). (c) CT chest shows multiple cavitary lesions (arrows) in the lungs. Diagnosis of multifocal TB (bone and lungs) was confirmed after growth of acid fast bacilli from the caseous aspirate

by CT and MRI show minimal change despite significant reduction in tumor viability. Since FDG PET is based on glucose metabolism, changes in tumor viability can become evident much earlier compared to morphological assessment. Several studies have evaluated the role of FDG PET/CT in assessing response to chemotherapy in bone sarcomas. These studies have shown the metabolic response measured as changes in SUV of the primary tumor is a fairly accurate predictor of pathological response and tumor necrosis [Figure 24].^[59,60] Metabolic response to chemotherapy seen on FDG PET also correlates with prognosis and survival, with metabolic responders having better outcome compared to metabolic nonresponders.^[61] Thus, FDG PET/CT can be potentially used as a noninvasive surrogate marker to predict pathological response as well for prognostication in patients of localized OS and EWS after chemotherapy.

Pitfalls and False Positives

Infection and inflammations affecting various organs of the body including the musculoskeletal system concentrate FDG. One of the proposed mechanisms explaining FDG uptake in inflammatory cells is the overexpression of GLUT-1 subtype receptors in activated macrophages,

neutrophils, and lymphocytes. This is the primary cause of FDG uptake in osteomyelitis [Figure 25].^[62,63] Likewise, FDG is known to concentrate in inflammatory arthritis, fractures, healing bone, and recent postsurgical changes.^[64] Pelvic insufficiency fractures post radiation therapy for malignancies of the pelvic organs also demonstrate varying intensities of FDG uptake.^[65] FDG uptake in these conditions can be a potential cause of false-positive result when FDG PET/CT is performed for an oncologic indication. Correlating the pattern of FDG uptake with clinical symptoms and treatment history along with knowledge of CT features of infection can help diagnose infections and inflammations and avoid potential diagnostic pitfalls.

Variations in physiological FDG uptake in muscles and bones can occasionally be confusing and simulate disease. Asymmetric physiological uptake in muscles of the head-neck region such as the masseter, pterygoid, and paraspinal muscles can mimic pathology.^[66] Excessive muscle activity due to coughing, abnormal muscular strain due to asymmetric weight bearing or a painful condition can also give rise to increased physiological FDG uptake.^[67] Focal areas of increased FDG avidity due to red marrow reconversion after administration of marrow stimulating agents is a common cause of abnormal appearing physiological bone uptake.^[68] Focal physiological uptake in the region of the growth plate and near tendons attachment of muscles can lead to an erroneous diagnosis.^[69] Awareness of these variable patterns of physiological uptake and knowledge of their causative factors is important to avoid potential diagnostic errors.

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Conflicts of interest

There are no conflicts of interest.

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