Pathol. Oncol. Res. (2019) 25:131–136
DOI 10.1007/s12253-017-0325-0

ORIGINAL ARTICLE

Advantages of ^{18}F FDG-PET/CT over Conventional Staging for Sarcoma Patients

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Received: 8 March 2017 / Accepted: 21 September 2017 / Published online: 9 October 2017

Abstract The effective management of patients with sarcomas requires accurate diagnosis and staging. Imaging, such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) are the most freqently used methods for the detection of the lesion location, size, morphology and structural changes to adjacent tissues; however, these modalities provide little information about tumour biology. MRI is a robust and useful modality in tumour staging of sarcomas, however metabolic-fluorodeoxyglucose positron emission tomography/ computer tomography (^{18}F–FDG PET/CT) provides greater accuracy to overall staging in combination with MRI [1]. The advantages of ^{18}F–FDG PET/CT method compared with CT and MRI is that it provides a whole body imaging, maps the viability of the tumour or the metabolic activity of the tissue. Additionally, PET detects the most agressive part of the tumour, demonstrates the biological behaviour of the tumour and therefore has a predictive value. Little data ara available on the role of ^{18}F–FDG PET/CT in the management of sarcomas. The present manuscript aims to provide a review of the major indications of ^{18}F–FDG PET/CT for diagnosis, staging, restaging and monitoring response to therapy and to compare its usefulness with the conventional imaging modalities in the management of patients with sarcomas.

Keywords ^{18}F–FDG pet/Ct · Standardized uptake value · Imaging modalities · Sarcoma

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Introduction

3Bone and soft-tissue sarcomas are rare and represent approximately 1% of all adult solid malignant cancers [2]. The majority of diagnosed cases are soft-tissue sarcomas, and the incidence rates have increased over recent decades. The five-year survival rate is approximately 58% for soft-tissue sarcomas and 62% for bone sarcomas [3]. In the European Union countries the incidence of sarcomas is 5.6 per 100,000 per year with an estimated 27,908 new cases yearly; 84% of these tumours are soft-tissue sarcomas (STS) and 14% bone sarcomas [3]. Regarding the histological heterogeneity of sarcomas, their management and diagnostic strategy is complex. In addition to the TNM (tumour-node- metastasis) stage, the histological grade (G) of the sarcomas is also important for determining the sarcoma stage. Currently, the FNCLCC (The Federation National des Centre de Lutte Contre le Cancer) grading system is the most commonly used [4], which is based on three parameters: tumour differentiation, mitotic index and tumour necrosis. For TNM staging in a node-negative patient without metastases the tumour size is a more important prognostic factor than the depth, and the grade has higher prognostic importance than the tumour size. Currently the management of sarcoma patients is challenging because of the varied manifestations of the disease and the wild spectrum of available therapy. Different types of sarcomas have variable responses to surgery, radiation and chemotherapy. Nevertheless, until more molecular targets are identified and more biological therapy becomes available the main curative management is the complete surgical excision of the tumour.

In soft-tissue sarcomas MRI is the main imaging modality in sarcomas localized in the extremities, but CT has a role in bone sarcomas, where the lesion derive from bone, or the lesions infiltrate osseal tissue.

The Response Evaluation Criteria in Solid Tumours (RECIST) assessment in these patients does not always truly

reflect the response to therapy, thus its value is limited. Using whole body ^{18}F–FDG PET/CT to follow the patient's progress is a promising new development in this regard.

Several guidelines, e.g. the National Comprehensive Cancer Network (NCCN) [5], and the European Society for Medical Oncology (ESMO) [6] recommend using PET/CT for sarcoma diagnosis, staging, monitoring response to therapy and follow-up [7, 8]. When preoperative treatment is an option, PET/CT may be useful as it also helps to estimate the malignancy grade.

Conventional Imaging for Sarcoma Diagnosis

Conventional radiography was the first diagnostic tool to image sarcomas. It is useful for the detection and characterization of skeletal sarcomas but it is not an accurate method for the evaluation of soft-tissue sarcomas. Characterization of sarcomas beyond plain radiography is better obtained by MRI compared with CT. MRI has excellent contrast resolution, higher sensitivity for the detection of marrow abnormalities, and it does not expose the patient to ionizing radiation. Thus, MRI may be used to detect, characterize and evaluate the extent of tumours [9]. MRI is less valuable for the characterization of skeletal sarcomas, but it is still the most authoritative method for the evaluation of bone marrow involvement. Nonetheless, the image acquiition time is significantly longer than for CT.

CT is a suitable method for sarcoma staging, especially for imaging skeletal lesions, and it shows bone destructions very well. CT angiography is appropriate for evaluation of tumour size, extent and vascularity. Chest CT scan is the most sensitive method for detecting lung metastases [8]. Morphological imaging, although necessary for TNM staging, does not assess the histology, although certain features of the images, for example necrosis, may suggest more aggressive disease. Tumour sampling is needed to define the histologic grade. A core biopsy isn't enough in every case for accurate grading, because of tumour heterogeneity [10].

Biopsies may miss the most aggressive part of the tumour: their results depend on which part of the tumour is sampled by the surgeon, and thus the severity of the disease may be underestimated. Guidelines suggest multiple core needle biopsies using > = 14–16-Gauge needles. Misinterpretation of the histological grade could lead to inappropriate patient management, which may result in fatal outcome.

Utility of ^{18}F–FDG PET/CT in Sarcoma

The advantages of ^{18}F–FDG PET/CT compared with the traditional imaging modalities described above include imaging the whole body and extremities, as well as the capability to evaluate tumour metabolic activity. FDG PET/CT and conventional imaging are complementary for detecting distant metastases. ^{18}F FDG accumulates at high concentration in tissues with elevated glucose uptake. The tumour grades show a close correlation with the glucose-uptake of cancers: benign tumours have lower rates of glycolysis than malignant tumours, and there are differences in FDG uptake values between low- and high-grade bone and soft-tissue sarcomas [11] ^{18}F FDG is a valuable method for staging, predicting prognosis, and evaluating the therapy response of STS. But neither guidelines nor consensus protocols are available for the use of ^{18}F–FDG PET/CT in sarcomas.

^{18}F–FDG PET/CT identifies the most biologically aggressive portion of a tumour and may predict patient outcome. The intensity of FDG uptake is usually characterized by using the maximum standardized uptake value (SUV_{max}), peak SUV (SUV_{peak}) or average SUV ($SUV_{average}$, SUV_{avg}) as semi-quantitative parameters. The average SUV should not be used for the evaluation of sarcomas, because it could often be falsely low due to the heterogeneity of the tumour.

Node-Positive and Metastatic Disease

^{18}F–FDG PET/CT could help to identify distant metastases. In a prospective multicentre study of patients with osteosarcomas and Ewing sarcomas ^{18}F–FDG PET is more reliable than conventional imaging modalities (CIMs) for the detection of lymph node involvement [12]. PET was more sensitive than CIMs regarding the detection of lymph node involvement (95% vs 25%, respectively) and bone manifestations (90% vs 57%, respectively) [13]. The lung is the first site of the metastases in patients with sarcomas. High-resolution chest CT is the most sensitive and most reliable imaging modality in the detection of lung metastases. The sensitivity of ^{18}F–FDG PET is reported to be 25%, because the pulmonary nodules are often too small to be investigated by this technique [13]. PET/CT can detect lung nodules that are larger than 7 mm in diameter [14]. ^{18}F–FDG PET has high sensitivity in the characterization of pulmonary nodules, as hypermetabolism means that malignancy is likely to be present, while the lack of FDG uptake means that cancer is unlikely to be present. The introduction of hybrid PET/CT scans impaired the low sensitivity of PET in the detection of pulmonary metastases [15].

PET is more sensitive than CIM in the identification of bone metastases including ^{99m}Tc-methylene diphosphonate-bone (^{9m}Tc-MDP-bone) scintigraphy, with a sensitivity of 98% vs 78% respectively [16].

Lesion-based analysis showed that ^{18}F–NaF (natrium fluoride) PET/CT is the most sensitive (100%) and specific (98%) method in the detection of bone metastases [17]. Co-administration of ^{18}F–NaF and ^{18}F–FDG therefore, provides an appealing approach [18].

FDG PET is more sensitive (100% vs 68%) and more specific (96% vs 87) than bone scintigraphy in patients with

Ewing sarcoma; however, FDG-PET and bone scintigraphy lack sufficient sensitivity to detect spinal metastases of myxoid liposarcoma [19]. Whole-spine MRI is the most reliable and could detect spinal metastases earlier in patients with osteosarcoma [19].

Metabolic Characteristics of Benign and Malignant Lesions

Several researchers investigated the role of ^{18}F–FDG PET/CT for differentiating benign from malignant lesions. In these studies the intensity of FDG uptake generally correlated with tumour grades and markers of cell proliferation [20].

A meta-analysis of 15 studies with 441 soft-tissue lesions published in 2003 [21] showed the clinical value of ^{18}F–FDG PET/CT [13] in the evaluation of both primary and recurrent soft-tissue lesions. The sensitivity and specificity of FDG PET for detecting malignant versus benign lesions was 79% and 77% using SUV > = 2.0 and 60% and 86% using SUV > = 3.0 as the critical threshold, respectively. Significant differences were found in FDG-uptake between the intermediate or high-grade malignant lesions and the low-grade or benign lesions, but the method offered inadequate discrimination between these latter two groups. ^{18}F–FDG PET/CT is a useful imaging modality in the evaluation of both primary and recurrent soft-tissue lesions, but there is an overlap in intensity of FDG uptake between grades as well as between subtypes. It has also been reported that some benign disease, such as giant cell tumours, are associated with FDG uptake that may be as high as that of high-grade sarcomas [22]. Thus, some investigators, recently stated that there is not an FDG uptake threshold that can reliably separate benign from malignant lesions [23].

In summary, the FDG uptake generally correlates with tumour grade, but cannot always differentiate between grades in mixed types of sarcomas.

Assessment of Therapeutical Response

Pathological response to primary systemic treatment is determined by the extent of tumour necrosis in the resected specimen. Some authors measured the standardized uptake values before (SUV1) and after (SUV2) chemotherapy. Disease-free survival increased if SUV2 values were less than 2.5 [24]. PET/CT may be useful in predicting the response to chemotherapy in stage II–III sarcomas for lesions that are larger than 3 cm, firm and deep, not superficial [24]. A study of 42 patients with resectable biopsy-proven high-grade soft-tissue sarcomas suggested that FDG-PET could predict histopathological responses to neoadjuvant treatment [25]. Each patient underwent a PET scan before and after neoadjuvant treatment to evaluate cellular function of the cancer. Among responders (19%), PET scan showed a significant reduction in the uptake of FDG. The per cent decrease in FDG uptake, which is suggested as an optimal cut-off value separating responders and non-responders, ranges from 25% to 60% in the literature. This difference in values is due to the fact that in the various studies a different number of cycles of chemotherapy was given to patients before the test. The subtypes of the sarcomas investigated in the studies are also variable. For the calculation of the cut-off value some investigators used the tumour-to-background ratio, others used the SUV, some investigators used the SUVmax, while others used the peak SUV. Moreover, attenuation correction was generally not performed before 2000, while more recent studies have used attenuation-corrected images [26]. Some studies showed that early changes in the SUVmax can predict survival even after one cycle of chemotherapy [27].

A Case Report: Illustration of the Value of PET/CT in Clinical Management

A 40-year-old male presented to the clinic with symptoms of a left gluteal mass ten years ago. The patient complained of intermittent throbbing in this region. He denied trauma to the affected area. Initial plain films and CT scan disclosed a 6.0 × 2.5 × 3.0 cm firm mass in the left gluteal region that was hard on palpation. Surgical excision was performed, and the histology showed scar tissue. However three months later a recurrence of the mass was detected, and it was highly suspicious for malignancy. The conventional imaging modalities indicated postoperative residuum, but ^{18}F FDG-PET/CT demonstrated high heterogeneous glucose uptake in the same region with a SUV_{max} 14.8 and prominent borders of the tumoural tissue. The firm mass was surgically removed and the histology revealed epithelioid sarcoma (ES). ES occurs rarely, comprising less than 1% of all sarcomas [28]. STS are highly ^{18}F FDG-avid lesions, like many tumours, and ^{18}F FDG-PET seems to be extremely useful in distinguishing tumour from scar tissue.

Twice in the two years followed the second operation a recurrent sarcoma was removed. The surgical margins were microscopically positive, consequently these operations were R1 resections. An antracycline-based adjuvant chemotherapy was applied post-operatively, in 2010. Later, in 2012, a fourth recurrence was unresectable, so the patient was treated by combined chemotherapy and radiation to the affected area as well. In the patient's work-up the conventional imaging modalities showed complete remission. Four years later in 2016 a fistula indicated suspicion of recurrence. MRI and CT scans indicated scar tissue, however the PET/CT revealed high glucose uptake in the gluteal region and the metabolic pattern suggested that the tumour involved the ischial bone and the

adductor muscle as well. ^{18}F FDG uptake was heterogeneous with a SUV_{max} of 9.3.

Recently, nine years after the second surgery, a recurrence was detected without signs of metastasis. Our experience emphasizes that the usefulness and high clinical impact of metabolic ^{18}F FDG PET/CT was superior to conventional imaging modalities in detecting soft-tissue recurrences (Fig. 1).

Novel PET Tracers

A tracer particularly suitable for PET imaging of tumour proliferation is 3′-dezoxi-3′-^{18}F-fluortimidin (^{18}F–FLT) because it does not degrade in vivo [29, 30]. FLT uptake has been shown to correlate with Ki-67 levels in several tumours, for example in patients with lung cancers [30], malignant lymphomas [31, 32], brain gliomas [33] and breast cancer [34].

In 2008 Buck et al. examined the role of ^{18}F–FLT PET to assess tumour grading and to differentiate malignant from benign tumours in patients with bone and soft-tissue tumours. In this study FLT uptake correlated significantly with the tumour grade, suggesting FLT as a superior PET tracer for non-invasive grading of sarcomas [35].

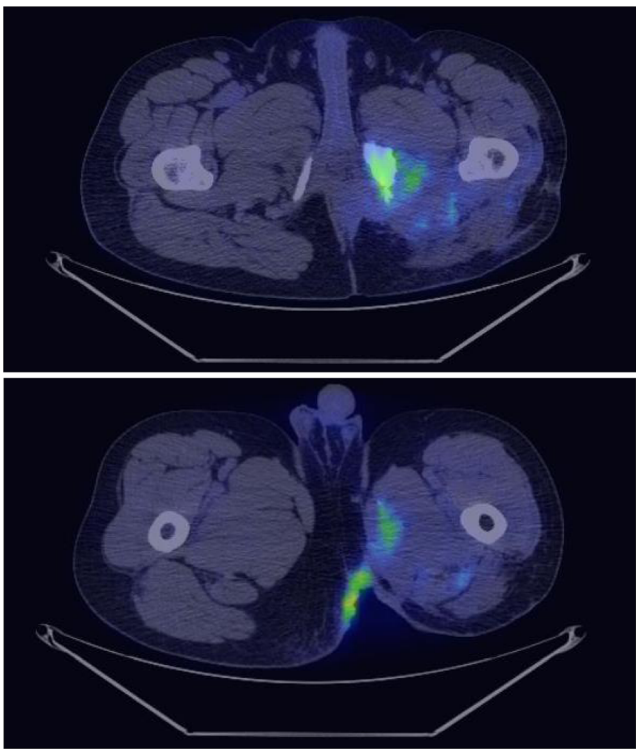

Fig. 1 Axial ^{18}F–FDG PET/CT images of the pelvis. High heterogeneous tracer uptake, (^{18}F–FDG-avid mass) infiltrating the left ischial bone and the adductor muscle

Another pilot study of 20 patients with resectable, high-grade soft-tissue sarcomas showed that [^{18}F] FLT PET/CT imaging did not reliably predict histopathological response to neoadjuvant therapy [36] and ^{18}F–FLT uptake was unrelated to TK1 and Ki-67 expression. These studies included 20 and 22 patients, respectively. FLT PET was used to assess response in advanced soft-tissue sarcomas with hyperthermic isolated limb perfusion SUVmean and SUVmax and a reduction during therapy was observed. Initially high uptake in the lesions showed higher response rates [37]. Further studies are warranted to determine the utility of this isotope in sarcomas.

The fluorinated nitroimidazole derivative ^{18}F–fluoromisonidazole or ^{18}F–FMISO [38] can be widely used as a valuable hypoxia tracer. ^{18}F FDG evaluates the glucose metabolism in tumours, whereas the FMISO uptake is commensurate with tissue hypoxia. Initial work with FMISO [39] shows a significant discrepancy between ^{18}F FDG and FMISO uptake in the 19 patients. Evidence of the utility of ^{18}F–FMISO PET in sarcomas is limited.

Summary

Sarcomas present higher ^{18}F FDG uptake than benign lesions and ^{18}F FDG uptake of the tumour generally correlates with the tumour grade. There may be an overlapping in intensity of ^{18}F FDG uptake between different grades and different types of tumours, for instance between low-grade sarcomas and benign lesions.

MRI is the imaging modality of choice for the evaluation of sarcomas involving extremities. CT and ^{18}F FDG PET/CT could be useful for the evaluation of nodal and metastatic disease. It is well known that biopsy is the gold standard for grading and staging of soft-tissue sarcomas. The metabolic map provided by PET helps to sample and detects the most metabolically active parts of the whole tumour mass. Accurate biopsy guidance is essential: 1. to avoid false diagnosis; 2. for the correct histological grade; 3. the identification of malignant transformation. Additionally, metabolic PET/CTmethod is especially sensitive in the evaluation of bone metastases. Although ^{18}F–FDG PET isn't sensitive for the detection of pulmonary metastases (<6–7 mm), it is very specific for larger nodules found on CT [40].

PET/CT has significant advantages in the monitoring of response to therapy compared to traditional imaging modalities. Core-biopsy is not reliable in this patient group due to the very heterogeneous tumour. Additionally, ^{18}F–FDG PET/CT is very sensitive and specific for the detection of recurrent tumours. Metabolic PET has become a common imaging modality in oncology, and the indications will continue to grow in the future. ^{18}F–FDG PET/CT is useful in sarcomas and has significant advances in the optimal management of patients

with sarcomas, including the most appropriate therapeutic decisions. Hybrid PET/CT and the development of new PET tracers could result in remarkable improvements of the management of sarcomas. Hybrid PET/MRI also seems to be a promising technology in cases where the MRI has a priority and superiority to CT scans due to its high intrinsic soft-tissue contrast, the difference in the radiation rate, or the different functional MRI sequences.

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