Diagnostic value of $^{18}$F-FDG-PET/CT for the follow-up and restaging of soft tissue sarcomas in adults

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KEYWORDS
$^{18}$F-FDG-PET/CT; Soft tissue sarcomas; Accuracy study; Recurrent disease

Abstract

Purpose: The purpose of this study was to evaluate the clinical utility of 2-$[^{18}$F$]$ fluoro-2-deoxy-D-glucose ($^{18}$FDG) positron emission tomography (PET)/computed tomography (CT) ($^{18}$F-FDG-PET/CT) in the follow-up of adult patients with soft tissue sarcomas.

Materials and methods: We prospectively evaluated 37 consecutive patients with known soft tissue sarcoma with $^{18}$F-FDG-PET/CT examination for suspected recurrence of disease. They were 21 men and 16 women with a mean age of 49.6 ± 10.6 (SD) years (range, 34–75 years). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of $^{18}$F-FDG-PET/CT examination were calculated on a per patient basis.

Results: $^{18}$F-FDG-PET/CT showed an overall diagnostic accuracy of 91.8%, sensitivity of 90% and a specificity of 100%. The positive predictive value and negative predictive value were 100 and 70%, respectively. The $^{18}$F-FDG-PET/CT interpretations were correct in 34/37 patients (91.8%). Incorrect interpretations occurred in three patients (8.1%). Reasons for false negative findings were low $^{18}$F-FDG uptake of local recurrence in one patient and low $^{18}$F-FDG uptake of subcentimetric inguinal lymph node metastases.

Conclusion: $^{18}$F-FDG-PET/CT has a high diagnostic value in the follow-up of patients with soft tissue sarcoma.

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Soft tissue sarcomas are uncommon neoplasms of mesenchymal origin [1]. Soft tissue sarcomas account for 0.7% of adult cancers [2]. They arise in mesodermal tissues of extremities in half of the cases, trunk/retroperitoneum in two fifth of the cases or head and neck in one tenth of the cases [3].

Soft tissue sarcomas have a tendency to generate hematogenous metastases. Their risk correlates with tumor size, histological subtype, location and grade [4]. Owing to that pattern of metastatic spread, 2-[18F] fluoro-2-deoxy-D-glucose ([18F]FDG) positron emission tomography (PET)/computed tomography (CT) ([18F]FDG-PET/CT) is considered as an effective tool in the evaluation of patients with soft tissue sarcomas particularly those with high-grade lesions [5]. Being a functional imaging modality, [18F]FDG-PET/CT has numerous applications in the diagnosis and management of soft tissue sarcomas. Sarcomas are usually highly [18F]FDG avid tumors [6].

[18F]FDG-PET/CT imaging has been used in Soft tissue sarcomas for guidance of biopsies [7], assessment of therapeutic response [8], staging [9], surveillance [10], and prognosis determination [11]. It is an ideal modality to evaluate the extent of disease and help with correct treatment planning [5].

The aim of this study was to evaluate the clinical utility of [18F]FDG-PET/CT in follow-up of adult patients with soft tissue sarcomas.

Patients and methods

Patients

From March 2014 to June 2015, we prospectively evaluated 37 consecutive patients with known soft tissue sarcoma who underwent [18F]FDG-PET/CT examination for the assessment of recurrence of previously treated soft tissue sarcomas. They were 21 men and 16 women with a mean age of 49.6 ± 10.6 (SD) years (range, 34–75 years). Eleven patients had undergone surgical excisions, 20 patients had operations followed by chemotherapy alone while 6 patients had surgeries followed by chemotherapy and radiotherapy. [18F]FDG-PET/CT was performed as regular post-therapeutic 6-month interval follow up in 16 patients. Referring oncologists asked for [18F]FDG-PET/CT in 21 patients who developed symptoms and whose conventional imaging studies were inconclusive. Time interval between the end of treatment and follow-up [18F]FDG-PET/CT ranged between 3 and 14 months. The study was approved by the Hospital Ethical Committee. Informed consents were obtained from all patients.

According to the soft tissue sarcoma histological diagnosis, lesions were categorized as leiomyosarcoma (n = 9, 24.3%), liposarcoma (n = 8, 21.6%), undifferentiated or pleomorphic sarcoma (n = 7, 18.9%), fibrosarcoma (n = 7, 18.9%), malignant peripheral sheath tumour (n = 2, 5.4%), angiosarcoma (n = 2, 5.4%), Kaposi sarcoma (n = 1, 2.7%) and rhabdomyosarcoma (n = 1, 2.7%). The soft tissues sarcomas originated from the upper limbs (n = 6 patients), lower limbs (n = 20 patients), anterior portion of the abdominal wall (n = 2 patients), anterior portion of the chest wall (n = 1 patient), retroperitoneum (n = 6 patients), lip (n = 1 patient) and maxillary sinus (n = 1 patient).

[18F]FDG-PET/CT protocol

All patients were scanned on integrated PET/CT scanner (Syngo PET VG 50A Biograph 20 VA 44A, Siemens Medical Solutions, Berlin, Germany). Patients fasted for at least 6 hours before receiving an intravenous injection of 370–410 MBq/kg of [18F]FDG. Blood glucose level was measured before injection of the tracer, to ensure a level below 130 mg/dl. After injection, patients were kept lying comfortably in a quiet place for 60 minutes.

First non-contrast low dose CT images were obtained for attenuation correction and fusion images. This was followed by PET scan in 3D mode with an acquisition time of 3 minutes per bed position (axial FOV 16.2 cm). The imaging field encompassed 6 to 8 bed positions depending on patient height. Images were acquired from the base of skull to mid-thigh level with additional images acquired according to the sarcoma location.

Lastly, a diagnostic contrast-enhanced CT scan was obtained using the following parameters (120 mA s, 130 kV, 5 mm slice collimation), with an application of 100 mL non-ionic iodinated contrast agent (ioversol 74%, [Optiray 350°, Covidien, Germany] in porto-venous phase (70 s delay).

Data analysis and interpretation

PET image datasets were reconstructed using the CT data for attenuation correction. The reconstructed attenuation-corrected PET, CT and fused PET/CT images were viewed using the manufacturer’s works station (Syngo™ software, Siemens Medical solutions).

The PET/CT imaging was assessed quantitatively and qualitatively for areas of increased FDG uptake. For visual analysis abnormal FDG uptake was defined as a substantially greater activity in the tissue than in the aortic blood on attenuation—correction images. Maximum standardized uptake value (SUV) was measured at every site of FDG uptake. The diagnosis of malignancy was also supported by a maximum SUV > 2.5 and > 3.5 for malignant extrahepatic and intrahepatic lesions respectively.

Standard of reference

The final diagnosis was made by histopathology whenever available, correlation with other imaging modalities together with clinical and imaging follow-up for at least 6 months. The accuracy of [18F]FDG-PET/CT examinations were assessed by histopathological analysis of surgically removed lesion (n = 12), fine needle biopsy (n = 6), follow-up PET/CT imaging (n = 17 with 13 patients had more than one follow-up PET/CT examinations) and follow-up CT chest examination (n = 2).

Statistical analysis

[18F]FDG-PET/CT findings were classified as true positive (lesion was defined as malignant with subsequent confirmed tumour involvement), true negative (lesion defined as benign with no further evidence of disease), false positive (lesion was defined as malignant with no further evidence of disease), or false negative (lesion was defined as benign showing subsequent evidence of malignancy).
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The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 18F-FDG-PET/CT were calculated on a per patient basis.

Results

Among the 37 patients, absence of recurrent disease was found in 9/37 patients (24.3%) (Fig. 1). Positive findings for 18F-FDG-PET/CT were found in 28/37 patients (75.7%). Of these, 3 patients (8.1%) had isolated local recurrence, 14 patients (37.8%) had distant metastasis and 11 patients (29.8%) had both local and distant recurrence (Figs. 2 and 3) (Table 1).

The plan of management was changed for these patients, as they needed further therapeutic measures. Five patients were subjected to radiotherapy, 7 patients received combined radiotherapy and chemotherapy whereas 8 patients

Figure 1. A 42-year-old man with history of prior resection of right thigh fibrosarcoma. (a) CT image in the transverse plane using lung window shows left upper lobe tiny pulmonary nodule (arrow). (b) Axial fused PET/CT image shows small right adrenal nodule measuring 1.5 cm in size and CT attenuation value of 10 Hounsfield Units (HU) (arrowhead). It demonstrates mild FDG uptake, with SUV max 2.2. The lesion was diagnosed as adrenal adenoma. (c) Whole body PET image showing no abnormal metabolic activity. The tiny lung nodule was considered of low likelihood of malignancy; we recommended close follow-up using CT chest, it had stable course during the follow up period (6 and 12 months after the initial PET/CT).

Figure 2. A 51-year-old man with history of popliteal sarcoma who underwent surgical excision and chemotherapy. (a and b) Axial fused PET/CT image, (c) Whole body PET image show right inguinal lymph node SUV max 10.6 measuring about 3.2 × 3 cm (arrowhead) and right popliteal soft tissue lesion SUV max 13.3 measuring about 5.8 × 4 cm (arrow) representing local recurrence.
had limb-sparing surgeries and 8 patients performed surgeries followed or preceded by adjuvant radiotherapy.

Distant metastases were identified in 25/37 patients in the following distribution: lung nodules (n = 15), lymph nodes (n = 14), liver (n = 1), peritoneum (n = 3) and bone (n = 2).

The 18F-FDG-PET/CT interpretations were correct in 34/37 patients (91.9%). Incorrect interpretations of 18F-FDG-PET/CT images occurred in 3 patients (8.1%). Reasons for false negative findings in these 3 patients were an inguinal lymph node metastases of 7 mm in its short axis with low 18F-FDG uptake (SUV max, 1.7) in one patient (Fig. 4) and local operative bed recurrence of low 18F-FDG uptake in two patients.

18F-FDG-PET/CT showed an overall diagnostic accuracy of 91.2% with a sensitivity of 90% and a specificity of 100%. The PPV and NPV were 100 and 70% respectively.

Discussion

The use of 18F-FDG-PET/CT in the initial staging and restaging of many cancers is clearly established [12]. Molecular imaging with 18F-FDG-PET/CT is certainly a powerful tool for initial assessment of sarcomas and detection of their recurrences [13].

In this study, we investigated the clinical utility of PET/CT in follow up and assessment of recurrence in adult patients with previously treated sarcomas. According to our results, the overall diagnostic accuracy, sensitivity and specificity of 18F-FDG-PET/CT were 91.2, 90 and 100% respectively. This was in concordance with previous literature findings. Fuglo et al. studied 59 patients with soft tissue sarcomas and found a sensitivity of 95%, specificity of 96% and accuracy of 95% [14]. Similarly, Tateishi et al. found a sensitivity of 92%, a specificity of 91% and an accuracy of 91% in a series of 117 patients with bone sarcoma and soft tissue sarcomas [15]. In another Tateishi et al. who evaluated 50 pediatric patients with bone sarcoma and soft tissue sarcomas found a sensitivity of 71%, a specificity 100% and an accuracy of 86% for the detection of distant metastatic disease [16].

Follow-up of patients with sarcomas could help detect local or distant recurrences in a timely approach allowing commencement of further treatment [17]. There are a few publications on the utility of 18F-FDG-PET/CT in the detection of recurrence in patients with sarcomas [18–20].

Soft tissue sarcomas, especially high-grade tumors also have a propensity to hematogenous spread to the lungs [5]. 18F-FDG-PET/CT is not as sensitive as CT for detection of small lung metastasis, due to its lower resolution [14]. Smith et al. reported limited sensitivity of 18F-FDG-PET/CT in detection of subcentimetric pulmonary nodules (50–86.5%) [20]. However, the development of combined PET–CT protocols associating CT on inspiration eliminates that problem as it allows the correct evaluation of the pulmonary parenchyma without the need for duplicating studies [12]. Metastases of 5 mm or smaller can be identified on the CT component of PET/CT [14]. In the present study, lung was the commonest site of distant metastases. 18F-FDG-PET/CT revealed metastatic pulmonary nodules in 15/25 patients with distant metastases.

Less than 5% of soft tissue sarcoma metastasize to the lymph nodes except in some tumours as rhabdomyosarcoma, angiosarcoma, epitheloid sarcoma and clear cell sarcoma.

**Table 1** 18F-FDG-PET/CT findings in 37 patients with suspected recurrence of soft tissue sarcoma.

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<td>No recurrence</td>
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<td>Local recurrence</td>
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<td>Distant recurrence</td>
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<td>Local and distant recurrence</td>
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Figure 4. A 25-year-old man with history of surgical excision of clear cell sarcoma of tendon sheath from the lower third of the right thigh in post-operative and chemotherapy state. (a) axial fused PET/CT image shows right inguinal lymph node measuring 0.7 cm in its short axis with low activity (SUV max 1.7). The lesion was considered of low likelihood of malignancy. (b) Five months later 5 axial fused PET/CT image and (c) whole body PET image show metabolic and morphologic progression of the lesion, currently measuring 1.1 cm with SUV max 7.2 (arrows) denoting its activity and metastatic nature. This was recorded as false negative finding in first study.

Previous studies have reported superiority of 18F-FDG-PET/CT or PET/CT in detecting of lymph node metastases in comparison to conventional imaging, with higher sensitivity (86–100 vs. 36–53%, respectively), however with equivalent specificity (93–98 vs. 97–98%, respectively) and accuracy (93–96 vs. 91–92%, respectively) [14–16,22].

The common cause of FN results in the detection of lymph node disease is small deposits (<4–5 mm) or metastasis derived from histologic subtypes with known low 18F-FDG uptake [12]. In the present study, we missed one small metastatic inguinal lymph node with low 18F-FDG uptake. However, it demonstrated morphological and metabolic progression (SUV max 7.2) on the follow-up PET/CT examination performed 5 months later. Close follow-up with 18F-FDG-PET/CT examination within 6 months in case of negative results would be beneficial guided by patient’s clinical condition particularly in known aggressive soft tissue sarcoma.

PET/CT scans showed higher specificity in comparison with other conventional imaging including CT and magnetic resonance imaging in the detection of local disease recurrence [19]. Anatomic imaging alone had not been accurate enough for surveillance of soft tissue tumors because of post treatment changes including anatomic distortion and disruption of normal tissue planes, fibrosis and scarring due to previous surgery or radiotherapy. The ability of 18F-FDG-PET/CT to demonstrate metabolic alterations makes this technique more sensitive in the detection of recurrence on the top of post-treatment changes [12,23].

In this series, local disease recurrence was detected in 14 patients. 18F-FDG-PET/CT helped discriminate between tumor growths from post treatment changes in 12 patients (85.7%). Two cases of small local recurrence were falsely diagnosed as post-operative scar due to low FDG uptake with absence of base line pre-operative PET/CT scan to assess the 18F-FDG uptake of the primary tumor.

Our study has few limitations including relatively small number of patients and different organs of origin. Lastly, the current study design included single scan post-18F-FDG administration. Dual-time imaging has been reported as a useful tool for differentiating benign from malignant lesions [24,25]. We believe that application of this technique in our study would have improved the sensitivity and allowed better discrimination of benign from malignant lesions.

In conclusion, 18F-FDG-PET/CT can be used effectively in the follow-up of soft tissue sarcoma patients. It provides whole-body examination allowing assessment of multiple body structures including limbs. Additionally, it detected metabolic alterations when anatomic imaging is not accurate for surveillance because of post-treatment changes.

Disclosure of interest

The authors declare that they have no competing interest.

References


