

Usefulness of FDG PET in Primary Bone Tumors

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Abstract: Positron emission tomography (PET) using [¹⁸F]fluorodeoxyglucose (FDG) is a useful modality to examine many kinds of tumors, including primary bone tumors. Malignant bone tumors show higher FDG accumulation than benign tumors and earlier reports mention that FDG-PET can differentiate malignancy from benignancy; however, some benign bone tumors present with high FDG accumulation, which increases false positive rates in FDG-PET. FDG accumulation reflects glucose metabolism and thereby FDG-PET can be used for staging malignant bone tumors, which require a large amount of glucose. Combined with conventional studies, such as magnetic resonance imaging (MRI) and scintigraphy, FDG-PET can more accurately decide the staging. Finally, FDG-PET is also applied to evaluate the chemotherapy response of malignant bone tumors and is expected to predict a patient's prognosis and to help to decide appropriate chemotherapy agents.

Keywords: FDG-PET, bone, tumor, grading, staging, SUV.

INTRODUCTION

Positron emission tomography (PET) using glucose analog [¹⁸F]fluorodeoxyglucose (FDG) as a tracer has been widely used in clinical oncology. Intravenously injected FDG is first transported into cells by glucose transporters and then phosphorylated into FDG-6-phosphate by hexokinase in the same way as glucose is phosphorylated into glucose-6-phosphate. While glucose-6-phosphate is further catalyzed in a normal glucose metabolic pathway, FDG-6-phosphate is not transformed by phosphoglucose isomerase and therefore remains trapped in cells [1]. The accumulated ¹⁸F-FDG-6-phosphate reflects glucose uptake and metabolism in the cells. Detecting photons generated *via* beta decay of ¹⁸F, PET can show the distribution of glucose metabolism in a human body [2]. Accumulation of FDG is generally quantified by the standardized uptake value (SUV). Quantification of glucose metabolism by FDG-PET has enabled physicians to differentiate malignancy from benignancy, identify the primary site of carcinoma of unknown origin, decide stages of malignant tumors, and evaluate chemotherapy responses in various cancers. Recently, Medicare-reimbursable oncologic FDG-PET applications as initial and subsequent treatment strategies are increasing [3]. In the current article, we review the usefulness of FDG-PET to diagnose and evaluate primary bone tumors.

DIFFERENTIATION OF MALIGNANT FROM BENIGN BONE TUMORS

Computed tomography (CT) and magnetic resonance imaging (MRI) have contributed to visualize tumor location, tumor extent and the internal structures of tumors; however,

these modalities cannot assess tumor activity and metabolism, which are crucial to differentiate malignancy from benignancy and to plan the first operative procedures. Since Warburg reported in 1956 that a cell line that had produced sarcoma in C3H/He mice showed higher glucose metabolism than a cell line that had not [4], malignant tumors, such as hepatoma [5, 6], leukemia [7], colon cancer, melanoma, carcinoma of the urinary bladder [6], and so on, have been known to show high glucose metabolism. Some authors have reported higher glucose uptake in malignant musculoskeletal tumors than in benign tumors, and tried to differentiate malignant from benign tumors using an SUV cut-off of 1.9–3.9. Earlier reports indicate the excellent ability of ¹⁸F-FDG-PET to differentiate malignant from benign musculoskeletal tumors [8-10] and compression fractures [11]. Recently, however, several authors, including us, have revealed benign tumors with a high SUV, causing a high false-positive rate in trials to differentiate malignancy from benignancy with FDG-PET [12, 13]. In our two studies with a SUV cut-off of 1.9, the sensitivity of FDG-PET to correctly diagnose malignancy was 72.7% and 84.6%, with a specificity of 66.0% and 80.0% and an accuracy of 68.0% and 81.8%, respectively [14, 15]. To overcome the relatively high false-positive rate in the FDG-PET study, other tracers, such as L-[3-¹⁸F]- α -methyltyrosine and [¹¹C]-choline, have been used and reported to be useful for differentiating malignancy from benignancy [14, 15]. Table 1 shows procedures reported to be useful for differentiating malignancy from benignancy [16-19]. Benign bone tumors with high SUV by FDG-PET are giant cell tumor, chondroblastoma, Langerhans cell histiocytosis, fibrous dysplasia and osteoid osteoma, a few of which have been included in earlier reports. Among these, fibrous dysplasias have a wide range of SUV from below the cut-off level to a high level, as shown by malignant tumors [12]. It remains unclear why some benign bone tumors show high glucose uptake; however, it may be noteworthy that most of the above benign tumors are giant cells or osteoclasts, which are speculated to originate from macrophages

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Table 1. Reports on Procedures Differentiating Malignancy from Benignancy

Procedures	Authors	Year	Materials	Sensitivity	Specificity
FDG-PET	Yanagawa <i>et al.</i>	2003	33 bone and soft tissue tumors	84.6%	80.6%
FDG-PET	Watanabe <i>et al.</i>	2000	75 bone and soft tissue tumors	72.7%	66.0%
Choline-PET	Yanagawa <i>et al.</i>	2003	33 bone and soft tissue tumors	92.3%	90.0%
FAMT-PET	Watanabe <i>et al.</i>	2000	75 bone and soft tissue tumors	72.7%	84.9%
Dynamic contrast-enhanced MR imaging	Kawakami <i>et al.</i>	2007	175 bone tumors	77%	78%
Dynamic contrast-enhanced MR imaging	Van der Woude HJ, <i>et al.</i>	1998	49 bone tumors	63-76%	50-76%
¹ H MR spectroscopy	Wang CK, <i>et al.</i>	2004	36 bone and soft tissue tumors	95%	82%
^{99m} Tc-MIBI scintigraphy	Pinkas <i>et al.</i>	2001	84 bone and soft tissue tumors	81%	87%

[20]. Kubota *et al.* reported that FDG was highly accumulated not only in tumors but also in macrophages and granulation tissues surrounding the tumors [21], which might explain why some benign tumors present with a high SUV by FDG-PET.

GRADING AND STAGING OF MALIGNANT BONE TUMORS BY FDG-PET

The propensity of FDG to accumulate in high metabolic areas has compelled clinicians to apply FDG-PET to tumor

grading. Several authors have reported that FDG uptake increased in parallel with the tumor grade in chondrosarcomas, although this could not be a substitute for histopathological assessment due to the wide range and overlap of SUVs in each grade [22-24]. Folpe *et al.* examined the relationship between FDG-PET SUVs and histopathological findings using the grading system by Unni and Dahlin with a modification [25] and the National Cancer Institute grading system [26] for bone tumors and soft tissue tumors, respectively. A significant difference was revealed between grade I bone and soft tissue sarcomas and grade II and III

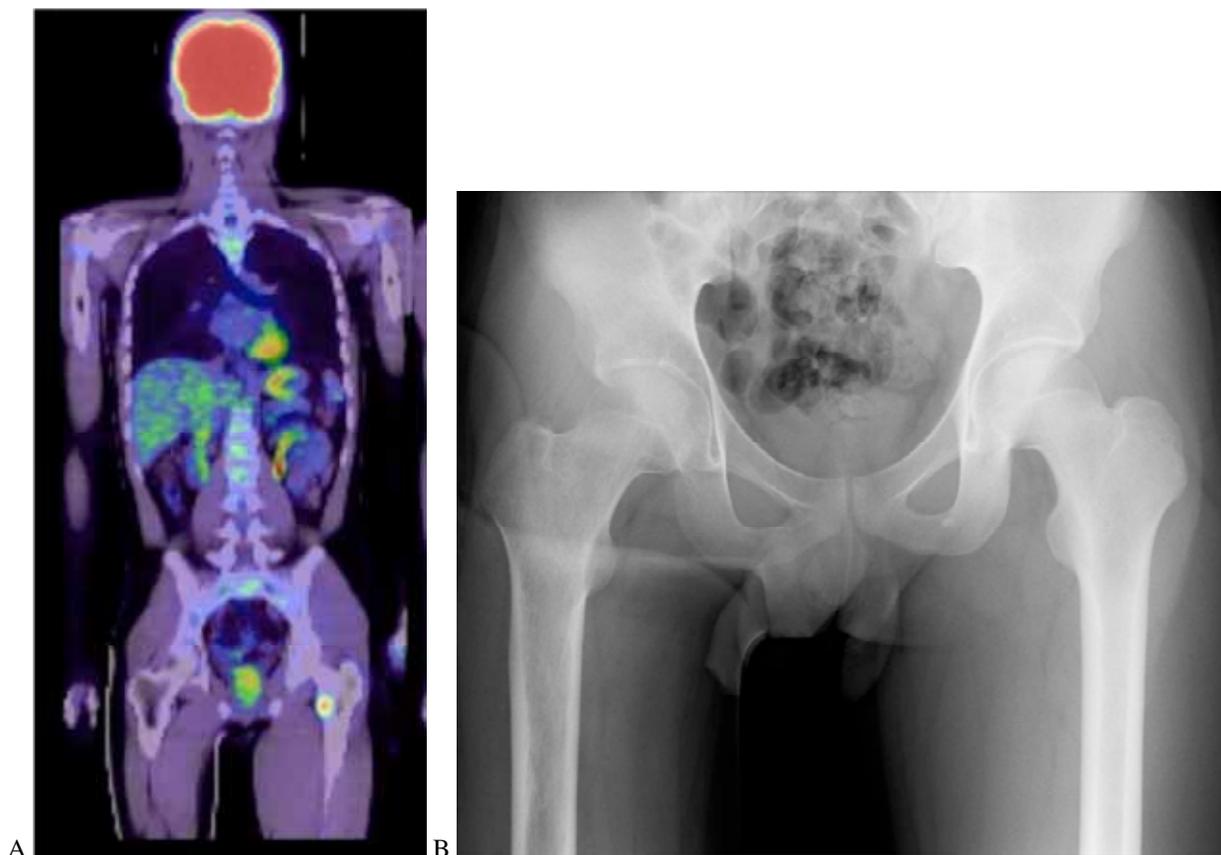


Fig. (1). (A) A 16-year-old patient with osteosarcoma in his lower leg. FDG-PET screening detected metastasis to the lesser trochanter of his femur one year after treatment. (B) Plain X-ray film did not show any lesions in the lesser trochanter at screening.

SUV by FDG-PET, although there was little difference between benign tumors and grade I sarcomas [27]. They also reported that high SUV was related with hypercellularity, high mitotic activity, the MIB labeling index, and p53 overexpression.

As for tumor staging, a prospective multicenter trial revealed that FDG-PET was superior to conventional imaging modalities, including ultrasound CT, MRI and bone scintigraphy, to detect lymph node involvement and bone manifestation in pediatric sarcoma patients, although CT could depict lung metastases more reliably [28]. Meanwhile, FDG-PET had the same sensitivity as MRI in assessing bone involvement in multiple myeloma, although is superior to whole-body X-ray [29]. Franzius *et al.* reported that FDG-PET was more sensitive than bone scintigraphy in the detection of osseous metastases from Ewing's sarcoma, although less sensitive in the detection of metastases from osteosarcoma [30].

Fig. (1A) is a patient with osteosarcoma of the right lower leg. Metastasis to the left lesser trochanter of his femur was found by FDG-PET screening one year after chemotherapy. He had no pain at screening and an X-ray examination did not show any changes in his femur (Fig. 1B). MRI after FDG-PET revealed a lesion invading the cancerous bone area, not the cortical bone area or the surrounding soft tissues, which explained why a plain X-ray film could not detect the lesion. In this case, FDG-PET seems to be superior to other examinations to screen a whole body and detect metastases. Tateishi *et al.* described that the accuracy of staging bone sarcoma according to the TNM classification of the International Union against Cancer is improved by combining conventional imaging, including MRI, chest radiography, CT, and bone scintigraphy with PET/CT [31].

EVALUATION OF THERAPY RESPONSES IN MALIGNANT BONE TUMORS

Evaluating responses to chemotherapy is very important in the treatment of osteogenic sarcoma because the degree of necrosis by chemotherapy is one of the most important prognostic factors [32-34], and a poor response to chemotherapy increases the local failure rate after limb salvage operations [35]. MRI is a good modality to detect tumor necrosis, although its ability to predict chemotherapy responses has a limitation [36]. Schulte *et al.* showed that a decreased ratio of post- and pre-therapeutic tumor-to-background in FDG-PET correlated with the amount of tumor necrosis by chemotherapy and FDG-PET could discriminate therapy responders from non-responders in all 27 but 2 patients with a tumor-to-background cut-off level of 0.6 [37]. Hawkins *et al.* reported that an SUV less than 2.5 after chemotherapy was predictive of progression-free survival in Ewing's sarcoma family of tumors [38]. Recently, we retrospectively examined FDG-PET data for patients with osteosarcoma treated with chemotherapy in our hospital and revealed that the SUV after chemotherapy, not before, could provide prognostic information about patients [39]. Interestingly, immunohistochemical analysis revealed that the expression of autocrine motility factor, which is identical to phosphoglucose isomerase and stimulates tumor

cell motility and metastasis [40], significantly correlated with SUVs after chemotherapy. Jones *et al.* also described that FDG accumulation in soft tissue and musculoskeletal sarcomas decreased after neoadjuvant therapies, although complete absence of FDG uptake could not be achieved. They speculated that the remaining FDG uptake seems to correspond with a pseudocapsule or infiltrating granulation tissues and fibrosis [41]. Fig. (2) shows a patient with osteosarcoma in his left tibia treated with chemotherapy and a subsequent operation. FDG-PET showed that the maximum SUV was 6.94 pre-treatment (A) and 3.74 post-chemotherapy (B), suggesting a moderate response to chemotherapy, although persistent FDG uptake was confirmed. Pathological findings of the tumor removed after pre-surgery chemotherapy revealed more than 90% necrosis and little remaining tumor tissue.

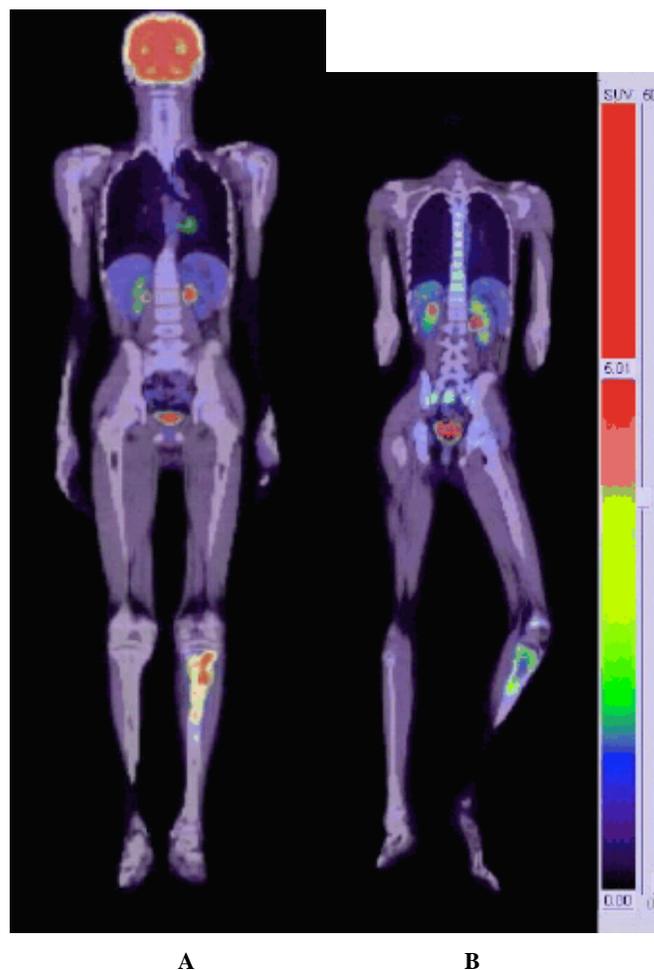


Fig. (2). A 13-year-old patient with osteosarcoma in his left tibia treated with chemotherapy. FDG-PET showed strong accumulation of FDG with 6.94 SUV pre-treatment (A) and decreased FDG post-chemotherapy (B) with 3.74 SUV. Histopathological findings revealed more than 90% of necrosis in the lesion.

In conclusion, when differentiating malignancy from benignancy, physicians have to keep in mind that some benign bone tumors show high glucose uptake, resulting in high accumulation of FDG. To accurately evaluate bone tumor metastases and dissemination, not only FDG-PET but also other available imaging studies should be used. At present, it can be said that if FDG-PET detects new

metastatic lesions or SUV does not decrease after chemotherapy, the treatment needs to be reconsidered, while with only FDG-PET, it remains difficult to precisely predict the rate of necrotic lesions in the treated tumor.

ABBREVIATIONS

CT = Computed tomography
 FDG = Fluorodeoxyglucose
 MRI = Magnetic resonance imaging
 PET = Positron emission tomography
 SUV = Standardized uptake value

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