Usefulness of ^{18}F -FDG PET/CT for the Evaluation of Bone Marrow Involvement in Patients with High-Grade Non-Hodgkin's Lymphoma

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Abstract

Purpose To assess the usefulness of ^{18}F -fluorodeoxyglucose PET/CT in the detection of bone marrow (BM) involvement of high-grade non-Hodgkin's lymphoma (NHL).

Methods One hundred twenty patients with newly diagnosed diffuse large B-cell lymphoma or peripheral T-cell lymphoma between January 2007 and June 2011, who received BM trephine biopsy and ^{18}F -FDG PET/CT before chemotherapy, were included in this retrospective study. We reviewed their ^{18}F -FDG PET/CT images and bone marrow biopsy (BMB) results. After reviewing the images, we reviewed the medical records and radiological findings of interesting patients.

Results There were 23 ^{18}F -FDG PET/CT scans in which the marrow was considered to be abnormal (either positive or equivocal), and 97 ^{18}F -FDG PET/CT scans were regarded as having negative FDG uptake. Of 120 patients, 100 (83.3 %) had a concordant result of BM interpretation between ^{18}F -FDG PET/CT and BMB, and the remaining 20 patients had discordant results. Among 23 patients with either positive or equivocal ^{18}F -FDG PET/CT scans, 1 of 12 patients with 'positive' ^{18}F -FDG PET/CT had a lymphomatous involvement on BMB. In contrast, 10 of 11 patients with 'equivocal' BM hypermetabolism were reported as having positive involvement by BMB. Patients with abnormal ^{18}F -FDG

PET/CT had significantly higher $\text{mSUV}_{\text{highest}}$ than those with normal FDG-PET/CT.

Conclusions ^{18}F -FDG PET/CT and BMB are complementary techniques in assessing the presence of BM involvement in patients with high-grade NHL. The increasing availability of ^{18}F -FDG PET/CT will raise the need for additional biopsy for FDG-avid lesions, especially in patients with negative standard BMBs. ^{18}F -FDG PET/CT can be useful as a decision-making tool for determining whether to perform a standard BMB or targeted biopsy to the FDG-avid lesion as an initial staging procedure. A direct bone biopsy for FDG-positive bone lesions should be included in staging guidelines in future. In ^{18}F -FDG PET/CT-negative cases, BMB is still a powerful procedure, but BMB alone is insufficient for full evaluation of BM.

Keywords ^{18}F -FDG PET/CT · Lymphoma · Bone marrow

Introduction

^{18}F -fluoro-2-deoxyglucose positron emission tomography with/without computed tomography (^{18}F -FDG PET or ^{18}F -FDG PET/CT) has been increasingly used for the evaluation of several malignant tumors, including lymphoma [1, 2]. Its most promising applications in lymphoma are the determination of the clinical stage of disease at initial presentation, and the evaluation of treatment response and recurrence [3]. The ability of ^{18}F -FDG PET to evaluate both nodal and extranodal sites, such as, spleen, liver, and bone marrow (BM), has been a matter of extensive investigation. In particular, BM infiltration is of crucial importance when staging lymphoma, since it signifies advanced-stage disease, and thus, may affect both treatment and prognosis. Several tools can be used to evaluate BM involvement. Iliac crest bone marrow biopsy (BMB) is considered the "reference

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standard” for detecting BM involvement, although it has been recognized to be an imperfect tool for some time. BMB is limited by technical constraints, for example, by sampling errors due to patchy BM disease, which occurs in one third to a half of high-grade non-Hodgkin’s lymphoma (NHL) and Hodgkin’s disease (HD) patients [4], by small sample sizes, which may be inconclusive, and by patterns of BM disease at presentation that diminish its ability to detect pathological conditions. Furthermore, when obtaining a biopsy specimen is inadequate, it is difficult to repeat the procedure because of its invasiveness. In addition, unilateral or bilateral iliac crest biopsy can miss disease with BM involvement at a site other than the iliac crest. Thus, although a positive biopsy result is usually accepted as proof of BM infiltration, a negative biopsy result does not exclude tumor involvement. Magnetic resonance imaging (MRI) is a valuable tool and is probably the most sensitive available for the detection of local BM involvement when a specific site is suspected, but it is anatomically limited, time consuming, and expensive. Contrast-enhanced computed tomography (CT) can be useful for the evaluation of cortical bone involvement, but its sensitivity for detecting BM disease is low, because the detection of malignant bone involvement by CT depends on the presence of a considerable amount of bone destruction.

However, early lymphomatous bone involvement with a normal CT appearance may be depicted by ^{18}F -FDG PET [5]. Moog and coworkers found ^{18}F -FDG PET/CT to be more sensitive and specific than $^{99\text{m}}\text{Tc}$ -methylene diphosphate bone scintigraphy for the detection of osseous involvement by lymphoma [6], and many recent studies have concluded that ^{18}F -FDG PET/CT has a significant role to play at baseline and for the evaluation of treatment response and restaging of malignant lymphoma. Recently, ^{18}F -FDG PET-based revised response criteria [7] have been widely used in patients with diffuse large B-cell lymphoma (DLBL) and HD, but ^{18}F -FDG PET/CT is not yet included in routine staging workups. ^{18}F -FDG PET/CT has been shown to be sensitive for lymph node staging and for the identification of organ involvement in HD or aggressive NHL. In fact, several studies have been conducted to determine the ability of ^{18}F -FDG PET or of ^{18}F -FDG PET/CT to evaluate BM infiltration during the staging of lymphoma [8, 9]. Furthermore, the majority of these authors of these studies agree with the idea that ^{18}F -FDG PET/CT could be useful during evaluations of BM involvement in combination with conventional BMB. However, the above-mentioned studies evaluated the role of ^{18}F -FDG PET/CT in NHL, HD, and other malignancies, and few studies have addressed NHL or HD in isolation.

Because BM involvement is a well-known poor prognostic factor that sometimes requires the adoption of a more aggressive therapy [10], it is important that lymphomatous

BM involvement be detected accurately in patients with newly diagnosed lymphoma. Because of its non-invasiveness, convenience, and ability to scan all hematopoietic BM, the evaluation of BM involvement by ^{18}F -FDG PET/CT is an area of considerable interest.

In this study, we examined the usefulness of ^{18}F -FDG PET/CT for the detection and evaluation of lymphomatous BM involvement in patients with FDG-avid high-grade non-Hodgkin’s lymphoma (DLBL) and peripheral T cell lymphoma (PTCL).

Methods

Patient Population

Patients with DLBL or PTCL newly diagnosed between January 2007 and June 2011, who received both a BM trephine biopsy and ^{18}F -FDG PET/CT before chemotherapy, were included in this retrospective study. All patients were ≥ 18 years old, had a diagnosis of DLBL or PTCL according to the World Health Organization Criteria [11], and were treated at Gachon University Gil Hospital.

The diagnostic workup included: a physical examination, complete blood count, erythrocyte sedimentation rate, serum biochemical tests, chest radiography, contrast-enhanced CT of the neck, chest, abdomen, and pelvis, whole body ^{18}F -FDG PET/CT, and bilateral iliac crest BM trephine biopsy. The time between ^{18}F -FDG PET/CT and BM trephine biopsy was < 7 days. Patients who received treatment between the two procedures were excluded. Other exclusion criteria were as follows: (1) lymphoma originating from transformation of an indolent lymphoma, primary involvement of the central nervous system, or human immunodeficiency virus associated disease; (2) the administration of granulocyte colony-stimulating factor or erythropoietin within 2 weeks prior to ^{18}F -FDG PET/CT imaging; (3) a history of chemotherapy for lymphoma or another cancer; (4) the presence of active inflammation at the time of ^{18}F -FDG PET/CT imaging; (5) recurrent lymphoma. One hundred twenty patients met the inclusion criteria and comprised the study cohort. The Institutional Review Board of our institution approved this retrospective study.

^{18}F -FDG PET/CT Scanning

^{18}F -FDG PET/CT studies were acquired using a Biograph6 PET/CT instrument (Siemens Medical Systems, Erlangen, Germany), equipped with lutetium oxyorthosilicate (LSO) crystal PET detectors and six slices of CT detectors. CT data acquisition was performed for anatomical localization and attenuation correction (without contrast agent) at 130 kVp, 110 mA, 2-mm pitch, and a 1-s tube rotation. Emission PET

data were acquired in a three-dimensional mode from the skull base to the upper thigh. Patients fasted for at least 6 h (water and medications were allowed) prior to radiopharmaceutical administration to facilitate tracer uptake. Blood glucose levels were measured in all patients and were <140 mg/dl. ^{18}F -FDG PET/CT imaging (6 to 8 bed position for at least 2 min per bed position) was performed 60 min after FDG administration (dose range: 370–555 MBq, i.v.). Acquired images were reconstructed by iteration using the ordered subset-expectation maximization (OSEM) algorithm. The reconstructed images were viewed as a series of transaxial, coronal, and sagittal images.

Analysis of FDG Uptake in Hematopoietic Bone Marrow

^{18}F -FDG PET/CT images were initially reviewed separately by three nuclear medicine physicians. Final interpretations of ^{18}F -FDG PET/CT images regarding the possibility of BM involvement were reported after consensus had been reached. The reviewers were unaware of reference test results (including BM trephine biopsy results) and clinical information at the time of the ^{18}F -FDG PET/CT review. BM sites with hematopoietic activity were defined as sternum, ribs, vertebrae, pelvic bones, proximal femora, and humeri. The intensity and distribution of FDG activity within marrow were scored visually. Marrow was assumed abnormal if uptake was equal to or greater than liver uptake, when liver uptake was greater than background uptake. ^{18}F -FDG PET/CT findings were classified as follows: (1) ‘negative,’ – undoubtedly normal finding. Uptake was not increased and $<$ to liver parenchymal uptake; (2) ‘equivocal,’ a finding raising suspicion of abnormality; (3) ‘positive,’ uptake $>$ liver parenchyma intensity in one or more lesions. We defined ‘equivocal’ for specific types of images. The first type concerns homogenous diffuse uptake in BM sites of any intensity, which can indicate reactive BM hyperplasia [12], and the second one concerns doubtful focal mild uptake in a BM site, which is more likely to reflect a benign condition, such as inflammation, but does not exclude the possibility of BM involvement.

Patterns of uptake were also classified as diffuse or focal by the three reviewers. Representative examples of cases with marrow uptakes of differing intensities and distributions are shown in Fig. 1. All detected FDG-avid lesions in marrow were objectively analyzed using calculated maximal standardized uptake values (mSUV) (defined as the average value of the three highest value pixels), and the highest mSUV value of three lesions ($\text{mSUV}_{\text{highest}}$) was recorded.

Bone Marrow Trephine Biopsy

Bilateral BM trephine biopsies were performed in all patients. A BM tissue with a length of 2 cm or more was

obtained from both sides of the posterior iliac crest. Samples were analyzed using a standard procedure and reviewed by an experienced hematological pathologist for the presence of lymphomatous involvement. BM biopsy analysis was based on histological examinations of hematoxylin-eosin-stained sections and on reticulin density determined using the Gordon-Sweet method [13]. In patients with histological lymphoid infiltrate, immunohistochemical analysis using markers for B (CD20) and T cells (CD3 and CD5) was performed.

Review of Medical Records and Radiological Findings

Due to the retrospective nature of this study, we could not confirm histologically suspicious lesions exhibiting hot uptake in ^{18}F -FDG PET/CT images by targeted biopsy. Instead, we reviewed all medical records and radiological findings to find patients who received targeted biopsy to suspicious FDG-avid lesions, especially in patients with a negative BMB result and a positive/equivocal ^{18}F -FDG PET/CT. In the absence of histological confirmation of all FDG-avid lesions, we were unable to calculate the sensitivity or specificity of ^{18}F -FDG PET/CT.

Statistical Analysis

The independent -samples t-test was used to compare the mean of mSUVs according to the pairs of groups (e.g., biopsy result (positive vs. negative) or ^{18}F -FDG PET/CT interpretation (abnormal vs. normal, etc.). ^{18}F -FDG PET/CT interpretations (abnormal vs. normal) were compared by chi-square test with the corresponding number of age and sex, for small numbers, by Fisher’s exact test. All values were two-sided, and statistical significance was accepted at P values of <0.05 .

Results

Patient Characteristics

One hundred twenty patients satisfied the inclusion criteria. DLBL was diagnosed in 101 patients (84.2 %), and they received CHOP-rituximab immunochemotherapy. Nineteen patients (15.8 %) had PTCL. All 19 received CHOP combination chemotherapy. Baseline patient characteristics are summarized in Table 1.

^{18}F -FDG PET/CT Findings

Final interpretations of the three reviewers are summarized in Fig. 2. In 97 ^{18}F -FDG PET/CT scans, BM was regarded as showing negative FDG uptake (2 patients who showed

Fig. 1 **a** A 71-year-old woman with angioimmunoblastic T cell lymphoma. Coronal ^{18}F -FDG PET/CT image showing homogenous diffuse hypermetabolism (mSUV 3.18) at the BM site. This scan was reported as “equivocal.” Iliac crest BMB pathology was highly suggestive of involvement. **b** A 62-year-old man with gastric DLBL stage I. Coronal ^{18}F -FDG PET/CT image showing no hypermetabolism at the BM site. This scan was deemed “negative,” which concurred with the iliac crest BMB finding. **c** A 46-year-old woman with high-grade B cell lymphoma stage IV E. Transaxial ^{18}F -FDG PET/CT image at the

pelvic level showing focal hypermetabolism (mSUV 6.09) in left proximal femur, which was deemed “positive.” However, iliac crest BMB was negative in this patient. **d** A 66-year-old man referred because of a splenic mass found during a regular medical checkup. He received splenectomy, and pathology proved DLBL. ^{18}F -FDG PET/CT image showing multifocal hypermetabolic foci in the spine (highest mSUV 13.35) and iliac bone (mSUV 7.24). However, the iliac crest BM result was negative. Abdominal and chest CT found “no evidence of bony involvement”

mild marrow uptake but with a hyper-metabolic mass near the marrow uptake were classified as negative, under presumption of a spillover effect). In 23 ^{18}F -FDG PET/CT scans, the marrow was considered abnormal (i.e., either positive or equivocal). Twelve patients with an area of definitely higher intensity (a hot spot) within a hypermetabolic marrow background were deemed positive, and the other 11 patients were classified as equivocal. As for patterns of hypermetabolism, all “positive” reported images had multifocal hypermetabolic patterns. However, in equivocal cases, only two patients had a single focal uptake pattern, and the other nine exhibited diffuse mild hypermetabolism.

Interobserver agreement rates among the three observers were 100 % (97 of 97) for negative BM uptake and 91.3 % (21 of 23) for scans showing abnormal (either positive or equivocal) uptake irrespective of uptake pattern, and thus overall agreement among observers was good-excellent.

The Relation between ^{18}F -FDG PET/CT and BM Trephine Biopsy Results

Nineteen of the 120 patients (15.8 %) had lymphomatous involvement by BM trephine biopsy. Of the 101 patients with DLBL, 15 (14.9 %) had BM involvement, and 4 of 19 patients (21.1 %) with PTCL showed lymphomatous BM involvement by BMB.

Concordant and discordant rates were calculated. ‘Equivocal’ cases were regarded as abnormal ^{18}F -FDG PET/CT results. One hundred of the 120 patients (83.3 %) had concordant BM results by ^{18}F -FDG PET/CT and BM trephine biopsy: 11 patients were positive by both ^{18}F -FDG PET/CT and BMB, and 89 were negative by both. However, 20 of the 120 patients (16.7 %) had discordant results. Eight had a positive BMB and a negative ^{18}F -FDG PET/CT finding, and the other 12 had a positive ^{18}F -FDG PET/CT findings but no lymphomatous involvement by BMB.

Table 1 Patient characteristics

N ^a =120	n	%
Median age in years (range)	59 (26–83)	
Sex		
Male	61	50.8
Female	59	49.2
Histologies		
Diffuse large B-cell lymphoma	101	84.2
Peripheral T-cell lymphomas (PTCLs)	19	
PTCL, not otherwise specified	10	
Angioimmunoblastic T-cell lymphoma	7	15.8
ALK-negative anaplastic large-cell lymphoma	2	
Age (years)		
≤ 60	64	53.3
> 60	56	46.7
Ann Arbor stage		
I	19	15.8
II	35	29.2
III	33	27.5
IV	33	27.5
IPI ^b Score		
0, 1 (low risk)	49	40.8
2 (low-intermediate risk)	27	22.5
3 (high-intermediate risk)	19	15.8
4, 5 (high risk)	25	20.8

a: N, number of patients

b: IPI, International Prognostic Index

When we compared positive and equivocal patients by ¹⁸F-FDG PET/CT, only 1 of 12 was ‘positive’ for lymphomatous involvement by BMB. However, 10 of 11 patients with an ‘equivocal’ BM hypermetabolism were positive for involvement by BMB (Fig. 2).

When ¹⁸F-FDG PET/CT and iliac crest biopsy results were compared, only 1 of 12 patients positive by ¹⁸F-FDG PET/CT had a positive BMB result. The other 11 patients all exhibited focal FDG uptake in other than the iliac crest and normal FDG uptake at the BMB site in the iliac crest. To identify the causes of discrepancies between ¹⁸F-FDG PET/CT and biopsy results, we reviewed all medical records and radiological findings. Two patients with a FDG hot spot distant from iliac crest who underwent targeted biopsy were found to have lymphomatous involvement but a negative iliac BMB results. This suggests that ¹⁸F-FDG PET/CT could be useful for detecting biopsy sites other than the iliac crest (Figs. 3 and 4). In the remaining nine patients with positive ¹⁸F-FDG PET/CT findings, histologies were not confirmed, but their clinical courses were poor and resembled those of patients positive by iliac crest BMB. In addition, these nine had no other malignancy or condition or clinical event, such as myeloid hyperplasia or previous

systemic chemotherapy or granulocyte colony-stimulating factor administration [14], that could have explained the presence of a multifocal hypermetabolic focus (mean mSUV_{highest} of 8.0±3.9) on ¹⁸F-FDG PET/CT images. These nine patients led to a change in the initially planned chemotherapeutic strategy. In addition, we reviewed the follow-up ¹⁸F-FDG PET/CT images (taken after 1 cycle of chemotherapy) of these patients and found that the mSUVs of previous hot uptake lesions were reduced, which indicated that these lesions represented lymphomatous involvement (Table 2).

That is, we could consider that ¹⁸F-FDG PET/CT determined 11 more patients with BM involvement that conventional BMB had missed, rather than regarding those 11 patients as false-negative ¹⁸F-FDG PET/CT findings of non-BM involvement. However, in the absence of histological confirmation of all FDG-avid focuses, we could not calculate the sensitivity and specificity of ¹⁸F-FDG PET/CT. Regarding the use of BMB as a reference standard, a large-scale prospective clinical trial is required, in which targeted biopsies of focal FDG uptake lesions are performed on all ¹⁸F-FDG PET/CT-positive lesions.

Cell type in NHL could also provide an explanation for the discrepancy between ¹⁸F-FDG PET/CT and BMB findings. It has previously been reported that some low-grade NHLs show low or no FDG uptake, which could limit the use of ¹⁸F-FDG PET in patients with these lymphoma types [15]. Paone and coworkers suggested that in DLBL patients with BM involvement, BM FDG uptake depends on the balance between small (discordant BM involvement) and

Fig. 2 Flowchart of FDG-PET/CT interpretation and bone marrow trephine biopsy result. **a** PET/CT, ¹⁸F-FDG PET/CT scan. **b** BMB, bone marrow biopsy

Fig. 3 A 74-year-old woman with a pathological fracture of the T10 vertebra by MRI and ^{18}F -FDG PET/CT (white arrow) presented complaining of back pain. Targeted biopsy of the hot spot lesion proved lymphoma involvement. She had a single hot uptake lesion in T10 on ^{18}F -FDG PET/CT images and a splenic lesion by CT. Iliac crest BMB was negative in this patient

large (concordant BM involvement) infiltrating cells [16]. In the present study, 10 of 11 patients (90.9 %) reported as “equivocal” by ^{18}F -FDG PET/CT showed lymphomatous BM infiltration by BMB. In most, the histological type was DLBL, which is a well-known FDG-avid NHL type (Table 3). A large-scale study is required to define the characteristics of BM uptake for different histological types.

Fig. 4 A 71-year-old man who received vertebroplasty for a compression fracture at a local clinic was referred to our hospital for the evaluation of continuous pain after surgery. **a** From the left, T2, T1, and an enhanced MR image of the lumbar spine. A massive extra-osseous mass formation was observed at the lumbosacral vertebra and T12 with epidural extension to the whole L spine level and paravertebral back muscle involvement. **b** ^{18}F -FDG PET/CT image showed multifocal hypermetabolic foci in spine, humerus, sternum, scapula, and pubis. He underwent targeted biopsy of the FDG-avid focus in the sternum (white arrow) and was found to have lymphoma involvement. **c** Transaxial image at the pelvic level showing that the conventional BMB region did not exhibit definite hypermetabolic foci, which explained the false-negative BMB finding in this patient

Standardized Uptake Value by ^{18}F -FDG PET/CT

The $\text{mSUV}_{\text{highest}}$ values of the analyzed patients were evaluated, and relations between mean values and ^{18}F -FDG PET/CT interpretations were examined. Patients with an abnormal ^{18}F -FDG PET/CT finding had a significantly higher mean $\text{mSUV}_{\text{highest}}$ than those with a normal ^{18}F -FDG PET/CT finding. Of the abnormal ^{18}F -FDG PET/CT patients, mean $\text{mSUV}_{\text{highest}}$ of those with a positive finding was greater than the mean $\text{mSUV}_{\text{highest}}$ of those with an equivocal finding. In addition, mean $\text{mSUV}_{\text{highest}}$ of patients with an equivocal finding was significantly higher than that of patients with a normal finding.

However, no significant difference was found between the mean mSUV values of patients with a positive and negative BMB finding (4.0 ± 3.0 vs. 3.3 ± 2.4 , $p=0.227$).

Discussion

In this retrospective study, all ^{18}F -FDG PET/CT-positive scans exhibited a multifocal FDG uptake pattern. In other words, interpreters all agreed that the multifocal hot spot

Table 2 Maximum SUV of follow-up ^{18}F -FDG PET/CT after chemotherapy in 11 patients with positive ^{18}F -FDG PET/CT and negative bone marrow biopsy results

Patient	Initial mean of mSUV ($\pm$ standard deviation)	F/U mean of mSUV ^a ($\pm$ standard deviation)	Changed value of mSUV
Patient 1	12.2 $\pm$ 0.9	1.5 $\pm$ 0.2	Decrease
Patient 2	3.0 $\pm$ 0.0	2.4 $\pm$ 0.3	Decrease
Patient 3	6.1 $\pm$ 0.2	1.2 $\pm$ 0.2	Decrease
Patient 4	6.0 $\pm$ 0.1	1.3 $\pm$ 0.0	Decrease
Patient 5	2.4 $\pm$ 0.4	0.7 $\pm$ 0.0	Decrease
Patient 6	7.4 $\pm$ 1.1	1.6 $\pm$ 0.7	Decrease
Patient 7	12.2 $\pm$ 1.1	2.7 $\pm$ 0.2	Decrease
Patient 8	8.4 $\pm$ 2.6	1.3 $\pm$ 0.0	Decrease
Patient 9	5.5 $\pm$ 2.1	1.3 $\pm$ 0.6	Decrease
Patient 10	12.1 $\pm$ 0.5	Expired	
Patient 11	10.7 $\pm$ 3.1	2.1 $\pm$ 0.3	Decrease

a: Mean period between first and second ^{18}F -FDG PET/CT images was 3.9 $\pm$ 2.3 months (range 1–8 months)

patterns undoubtedly showed BM uptake. However, no standardized guidelines have been issued regarding the interpretation of ^{18}F -FDG PET/CT images with respect to BM involvement in lymphoma. ^{18}F -FDG PET/CT positivity is based on visual interpretation and thus is unavoidably subjective. Semi-quantitative calculations of mSUV values are helpful but are inadequate for clear decision-making. Furthermore, basal metabolic activities are diverse among individuals, further complicating the issue, and thus interpretation criteria vary considerably [17]. We reviewed 14 previous ^{18}F -FDG PET/CT studies that examined BM involvement by lymphoma. Elstrom et al. considered a scan “positive” if the specific SUV of a suspicious lesion was >2.5 . This dichotomous classification is convenient, but has substantial limitations because of basal metabolic activity variations among individuals. Four studies defined “positive” and an uptake greater than that of the mediastinum or liver, and seven interpreted all FDG-avid lesions as “positive.” In an observer variation study conducted by Josée et al. [18], likelihood of malignancy was assessed as positive, negative, or equivocal. Gerard Moulin-Romsee et al. also classified lesions into three categories (negative, doubtful, and positive) [19]. In the present study, we also used a three-category classification of positive, negative, and equivocal, because it was difficult to distinguish benign situations with lymphomatous involvement by ^{18}F -FDG PET/CT image alone. More discussion of this topic of interpretation standards is required among experts.

According to the Ann Arbor criteria, bone involvement through direct extension does not affect staging, whereas hematogenous spread upgrades disease to stage IV. BM involvement is diagnosed in 50 % to 80 % of low-grade

NHL patients, 25 % to 40 % of high-grade NHL patients, and 5 % to 14 % of HD patients [20]. Our findings agree with those of other investigators in terms of the ability of ^{18}F -FDG PET/CT to screen entire patients and to detect BM involvement with a high degree of sensitivity anywhere in the body [21, 22]. Cheng et al. investigated 54 pediatric patients with lymphoma (31 HD and 23 NHL) who underwent soft tissue biopsy, BMB, and ^{18}F -FDG PET/CT. Overall sensitivities for detecting BM involvement were 92 and 54 % ($p<0.05$) for ^{18}F -FDG PET/CT and BMB, respectively. The authors also noted more positive BMB findings in patients with abnormal FDG activity in the biopsy sites by ^{18}F -FDG PET/CT, and demonstrated that ^{18}F -FDG PET/CT has high sensitivity and accuracy, and substantial complementary value to BMB in the initial diagnosis of pediatric lymphoma [21]. Fuster et al. compared the values of ^{18}F -FDG PET/CT and BMB for the detection of BM disease in HD and NHL patients. It was found that ^{18}F -FDG PET/CT was more sensitive than BMB in HD and NHL, except for grade 1 and 2 follicular lymphoma [22].

In the present study, we reviewed medical records and radiological findings of patients with equivocal ^{18}F -FDG PET/CT images to determine the cause of discrepancies between ^{18}F -FDG PET/CT interpretations and BMB results. As was mentioned above, discrepancies may arise because BM involvement does not occur at the same time and rate at different marrow sites. In addition, histological type should be considered, and the characteristic nature of BM, which is unlike any other organ, might contribute. The spleen, which appears to be the primary disease site, is usually grossly enlarged and exhibits high FDG uptake. The presence of increased FDG uptake within the spleen but not within marrow might be explained by the high density of malignant lymphocytes in spleen as compared with marrow, especially for tumors with inherently low FDG uptakes. Furthermore, FDG uptake can also be negative/equivocal in the presence of minimal BM disease, whereas histological diagnosis can be made during the early, minimally involved state if a

Table 3 Histological type of patients with equivocal ^{18}F -FDG PET/CT images

Histologies	Total number	Number of equivocal Images
Diffuse large B-cell lymphoma	101	7 (6.9 %)
Peripheral T-cell lymphomas (PTCLs)	19	4 (21.1 %)
PTCL, not otherwise specified	10	1 (10.0 %)
Angioimmunoblastic T-cell lymphoma	7	3 (42.9 %)
ALK ^a negative anaplastic large cell lymphoma	2	0 (0.0 %)

a: ALK, anaplastic lymphoma kinase

proper biopsy specimen is taken. Equivocal ^{18}F -FDG PET/CT images were homogeneously diffuse with mild BM hypermetabolism, reminiscent of reactive hematopoietic changes. In the present study, equivocal images showed a high proportion (90.9 %) of positive BMB cases, which suggests that interpreters should be careful when reading such patterns of ^{18}F -FDG PET/CT images.

Schaefer et al. evaluated the diagnostic impact and clinical significance of FDG-avid bone lesions in patients with malignant lymphoma. They studied HD ($n=22$) or high-grade NHL ($n=28$) patients with uni- or multi-focal BM involvement. In these patients, ^{18}F -FDG PET/CT was found to be a useful tool aid in terms of the diagnosis and the identification of BM disease. All patients underwent either direct biopsy of FDG-avid bone lesions ($n=18$), standard BMB ($n=43$), or both procedures ($n=11$). In 15 patients, additional MRI of the bone lesions was performed. One hundred ninety-three FDG-avid lesions were found by ^{18}F -FDG PET/CT, and their mean SUV was $6.26 (\pm 3.22)$. All direct biopsies of FDG-avid lesions proved the presence of lymphomatous infiltration. BMB ($n=43$) was positive in 12 patients (27.9 %). In CT, 32 of 193 (16.6 %) lesions were detected without the ^{18}F -FDG PET/CT information. No additional morphological bone infiltration was detected on CT compared with ^{18}F -FDG PET/CT. All morphological bone alterations on CT scans persisted after the end of therapy. Additional ^{18}F -FDG PET/CT information regarding uni- or multifocal bone involvement resulted in lymphoma upstaging in 21 (42 %) patients compared with the combined information provided by CT and BMB.

The authors concluded that: (1) ^{18}F -FDG PET/CT should be used as an initial staging procedure for HD and aggressive NHL; (2) BMB is still warranted in ^{18}F -FDG PET/CT negative cases; and (3) FDG-positive lesions should be further evaluated by direct bone biopsy or MRI [23].

Conclusions

The increasing availability of ^{18}F -FDG PET/CT will raise the need for the biopsy for FDG-avid lesions, especially in patients with a negative standard BMB. ^{18}F -FDG PET/CT can be useful when deciding whether to perform standard BMB or targeted biopsy of FDG-avid lesions as an initial staging procedure. Furthermore, our findings indicate that a direct bone biopsy of FDG-positive bone lesions should be included in future staging guidelines. In ^{18}F -FDG PET/CT negative cases, BMB is a powerful procedure, but BMB alone is insufficient to evaluate BM fully.

Conflict of Interest Disclosure We declare that we have no conflict of interest.

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