Diagnosis of Bone Marrow Involvement in Pediatric Lymphoma Patients: FDG PET/CT Versus Bone Marrow Biopsy

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Contents

Abstract

Bone marrow infiltration (BMI) is common in patients with Hodgkin's disease (HD) and non Hodgkin's lymphoma (NHL), often indicates poor prognosis. Accurate assessment of BMI is critical for staging and selection of proper therapeutic options in lymphoma patients. Up to now, bone marrow biopsy (BMB) is an integral part of initial work-up in these patients, although it has a high false negative rate. In recent years, FDG PET/CT has established as a highly accurate imaging tool in the assessment of Hodgkin's disease and non-Hodgkin's lymphoma. Multiple studies have found that FDG PET/CT in the initial diagnosis work-up detects more bone marrow involvement in lymphoma patients thus are more sensitive and more accurate than bilateral bone marrow biopsy performed at the iliac crest. At the same time, it has been shown that BMB performed based on findings of FDG PET/CT significantly decreased false negative findings and improved accuracy of BMB. In this review, we discuss the value of FDG PET/CT in identifying BMI and in guiding BMB in the initial evaluation of pediatric lymphoma patients.

Introduction

Lymphoma is a common malignancy. Based on the data from the American Cancer Society in 2011, lymphoma is the fifth most common cancer in males and the seventh most common cancer in

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females, with predicted 75,190 new cases (8,830 cases for HD and 66,360 cases for NHL) and 20,620 deaths in 2011. It represents the ninth leading cause of death in male and sixth leading cause of death in female. Bone marrow involvement in Hodgkin's disease (HD) or aggressive non-Hodgkin's lymphoma (NHL) indicates advanced stage of disease and also poor prognosis. However, bone marrow infiltration (BMI) is not uncommon and can occur in patients at seemly early stage of disease. The incidence of lymphoma bone marrow involvement ranges approximately 5–21% in HD patients (Moulin-Romsee et al. 2010; Cheng et al. 2011), 30–50% in NHL patients (Schaefer et al. 2007a; Cheng et al. 2011), and as high as 50–80% in low-grade NHL (Pelosi et al. 2008a). To guide therapeutic planning and to minimize side effects and toxicity when aggressive treatment can be avoided, bone marrow biopsy (BMB) has been performed routinely for decades as an integral part of initial work up in lymphoma patients to assess bone marrow status, and has been considered as a "gold standard".

However, BMB is not a perfect procedure for this purpose. A positive finding on BMB confirms the status of bone marrow infiltration, but a negative BMB finding is less informative. It has been recognized for years that BMB is associated with a high false negative rate. BMB is most commonly performed blindedly at the unilateral or bilateral iliac crest, either anteriorly or posteriorly. Traditionally, this selection of biopsy site is because of the convenience of the procedure and easy access to bone marrow, without considering whether there is evidence of BMI at the biopsy site. At the same time, only limited sampling of small amount of the bone marrow is obtained, because of an invasive nature of the procedure. The blinded selection of biopsy sites and a small specimen make sampling error inevitable, leading to a high false negative rate.

Pathologists were among the first to recognize a high false negative rate (the number of false negative cases on BMB/total positive cases, FNR) of BMB in the assessment of lymphoma patients (Wang et al. 2002). Levis et al. (2004) reported that positive bone marrow involvement was limited to only one of the two specimens of BMB in 35% of cases in a study involving 1,161 HD patients. Similarly, among NHL patients with positive bone marrow involvement of lymphoma, 30% had positive BMI only on one side biopsy specimens (and up to 50% in diffuse large cell lymphoma) (Juneja et al. 1990). The fact that bilateral iliac crest BMB detects more lesions than unilateral BMB confirms potential false negative findings of unilateral as well as bilateral BMB, as demonstrated in numerous studies. For example, Menon and Buchanan (1979) reported that bilateral BMB increased the yield of positive marrow lesions by 26%, as compared with unilateral examination, in a series of 145 patients with HD and NHL.

18F-Fluoro-2-Deoxyglucose (FDG) Positron Emission Tomography and Computed Tomography (PET/CT) Is a Valuable Imaging Modality for Lymphoma

18F-Fluoro-2-Deoxyglucose (FDG) positron emission tomography (PET) is a valuable imaging tool in the evaluation of multiple malignancies. A unique aspect of FDG PET imaging is that it is a functional study independent on morphological changes. FDG is actively transported into a cell via glucose transporters, converted into FDG-6-phosphate by hexokinase, which is trapped within the cell because FDG-6-phosphate cannot be further metabolized. In general, tumor cells have higher expression level of glucose transporters and are metabolically more active, thus will demonstrate as increased FDG activity on a PET imaging (Cheng et al. 2011).

Available data indicate that FDG PET has become a valuable imaging modality in the evaluation of lymphoma, either in adults or in pediatric patients (Cheng et al. 2012). The value of FDG PET in the evaluation of bone marrow involvement in lymphoma patients has been recognized more than 10 years ago (Moog et al. 1998). More recent studies confirmed this finding and provided clear evidence that FDG PET outperforms BMB with more additional positive

findings of bone marrow lesions on the initial evaluation of HD or NHL patients (Fuster et al. 2006; Schaefer et al. 2007a; Pelosi et al. 2008b; Ribrag et al. 2008; Cheng et al. 2011; Purz et al. 2011). The application of FDG PET staging led to changes of clinical management ranging from 8 to 45% in adults lymphoma patients (Allen-Auerbach et al. 2008), and in 10–23% in pediatric patients (Depas et al. 2005), often with upstaged diagnosis due to additional findings of BMI on PET. FDG PET (now more commonly, PET/CT) is now widely with high sensitivity and specificity in the evaluation of lymphoma. In addition to initial diagnosis, FDG PET has been used successfully for response assessment, prognosis prediction, and for detection of residual lesions or recurrence.

In our own study (Cheng et al. 2011), we evaluated BMI in 54 pediatric patients with pathologically proven lymphoma (31 HD, 23 NHL) and 13 of them had BMI. FDG PET/CT revealed additional BMI in six patients who were false negative on BMB, while BMB revealed only one additional case with BMI who was false negative on FDG PET/CT imaging. The overall sensitivity of FDG PET/CT was much higher than that of BMB in detecting BMI by lymphoma (92% versus 54%; $p<0.05$) (Cheng et al. 2011). Our data was similar to previous reports. For example, Fuster et al. (2006) reported that FDG PET had a sensitivity and specificity of 86 and 99% respectively, in contrast to 57 and 100% by BMB, in detecting BMI in lymphoma patients. Schaefer et al. (2007a) found that FDG PET/CT upstaged up to 42% of all cases of lymphoma as regarding to uni- or multifocal BMI. More recently, Purz et al. (2011) reported a retrospective study involving 175 pediatric patients with newly diagnosed classical HD, and found that FDG PET scans correctly detected all 45 cases with BMI out of 175 patients without false positive or false negative findings, achieved 100% sensitivity and 100% NPV in the diagnosis of BMI. In contrast, BMB detected only seven cases among all 45 patients with BMI with a sensitivity of 16% and NPV of 77%.

We noticed that there was a meta-analysis of the value of FDG PET in the assessment of BMI in lymphoma patients, which demonstrated a discrepancy and variable effectiveness of FDG PET for identifying BMI (Pakos et al. 2005). After careful examination of this analysis, we noted that the majority of data cited in this meta-analysis were obtained from old style instruments, on PET-alone machines without corresponding CT images, and many of them did not even have attenuation correction, which is now totally obsolete. These factors could have negative impact on accurate interpretation of FDG PET studies thus on the conclusions as derived from this meta-analysis. Current PET machines are coupled with an integrated CT scanner to obtain complementary PET and CT images and are equipped with multiple artifact correction capabilities, which significantly improve the accuracy of diagnosis. Table 16.1 is a short list of recent published data on the application of FDG PET/CT versus BMB in the assessment of BMI in lymphoma patients, and only studies on the initial diagnosis were included. Three FDG PET/CT studies (Ribrag et al. 2008; Moulin-Romsee et al. 2010; Pelosi et al. 2011) are included in Table 16.1 for the general patient population of lymphoma, and three available PET or PET/CT studies for pediatric patients (Kabickova et al. 2006; Cheng et al. 2011; Purz et al. 2011) are also included. In either general patient population or in pediatric patients, FDG PET outperforms BMB in detecting BMI in the initial evaluation of lymphoma. While BMB and FDG PET both are very specific in detecting BMI in lymphoma patients, FDG PET has an important advantage over BMB, i.e., FDG PET is much more sensitive in this regard (thus less false negative findings), especially for pediatric patients. These studies show that FDG PET or PET/CT had a sensitivity ranging 69–100% (92–100% for pediatric patients) and an accuracy ranging 91–100% (98–100% for pediatric patients), while BMB had a sensitivity ranging 0–60% and an accuracy ranging 78–90%, while the specificity was similar for PET and BMB.

On FDG PET/CT, tumor infiltration of the bone marrow in lymphoma patients is often manifested as focal or multifocal increased FDG uptake (Fig. 16.1). Multiple studies (including our own experience) indicated that multifocal

Table 16.1 Performance of FDG PET/CT versus BMB in detecting BMI in the initial diagnosis of lymphoma

	Studies	Case number	Total BMI	BMI incidence	Accuracy PET	Sensitivity PET	Specificity PET	Accuracy BMB	Sensitivity BMB	Specificity BMB
General patient population	Pelosi et al. (2011)	337	87	26%	91%	69%	99%	90%	60%	100%
	Moulin-Romsee et al. (2010)	83	18	22%	100%	100%	100%	87%	39%	100%
	Ribrag et al. (2008)	47	10	21%	98%	90%	100%	85%	30%	100%
Pediatric patients	Purz et al. (2011)	175	45	26%	100%	100%	100%	78%	16%	100%
	Cheng et al. (2011)	54	13	24%	98%	92%	100%	89%	54%	100%
	Kabickova et al. (2006)	55	8	15%	100%	100%	100%	85%	0%	100%

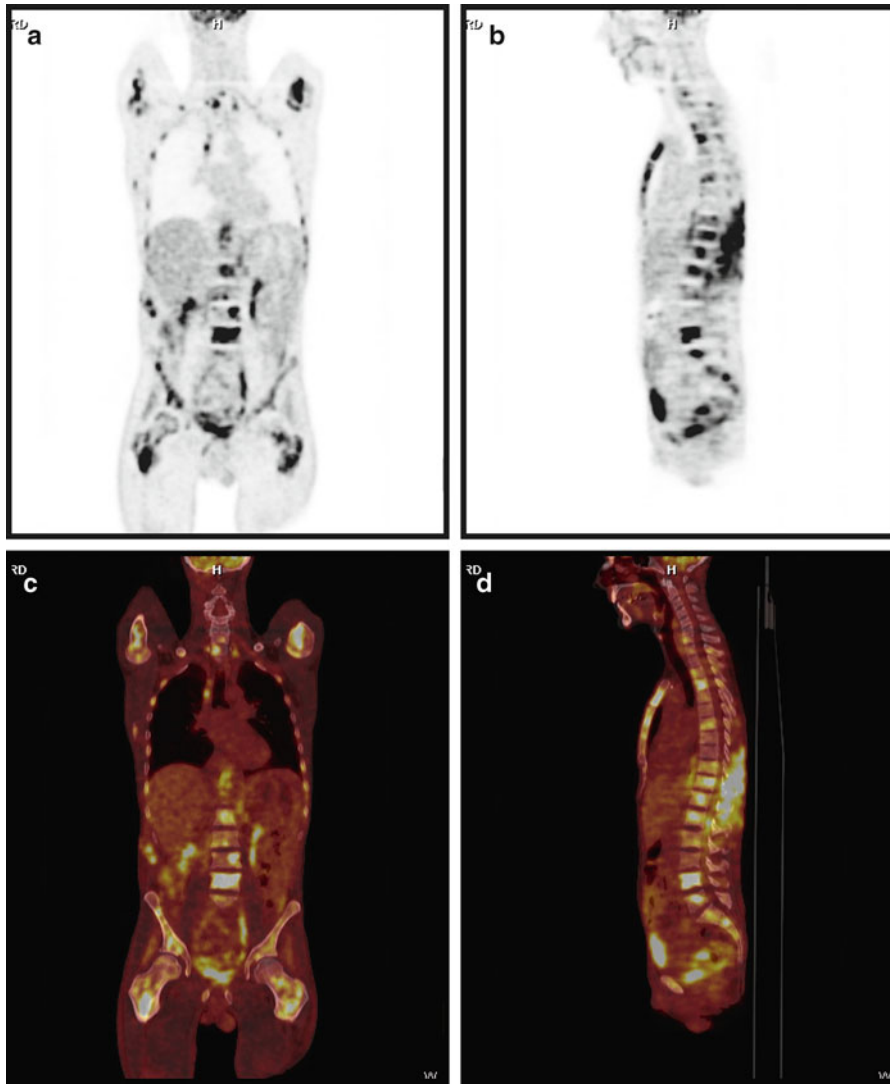

Fig. 16.1 FDG PET/CT was performed in a 54-year old male for initial staging of NHL and revealed numerous foci of FDG-avid bone marrow lesions, characteristic of bone marrow infiltration of lymphoma. FDG-avid soft tissue tumor masses are also noted in the posterior back and in the mediastinum. (**a**, **b**) coronal and sagittal view of PET images; (**c**, **d**) coronal and sagittal view of fused PET/CT image

intense FDG uptake in bone marrow without other clinical explanation is very specific for the diagnosis of BMI (Schaefer et al. 2007a; Moulin-Romsee et al. 2010; Cheng et al. 2011), as confirmed by post FDG PET biopsy. It has to be recognized that focally increased FDG uptake on a PET scan is, by itself, not specific. Many other etiologies (such as osteomyelitis or fracture) can cause similar changes. However, multifocal FDG uptake on a PET scan can be a very specific finding for BMI in appropriate clinical settings: if the patient has no other clinical history (for osteomyelitis, or fracture, etc.), and if the patient has a recently diagnosed lymphoma, and the multifocal FDG uptake on a PET imaging has a typical pattern suggestive of BMI. It is more common for a lymphoma patient to have multifocal lesions of BMI on FDG PET imaging although occasionally a patient may have only one or two bone marrow lesions. Purz et al. (2011) recently

reported in the study involving 175 pediatric HD patients that the majority (32 out of 45 patients) had three or more skeletal lesions on FDG PET imaging.

Several factors may contribute to high accuracy of FDG PET/CT in the identifying BMI in lymphoma patients. First, FDG PET is a functional study independent on morphological changes. It is well known that FDG PET is more accurate than CT imaging in detecting bone marrow lesions. A recent report provided clear evidence that in some cases, morphologic changes on a CT scan occurs after resolution of FDG PET abnormalities (after successful treatment) (Gemmel et al. 2012). Second, PET allows convenient whole body scan and allows assessment of the majority of the whole skeleton system. Third, simultaneous CT images provide important information for anatomic correlation, which is very helpful in the differential diagnosis (for example, to rule out fractures or acute inflammatory disease).

High FNR of BMB Is Due To Sampling Error

The focal or multifocal localization of bone marrow infiltration on FDG PET/CT indicates heterogeneous nature of BMI in lymphoma patients, and that this heterogeneous nature of BMI is likely the underlying cause of high false negative rate of BMB. BMB is a well-established method with sound technique and successful application in soft tissue biopsies, as demonstrated in years of clinical practice. However, if the biopsy missed the location of malignancy, sampling error occurs and false negative finding is inevitable.

In fact, data from bone marrow pathological findings provided strong evidence of the heterogeneous nature of bone marrow involvement in lymphoma patients, indicating a negative effect of inadequate sampling on the diagnosis. Bone marrow aspiration is less accurate than BMB in detecting BMI. For example, Moid and Depalma (2005) reported that among 20 cases of HD patients with a positive bone marrow trephine biopsies, bone marrow aspirate was positive on only one case. Similar findings were reported by others (Subramanian et al. 2007). However, iliac BMB is far from perfect. It is well-recognized that bilateral iliac BMB is more accurate than unilateral BMB in detecting bone marrow lesions in lymphoma and other malignancies (a discrepancy between the left and right side biopsy specimen was identified in 39% for HD samples, 9.2% for NHL samples, 29% for sarcoma samples, 23% for carcinoma samples) (Wang et al. 2002). The fact that an additional biopsy site leads to additional positive finding of bone marrow lesions on BMB indicates focal rather than diffuse pattern of marrow infiltration by lymphoma. Similarly, additional positive finding of bone marrow lesions on BMB can be achieved by increasing the size of biopsy specimen. For example, Campbell et al. (2003) reported that in patients with diffuse large cell lymphoma, 35% of BMB biopsies were positive for BMI if the length of biopsy specimen were ≥ 20 mm, in contrast to only 20% positive finding for BMI if the specimen length were < 20 mm.

A common feature to these techniques (increasing the size of BMB specimen, or by adding additional biopsy site, or by changing bone marrow aspirate to biopsy) to increase accuracy of pathologic examination is increasing the size or tissue volume of bone marrow specimen to be examined. However, the size of BMB specimen is limited, due to invasive nature of biopsy. No matter what biopsy method employed, only a very limited volume of the bone marrow can be directly examined. Because lymphoma infiltration of bone marrow is non uniform, it is easy to understand the underlying reason for high false negative rate of BMB.

While the lymphoma infiltration of bone marrow is often multifocal, it has to be realized that these lesions are often localized in red marrow region regions (including the ribs, spine, sternum, clavicles, scapulas, pelvic bones, the proximal humeri and proximal femurs) in a rather random pattern. FDG PET/CT imaging provides clear evidence that the iliac crest (the site of blinded BMB) is frequently spared even

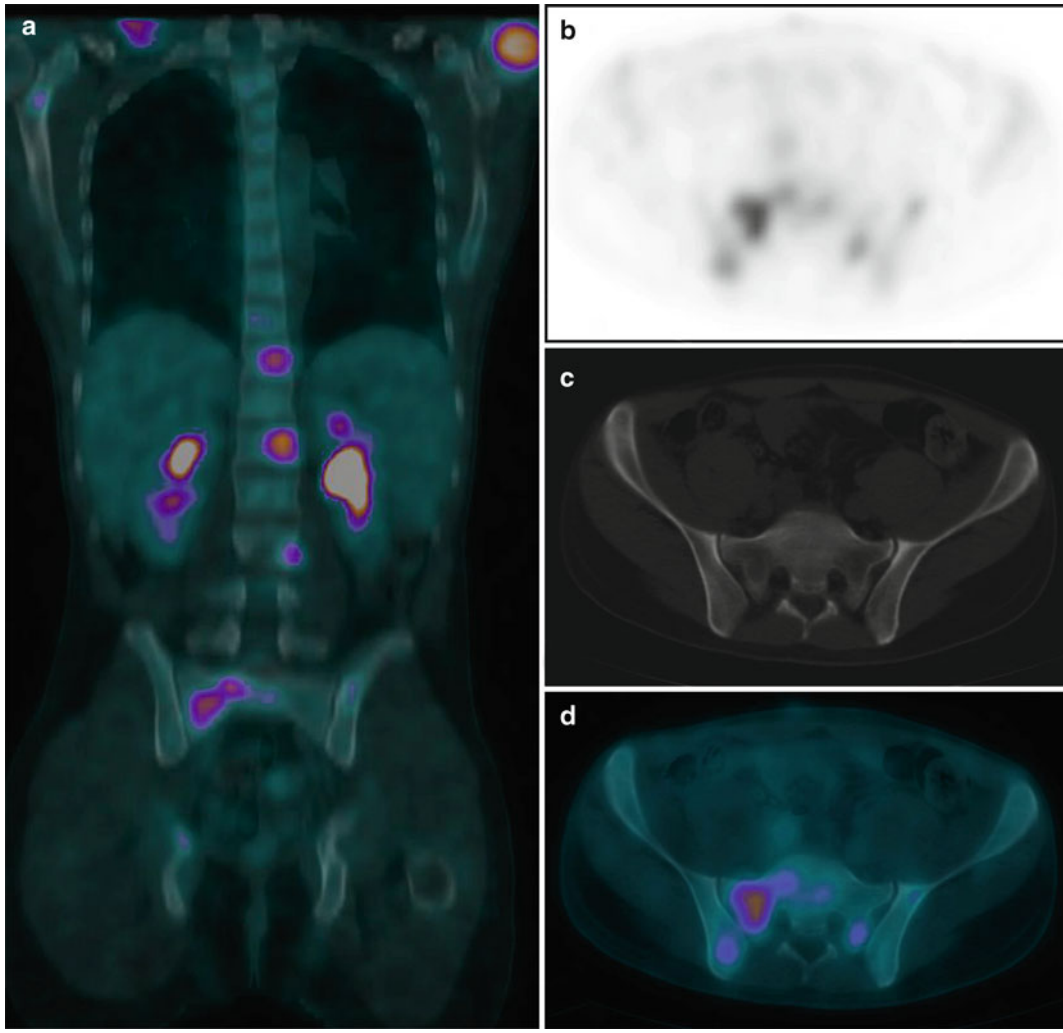

Fig. 16.2 FDG PET/CT was performed in a 22-year old male for initial staging of Hodgkin's lymphoma and revealed multiple foci of bone marrow infiltration including the right scapula, the left humerus, multiple thoracolumbar vertebrae, and the sacrum. FDG-avid soft tissue tumor masses in the *right lower neck* and the mediastinum are not shown. Blind BMB performed on bilateral anterior iliac crests were negative as there was no FDG-avid lesion in the anterior iliac crests. All FDG-avid lesions resolved on repeat PET imaging after chemotherapy. (**a**) coronal fused PET/CT image; (**b**-**d**) transaxial images of PET, CT, and PET/CT, respectively, showing BMI in the sacrum but not in the anterior iliac crests

though there are multiple lesions of BMI elsewhere in the skeleton (Ribrag et al. 2008; Moulin-Romsee et al. 2010; Cheng et al. 2011). An example is provided on (Fig. 16.2). These data indicated that the high false negative rate of BMB is due to sampling error (more specifically, due to blinded selection of the biopsy site), rather than the technique itself.

The High FNR of Iliac BMB Can Be Avoided by Targeted BMB

The high FNR of iliac BMB is not observed in soft tissue biopsy. Upon analyses of the biopsy yielding (the percentage of positive findings among all biopsies) of soft tissue biopsy versus BMB in the same group of pediatric patients with

lymphoma, we found that soft tissue biopsy had a very high yield (91.9% of HD cases and in 96.0% of NHL cases) while the yield of blinded BMB in the same patients was low (only in 6.5% of HD cases and in 20.0% of NHL cases, with an overall false negative rate of 46.2%) (Cheng et al. 2011). This discrepancy can only be explained by sampling error: while soft tissue biopsy sites were chosen based on findings from either physical examination or structural diagnostic imaging tests that suggest a high likelihood of malignancy (Weiss et al. 2008), there was no selection of biopsy site for BMB, as BMB is performed on predetermined site, regardless of potential chance of tumor involvement.

It was interesting to note that the FNR of BMB was low if there was evidence of bone marrow infiltration in the iliac crest on FDG PET imaging. For example, Moulin-Romsee et al. (2010) analyzed 83 cases of HD patients who underwent FDG PET/CT imaging for initial evaluation. All seven cases with positive BMB on the iliac crest had abnormal FDG uptake on FDG PET scan, while BMB was false negative in other 11 cases with bone marrow lesions on FDG PET/CT, because in these 11 patients, BMI was found in regions other than the iliac crest (the biopsy site) on FDG PET. Similarly, we noticed that BMB had a higher yielding in patients with abnormal FDG uptake in the biopsy sites. For all 54 pediatric HD or NHL patients, BMB was positive for malignancy in 85.7% of patients with abnormal FDG PET findings in the biopsy site of the iliac crests, and was positive only in 2.1% of patients with normal FDG PET findings in the biopsy sites. In another ward, except for one case that was false negative on FDG PET/CT, all other cases with positive BMB had focal lesions of abnormal FDG uptake at the biopsy site (Cheng et al. 2011). In addition, it has been reported that targeted BMB performed in regions with suspicious bone marrow involvement (based on abnormal FDG PET findings) is almost always positive (Schaefer et al. 2007a; Muslimani et al. 2008). For example, Schaefer et al. (2007a) reported none of the 18 targeted BMB procedures in lymphoma patients was negative for BMI if performed based on abnormal FDG PET findings, although some of these patients had negative blind iliac BMB.

As discussed above, FDG PET/CT outperforms BMB in detecting BMI. Then the question is BMB still needed? There is no doubt that BMB has a role in confirming a diagnosis of a malignancy that cannot be replaced by any other study. However, in patients undergoing BMB, most likely these patients already had a soft tissue mass biopsy and had a pathologically proved diagnosis of lymphoma. Whether these patients benefit another biopsy of the bone marrow remains controversial and should be further evaluated (Quereux et al. 2009), especially now that FDG PET/CT provides better diagnosis in this regard. However, it is becoming clear that BMB has little additional value of FDG PET/CT in detecting BMI in lymphoma patients (Cheng et al. 2011). While it remains to be determined if these patients should have a BMB procedure, it is more clear as regard to when and where the biopsy should be performed, if it is performed anyway.

Since FDG PET/CT detects more BMI in lymphoma patients, and since BMB performed at the site with focally abnormal FDG uptake on a PET/CT imaging has a high accuracy to reveal malignancy, it is reasonable to recommend that BMB should be performed in the region of bone marrow with abnormal FDG uptake, and for this purpose, BMB should be performed after FDG PET/CT. It is important that BMB is performed based on the findings of FDG PET/CT so that the findings on bone marrow pathology can best reflect the tumor status of a patient. We believe that BMB should no longer be performed in a blinded area of the iliac crest and should not be used as a screening technique. If BMB is performed in selected regions in selected patients with high risk of bone marrow involvement, its finding will be more valuable in guiding our clinical practice.

The Value of FDG PET/CT in Post-Therapy Bone Marrow Evaluation Remains to Be Defined

Please note that above discussion is limited to initial diagnostic evaluation of lymphoma. Whether these findings apply to interim evaluation or post-therapeutic follow up remain to be determined. It has to be emphasized that focal increased FDG uptake on a FDG PET scan is a

nonspecific finding (i.e., not specific for malignancy) although the pattern of multiple focal abnormality can be specific enough to represent BMI under appropriate clinical settings. Two factors complicate the evaluation of lymphoma patients who had received treatment. The first is chemotherapy. Most chemotherapy will significantly compromise the immune system and make patients prone to infection, and infection of any kind is a common cause of false positive findings on a FDG PET. The second is that these patients on chemoradiation therapy will likely receive supportive treatment such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF). These growth factors stimulate proliferation (and the metabolism) of the bone marrow, leading to increase background FDG uptake (Salaun et al. 2009). On FDG PET imaging, these patients often have significantly increased and diffuse FDG uptake throughout the bone marrow, making it difficult to detect occult bone marrow lesions, although a negative finding on FDG PET may still have a good negative predictive value. Still, available data indicate that FDG PET/CT is highly accurate and outperforms CT alone or CT in combination with iliac BMB in lymphoma patients after the end of treatment and at further follow-up, with overall sensitivity, specificity, PPV and NPV of 100, 91, 85, and 100%, respectively (66 patients with Hodgkin lymphoma were analyzed, and all patients with positive FDG lesions had surgical biopsy for histopathologic confirmation) (Schaefer et al. 2007b). However, data is limited regarding to FDG PET/CT performance in this patient group, and further evidence is needed to establish the clinical value of FDG PET/CT in this regard.

FDG PET Has Been Used Experimentally in Guiding Biopsy in Real Time

In addition to select a biopsy site based on findings of FDG PET/CT findings, we are seeing some pioneering work in recent years to perform percutaneous bone marrow biopsy under direct guidance of FDG PET/CT imaging. This is because that some lesions (especially bone marrow metastases) do not have distinctive structural abnormalities on CT or ultrasound. Klaeser et al. (2010) performed percutaneous PET/CT-guided bone biopsies to histologically verify the etiology of hypermetabolic bone lesions in patients with breast cancer, non-small cell lung cancer, cervical cancer, soft tissue sarcoma, and osteosarcoma. The procedure was performed with patients repositioned according to the findings in PET-CT, and the biopsy needle being adjusted based on a subsequent single-bed PET-CT acquisition of the region concerned and with the guidance of repetition of a single-bed PET-CT acquisition before sampling. The procedure was technically successful in all 20 patients, reached a definite histological diagnosis in 95% of cases without any complications or adverse effects (Klaeser et al. 2010). In addition, percutaneous PET/CT-guided biopsy has been performed in other locations with potential malignancy (including liver lesions, the spleen, pancreas, presacral soft tissues, retroperitoneal lymph nodes) (Tatli et al. 2010). While PET/CT-guided bone biopsy seems to be a promising alternative to conventional techniques to accurately target metabolically active bone lesions, more research work is needed to establish its clinical value.

Conclusion

Current literatures indicate that FDG PET/CT is more accurate in the initial evaluation of bone marrow involvement, and detects substantially more bone marrow lesions with similar specificity as compared with BMB, in the initial diagnosis of lymphoma patients. As it becomes wide available in clinical practice, FDG PET/CT is changing the evaluation workup for lymphoma patients, with high positive and negative predictive values in the evaluation of BMI. BMB performed at the predetermined regions of the iliac crests has a high false negative rate, thus a negative BMB does not exclude BMI. The high FNR of BMB is due to sampling error because the blinded biopsy sites (the iliac crests) may have no lymphoma involvement. Although BMI is often multifocal with frequent involvement of

the spine and pelvic bones, in approximately one third of cases with positive findings on FDG PET, the iliac crests are not involved at all. The FNR of BMB can be significantly decreased if BMB is performed at selected regions based on FDG PET findings.

Based on available data and our own experience, we believe that BMB should no longer be regarded as the "gold standard" in the initial evaluation of BMI in HD and aggressive NHL patients, because it has high FNR, and biopsy from one or two iliac crests cannot accurately reflect the status of the bone marrow as a whole. FDG PET/CT should be employed as a first-line study and should be performed in all patients, to evaluate the bone marrow status as well as to evaluate other parts of the body. BMB should be performed in selected patients rather than as a screening examination. If BMB is planned, BMB should be performed after FDG PET/CT, and that the biopsy site should be selected according to FDG PET/CT findings, i.e., to biopsy bone marrow with abnormal FDG uptake, so as to minimize false negative finding of BMB.

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