

Clinical utility of ¹⁸F FDG-PET/CT in the detection of bone marrow disease in Hodgkin's lymphoma

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Objective: The aim of the study was to evaluate the potential role of fludeoxyglucose (FDG)-positron emission tomography (PET)/CT in the detection of bone/bone marrow disease in patients with Hodgkin's lymphoma (HL).

Methods: We retrospectively reviewed (¹⁸F)-FDG-PET/CT scans of 122 newly diagnosed, biopsy-proven cases of HL performed between November 2009 and June 2010. All the patients were staged before treatment by both PET/CT and bone marrow biopsy (BMB). Patients were subdivided into three groups based on the findings of FDG-PET/CT. Group A consisted of patients showing diffuse FDG uptake, Group B consisted of patients showing unifocal FDG uptake and Group C patients showed multifocal FDG-avid foci on PET/CT scans. Bone marrow results were also reviewed and considered positive if lymphomatous involvement was detected on bone marrow trephine biopsy. BMB results were correlated with FDG-PET/CT findings.

Results: There were 122 patients in total—81 (66.4%) were male and 41 (33.6%) were female. The age range was from 6 years to 78 years (mean 35.70 years). PET/CT was reported as negative for bone/bone marrow involvement in 85 (69.7%) patients, while the remaining 37 showed abnormal FDG uptake. The sensitivity of FDG-PET/CT was calculated to be 100%, the specificity was 76.57%, the negative predictive value was 76.57%, the positive predictive value was 29.72% and the diagnostic accuracy was 78.62%.

Conclusion: ¹⁸F-FDG-PET/CT and BMB are complementary in the evaluation of bone marrow disease.

Received 2 February 2011

Revised 26 September 2011

Accepted 4 October 2011

DOI: 10.1259/bjr/29583493

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Fluorine-18 (¹⁸F)-fludeoxyglucose (FDG) has found widespread use in the diagnosis and staging work-up of lymphomas. One of the most promising applications is in the determination of clinical stage of disease at presentation or recurrence [1]. Accurate staging is essential for planning an effective treatment regimen and minimising side effects and toxicity [2]. Bone marrow infiltration is of prime importance not only in staging the disease but also in the tailoring of treatment protocols [3]. Bone involvement can result from haematogenous spread or by extension from adjacent soft tissues [4, 5]. Bone marrow involvement in patients with lymphoma is considered as a sign of generalised disease and with less favourable prognosis. Bone marrow biopsy (BMB) is the established method for the detection of bone marrow infiltration. BMB is generally safe but should not be considered as a risk-free procedure; adverse events (haemorrhage, infection etc) have been reported in about 0.12% of cases [6]. It is an invasive and painful experience for the patients and it sometimes results

in only a small sample which may turn out to be inconclusive. Bone marrow involvement is diagnosed in 50–80% of patients with low-grade non-Hodgkin's lymphoma (NHL), 25–40% of those with high-grade NHL and 5–14% of those with Hodgkin's lymphoma (HL) [6, 7]. Lymphoma staging is based on Ann Arbor classification with Cotswolds modifications [8], which includes CT and BMB. Radiologically, CT may depict cortical bone changes but has low sensitivity for early bone marrow involvement [8, 9]. Unilateral or bilateral BMB of the dorsal iliac crest is considered as the standard method for detecting bone marrow involvement complemented by MRI when needed [2, 10–12]. The potential role of FDG-positron emission tomography (PET)/CT is yet to be determined for the assessment of bone marrow involvement, as very few systematic studies have been carried out in this regard. Since the advent of FDG-PET/CT, functional imaging has emerged as an important imaging tool in differentiating viable tumour tissue from necrotic and therapy-induced fibrosis [13, 14]. The aim of the current study was to correlate BMB and PET/CT results as part of baseline staging work-up and to assess the clinical utility of FDG-PET/CT in the detection of bone/bone marrow disease.

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Methods and materials

Patients

A retrospective study was conducted, reviewing 122 biopsy-proven and untreated patients with HL who underwent ^{18}F -FDG-PET/CT scanning between November 2009 and June 2010. All the patients were staged before treatment by both PET/CT and BMB. The routine lymphoma staging at our institution involves whole-body contrast-enhanced PET/CT along with iliac crest marrow aspirate (bilateral) and trephine biopsy. In all patients, PET/CT was performed within 2 weeks of the marrow biopsy as a baseline scan followed by a follow-up PET/CT (either mid treatment or end of therapy as per oncologist's protocol). The repeat or follow-up PET/CT scan was carried out to assess the response to therapy.

Marrow histology

Trephine biopsy samples were decalcified and stained with haematoxyline and eosine (Gordon and Sweet's reticulin method) [15]. Accompanied marrow aspirates were stained with the May-Grunwald/Giemsa stain. All trephine biopsies were phenotyped with CD20 (B cell marker), CD3 (T cell marker), CD15 and CD30 (markers for Reed-Sternberg cells) and leukocyte common antigens (CD45). The marrow infiltration for Hodgkin's lymphoma was interpreted by two pathologists who were blinded to the PET/CT results.

^{18}F -FDG-PET/CT scanning

PET/CT studies were obtained using a Philips Gemini TF (Philips Healthcare, Eindhoven, Netherlands), combining a germaniumoxyorthosilicate-based PET scanner and a 16-slice CT scanner. After fasting for 4–6 h and with a blood glucose level of $<150\text{ mg dl}^{-1}$ at the time of injection, patients were injected with 5 MBq kg^{-1} of ^{18}F -FDG (maximum 400 MBq). A ^{18}F -FDG-PET/CT scan was acquired 60 min post injection from head up to mid-thigh level. A CT scan was performed first with intravenous contrast using a current of 100–150 mA and was taken as a diagnostic scan. On completion of the CT scan, PET study was acquired by advancing the patient couch into the field of view and acquiring multibed (8–10 positions) over the same range as the CT scan. CT images were used for attenuation correction of the ^{18}F -FDG-PET emission data as well for exact anatomical localisation. PET images were reconstructed using a three-dimensional row action maximum likelihood algorithm.

Analysis of bone/bone marrow FDG uptake

In this study, the intensity and distribution of FDG activity within the bone/bone marrow was visually scored independently by two experienced nuclear medicine physicians and two radiologists. The marrow was assumed to be abnormal when the uptake was equal to or greater than the liver uptake, taking into account that the liver uptake was more than the background. The PET/CT scan was reported as positive (having focal or diffuse tracer uptake in the bone/bone marrow that could

not be explained by benign findings on underlying CT or clinical history). The number and location of FDG-avid lesions in the bone/bone marrow were also noted as well as the underlying sclerotic or osteolytic abnormality found on the CT bone windows. The negative PET/CT scan did not show any abnormal FDG uptake in the bone/bone marrow. The BMB was taken as the gold standard in calculating the sensitivity of ^{18}F -FDG in detecting bone/bone marrow involvement by lymphoma.

Patients were broadly divided into three groups based on the pattern and number of FDG avid focal lesions:

Group A: intense homogeneous FDG uptake in the axial and proximal appendicular skeletons.

Group B: unifocal (one or two sites) of increased FDG uptake in the bone/bone marrow.

Group C: multifocal (at least three sites) of increased FDG uptake in the bone/bone marrow.

True-positives were patients with a positive BMB and PET/CT scan. True-negatives were patients with a negative BMB and PET/CT scan. False-positive cases were those with positive PET/CT and negative BMB. False-negative cases were those with negative PET/CT and positive BMB.

Ethical considerations

BMB and whole-body contrast-enhanced PET/CT is part of the routine clinical work-up for the established diagnosis of HL at Shaikat Khanum Memorial Cancer Hospital & Research Center. All the patients were informed and written consent was obtained, explaining the need for this investigation and treatment. All the data were reviewed retrospectively, which complies with the institutional laws. None of the authors had any conflict of interest.

Results

There were 122 patients in total—81 (66.4%) were male and 41 (33.6%) were female. The age range was from 6 to 78 years (mean 35.70 years). There were 114 patients with classic HL subtypes (92 mixed cellularity and 22 nodular sclerosis), while 8 patients had lymphocyte predominant HL.

PET/CT was reported as negative for bone/bone marrow involvement in 85 (69.7%) patients as no abnormal FDG uptake was noted; all of these patients also had negative BMB results and were regarded as true negatives. The remaining 37 (30.3%) patients showed abnormal FDG uptake, independent of the BMB results.

Group A

11/37 (29.7%) patients with diffuse bone/bone marrow FDG uptake were included in this group. No radiological correlate was identified on the CT component in any of these patients. Only 2 out of 11 patients showed BMB evidence of disease involvement (Figure 1). Follow-up PET/CT performed in all Group A patients showed normal FDG uptake in the bone/bone marrow.



Figure 1. Diffuse homogenous fludeoxyglucose (FDG) uptake in the axial and proximal appendicular skeletons in the maximal intensity projection image. FDG-avid disease is identified in bilateral cervical regions, the right axilla and the spleen. Bone marrow biopsy was negative in this patient.

Group B

6/37 (16.2%) patients showed unifocal FDG abnormality in the bone/bone marrow. Only one of these six (16.6%) patients had positive BMB. A follow-up PET/CT scan of this patient showed normal FDG uptake. Another patient from this group, who had a negative BMB at baseline, later developed FDG-avid disease progression. CT correlate of FDG-avid unifocal bony uptake was

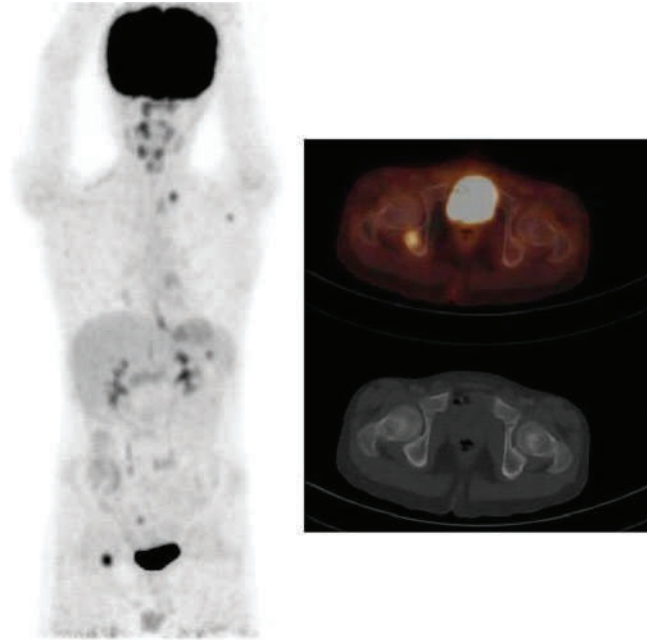


Figure 2. Fluorine-18-fludeoxyglucose (¹⁸F-FDG)-positron emission tomography/CT shows an FDG-avid focus in the right ischium in the maximal intensity projection and transaxial fusion images. The corresponding CT image shows no matching abnormality. FDG-avid disease identified in the left supraclavicular region, the left axilla and the spleen. Bone marrow biopsy was negative in this patient.

found in three patients. Figure 2 shows an example of discordance between CT and PET (right ischium) while Figure 3 shows a concordant lesion in thoracic vertebra.

Group C

20/37 (54.1%) patients showed multifocal FDG abnormalities. 8 (40.0%) out of these 20 had positive BMB. CT correlate of FDG-avid bone/bone marrow uptake was found in 12/20 (60.0%) patients (Figure 4). Follow-up PET/CT scans showed progressive disease in 2/20 patients, 1 of these had a positive BMB at baseline. The remaining 18 patients showed normal FDG uptake in the bone/bone marrow on follow-up PET/CT scanning.

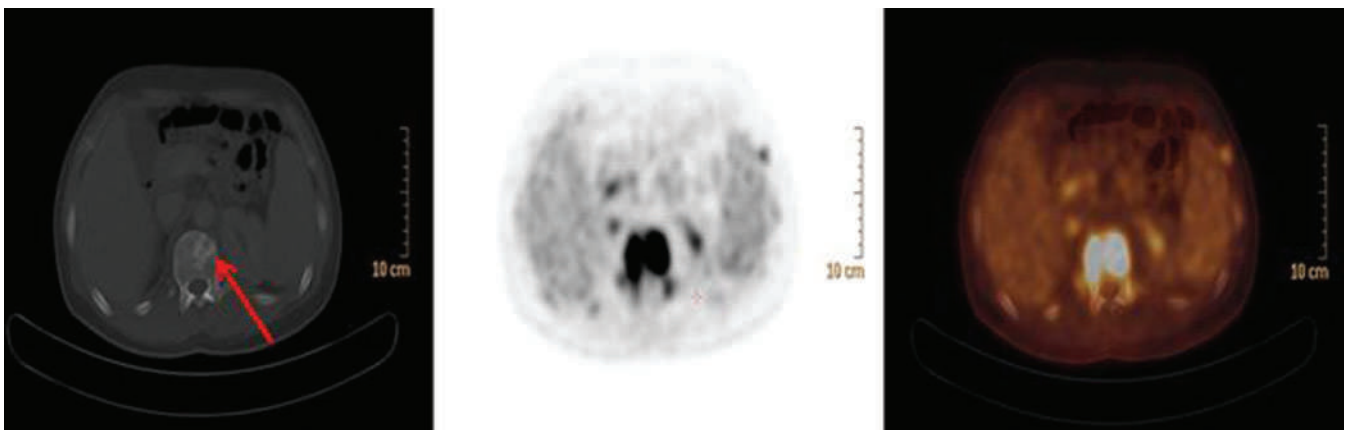


Figure 3. Sclerosed thoracic vertebra shows abnormal increased fludeoxyglucose uptake, consistent with lymphomatous involvement. Bone marrow biopsy was positive for lymphomatous involvement in this patient.

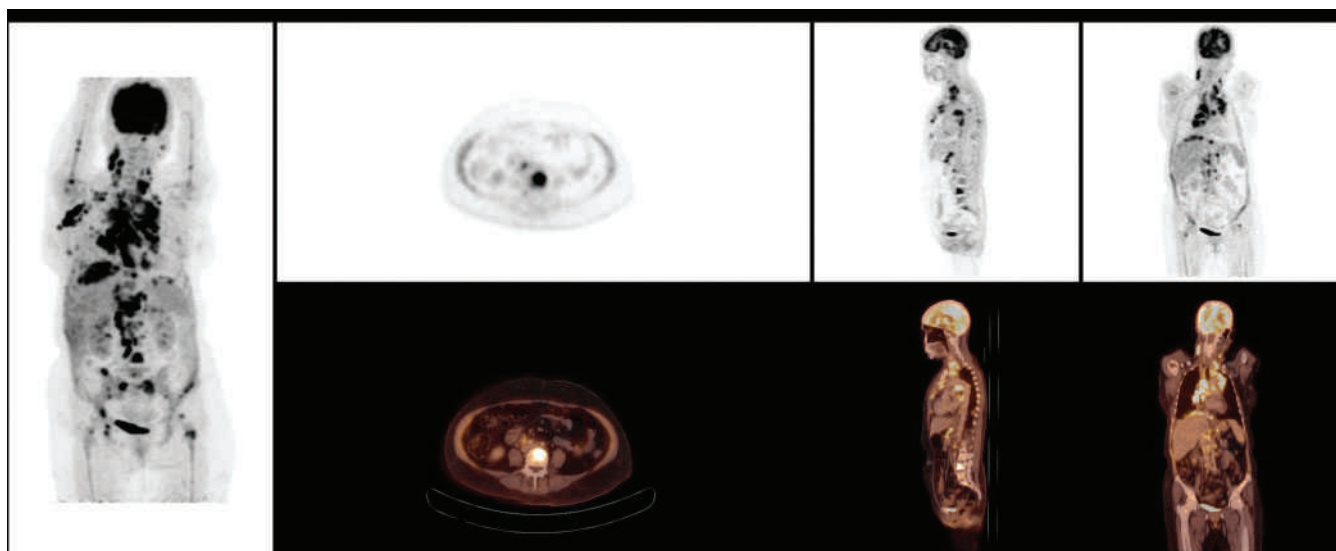


Figure 4. Fludeoxyglucose-positron emission tomography/CT shows multiple hypermetabolic bone lesions involving mainly the axial skeleton, the ribs, the proximal humeri and both femurs. Bone marrow biopsy was negative in this patient.

Table 1 gives an elaborate overview of the three groups. All the patients were clinically followed, the median follow-up was 7 months (range 3–12 months). The sensitivity of FDG-PET/CT was calculated to be 100%, the specificity was 76.57%, the negative predictive value was 76.57%, the positive predictive value was 29.72% and the diagnostic accuracy in detecting bone/bone marrow disease in HL patients was 78.62%.

The results of PET/CT *vs* BMB are summarised in a 2 × 2 table (Table 2). Table 3 gives detailed data of all 37 patients with positive bone/bone marrow findings on PET/CT, independent of BMB results.

Discussion

PET/CT is being exclusively used in lymphomas for baseline staging work-up and response evaluation. PET has a well-established role in the staging as well as restaging of patients with HL and aggressive NHL [16–18]. It has been found that FDG-PET exhibits higher sensitivity than CT in the evaluation of lymph node involvement as disease involvement is picked up in lymph nodes considered normal by CT criteria [3, 19, 20]. The prevalence of bone marrow involvement is <1% among patients with early-stage disease, and hence BMB is not routinely recommended in such patients in the absence of adverse prognostic factors [21–24]. The role of PET/CT in the evaluation of bone/bone marrow disease is still emerging as very few studies have

evaluated this [1, 2]. BMB is considered the gold standard for bone marrow involvement; however, the approach of unilateral *vs* bilateral BMB has limitations that need to be taken into account. Brunning et al have shown that in patients with a positive biopsy for HL, only one side is involved in about 40% of cases and a unilateral biopsy would miss 20% of cases compared with a bilateral biopsy [25]. In the present study, all the patients underwent bilateral BMB and 26 patients showed bone/bone marrow uptake on ¹⁸F-FDG-PET/CT scan with negative BMB. In every case, the iliac crest had no FDG-avid foci. There have been very few studies that examine the sensitivity of ¹⁸F-FDG-PET/CT for bone marrow involvement in a pure population of HL [9]. The meta-analysis by Pakos et al [1] summarising the results of 13 studies comprising a total of 587 patients showed that compared with BMB, the weighted sensitivity and specificity of FDG-PET were 51% and 91%, respectively. In the sub-group analysis, BMB showed better sensitivity in HL (76%) and in aggressive NHL, while FDG-PET gave false negative results in two-thirds of patients with bone marrow involvement in more indolent histological forms of NHL, leading to the conclusion that the role of PET/CT would be complementary [26–33]. Fuster et al [34] investigated the role of FDG-PET *vs* bone marrow disease in detecting bone marrow disease in patients with HL and NHL and found out that FDG-PET was more sensitive than BMB in HL and NHL with the exception of Grade 1 and 2 follicular lymphomas. Their findings were consistent with those of Pakos et al [1] regarding the overall accuracy and high sensitivity of PET compared with BMB. In our retrospective study, we found that the sensitivity of FDG-PET/CT is 100% in picking up bone/bone marrow disease while the specificity was found to be 76.57%. The negative predictive value was 76.57%, the positive predictive value was 29.72% and the diagnostic accuracy was 78.62%. The high sensitivity in this study was due to the fact that all the patients with a positive BMB had a positive PET/CT scan as well. It has been cited in literature that diffuse homogeneous FDG uptake in the

Table 1. Positron emission tomography (PET)/CT positive groups

Group	PET positive	BMB positive	CT correlate
A	11/37	2/11	0/11
B	6/37	1/6	3/6
C	20/37	8/20	12/20

BMB, bone marrow biopsy.

Table 2. Summary of bone marrow biopsy (BMB) and positron emission tomography (PET)/CT results in 122 patients with Hodgkin's lymphoma

PET/CT status	BMB status	
	BMB positive (n=11)	BMB negative (n=111)
Positive (n=37)	11 (TP)	26 (FP)
Negative (n=85)	0 (FN)	85 (TN)

FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

axial and appendicular skeletons often reflects benign enhancement owing to inflammation or cytokine release; however, bone marrow involvement cannot be entirely excluded [9]. In our study we found that only 2/11 patients with diffuse skeletal uptake had a positive BMB. All 11 patients showing diffuse FDG uptake showed normal bone/bone marrow uptake on the follow-up PET/CT scan. These findings highlight that homogeneous increased FDG uptake is a non-specific finding that could be due to resolution of cytokine-induced reactive marrow.

With negative BMB which is considered the gold standard, diffuse bone/bone marrow FDG uptake should not be interpreted as disease involvement. In the present study, we found that 85/122 patients had a negative PET/CT scan for bone/bone marrow involvement along with negative BMB, which suggests that routine BMB might be unnecessary when ^{18}F -FDG-PET/CT is negative. It has been reported that focal mono or polyostotic bone marrow disease may produce abnormal FDG-PET/CT scans, but if the disease does not extend to the dorsal iliac crests then

Table 3. Patients with positive bone/bone marrow findings on fluorine-18 (^{18}F)-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT

Number	Sex	Age (years)	H/P	Stage	BMB	FDG-avid foci	CT: bone findings ^a	Response PET	Follow-up (months)	Status
1	M	21	MC	IV-B/LS	+	Diffuse	+ve CT	CMR	6	CR
2	M	48	MC	IV-BLS	-	Multifocal	+ve CT	CMR	8	CR
3	M	59	MC	IV-BS	-	Multifocal	+ve CT	PD	3	Died
4	M	18	MC	III-S	-	Multifocal	+ve CT	CMR	10	CR
5	M	66	NS	II-A	-	Unifocal femur	+ve CT	CMR	4	CR
6	M	10	MC	IV-S	+	Multifocal	+ve CT	PD	9	Che
7	F	21	MC	IV-BLS	-	Unifocal D-12	-ve CT	CMR	12	CR
8	M	53	MC	II-B	-	Diffuse	-ve CT	CMR	7	CR
9	M	40	MC	IV-BSX	-	Multifocal	-ve CT	CMR	6	CR
10	F	28	NS	III-AS	-	Diffuse	-ve CT	CMR	10	CR
11	F	35	NS	III-BS	-	Unifocal L-1	-ve CT	CMR	8	CR
12	M	28	NS	III-B	-	Multifocal	+ve CT	CMR	6	CR
13	M	23	NS	III-B	-	Diffuse	-ve CT	CMR	6	CR
14	M	45	MC	III-AS	-	Unifocal	-ve CT	CMR	6	CR
15	M	40	MC	III-S	-	Diffuse	-ve CT	CMR	7	CR
16	M	43	MC	IV-BLS	-	Multifocal	-ve CT	CMR	6	PR
17	M	06	MC	III-S	-	Multifocal	-ve CT	CMR	9	CR
18	M	12	MC	IV-LS	+	Multifocal	+ve CT	CMR	8	CR
19	M	28	MC	II-B	-	Diffuse	-ve CT	CMR	10	CR
20	F	50	MC	IV-S	-	Multifocal	-ve CT	CMR	9	CR
21	M	15	MC	III-S	-	Diffuse	-ve CT	CMR	6	CR
22	M	21	LP	IV	+	Unifocal ischium	+ve CT	CMR	9	CR
23	F	24	NS	II-AX	-	Diffuse	-ve CT	CMR	6	CR
24	M	17	MC	II-A	-	Diffuse	-ve CT	CMR	10	CR
25	F	14	MC	IV-L	+	Multifocal	-ve CT	CMR	6	CR
26	F	17	MC	IV-L	-	Unifocal ilium	+ve CT	PD	6	Che
27	M	19	MC	IV-L	-	Multifocal	-ve CT	CMR	7	CR
28	M	22	NS	IV-BS	-	Multifocal	+ve CT	CMR	9	CR
29	M	23	NS	IV-LS	+	Multifocal	-ve CT	CMR	12	CR
30	M	11	MC	III-S	-	Multifocal	+ve CT	CMR	6	CR
31	F	24	NS	IV-BL	+	Multifocal	-ve CT	CMR	8	CR
32	F	29	MC	III-A	-	Multifocal	+ve CT	CMR	7	CR
33	M	49	NS	IV-BS	+	Multifocal	+ve CT	CMR	6	CR
34	M	30	MC	IV-BS	+	Multifocal	+ve CT	CMR	6	CR
35	M	26	NS	II-BX	-	Diffuse	+ve CT	CMR	6	CR
36	M	15	MC	IV-BS	+	Multifocal	+ve CT	CMR	8	CR
37	M	64	MC	IV-BS	+	Diffuse	-ve CT	CMR	12	CR

A, without B symptoms; B, B symptoms (fever, night sweats, weight loss); Che, second-line chemotherapy; CMR, complete metabolic response; CR, complete remission of Hodgkin's lymphoma; F, female; L, liver involvement; LP, lymphocyte predominant; M, male; MC, mixed cellularity; NS, nodular sclerosis; PD, progressive disease; PR, partial response; S, spleen involvement; X, bulky disease (>10 cm); -ve, negative CT of PET/CT; +ve, positive CT of PET/CT.

bone marrow sampling would be negative [2]. In our study, 26 patients with negative bilateral BMB had uni- or multifocal abnormal bone/bone marrow FDG uptake. When divided into subgroups, 12/20 patients with multifocal abnormal FDG uptake and 5/6 patients with unifocal abnormal FDG uptake had negative BMB. These findings suggest that the probability of bone marrow involvement is low with a solitary FDG abnormality, whereas multifocal FDG abnormalities have a greater likelihood of yielding a positive BMB. To establish this concept, FDG-avid sites, other than the conventional site of BMB (*i.e.* posterior iliac spine in the pelvis) should be biopsied and characterised histopathologically [27]. However, this was beyond the scope of our current study. The use of combined PET/CT is helpful for correlating bone FDG uptake with CT findings and improves specificity [35]. In our study, CT was able to identify corresponding bony abnormality in 17/37 (46%) patients with abnormal bone/bone marrow FDG uptake. Routine reading of CT has a low yield in depicting bone/bone marrow lesions. Schaefer et al examined a selected population of 50 lymphoma patients (22 HL) with FDG-avid bone lesions on PET/CT and found only 32 of the 193 lesions on CT without the PET information [24]. In our study, we decided to report bone and bone marrow lesions together and did not try to make a distinction between bony involvement and bone marrow involvement in every patient and for each lesion. Even with FDG-PET/CT, it would be difficult to make a clear distinction in every patient and each lesion as it is known that one type of invasion may lead to the other by local spread, making distinction less easy, and sometimes both types of lesion do coexist at the same time [9]. In the meta-analysis carried by Pakos et al [1], the number of biopsies directed at PET/CT-positive lesions is low. In our cohort, only 1 (17%) out of 6 patients with unifocal FDG abnormality had positive BMB in contrast to 8/12 (67%) patients with multifocal FDG abnormalities. This observation highlights the significance of the "pattern of FDG abnormality" in the likelihood of bone/bone marrow disease involvement [27]. However, as no FDG-avid bone lesion was biopsied, the specificity of these findings cannot be calculated. "Response to treatment", as seen on follow-up PET/CT, is also not a suitable criterion from which to draw a conclusion because, with the exception of 4/26, all patients with focal bone lesions and negative BMB had non-skeletal evidence of Stage IV disease and were treated accordingly. As BMB was the gold standard of staging and treatment in our cohort, the treatment strategy was not altered based on FDG uptake in the bone/bone marrow. MRI is a useful technique for assessing bone marrow [36]; however, so far the role of whole-body MRI is not well-established when compared with whole-body PET/CT.

Our study confirms the observation of many authors cited earlier that PET/CT has a high negative predictive value and is a useful tool in the evaluation of the bone/bone marrow along with BMB. Our findings support the emerging evidence that normal bone/bone marrow FDG uptake may eventually obviate the need for BMB. Additionally, the significance of multifocal abnormal bone/bone marrow FDG uptake, highlighted by cases of discordance between FDG uptake and BMB findings, warrants further investigation. Future studies might seek to confirm discordant findings with correlative imaging or targeted biopsy.

Conclusion

¹⁸F-FDG-PET/CT plays a complementary role with BMB in the staging of patients with HL. However, prospective studies are needed to further determine and validate the potential role of FDG-PET/CT in this arena.

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