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PET/CT and bone marrow biopsy (BMB) in evaluating bone marrow in lymphoma



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Abstract

Background: Bone marrow assessment is an important part in the Ann Arbor staging system in lymphoma. It is done routinely through posterior iliac crest bone marrow biopsy (BMB) which is an invasive technique with limited examination of one site. 18F-FDG PET/CT is now used for staging of lymphoma. The purpose of this study was to compare the sensitivity of PET/CT and BMB in detecting bone marrow infiltration (BMI) in lymphoma and determine agreement between both in assessing bone marrow and whether we can evaluate the bone marrow by PET/CT without the need of the routine BMB.

Results: PET/CT detected 24 (16.5%) cases with positive BMI that were missed by BMB. BMB detected only 2 (1.4%) cases that were missed by PET/CT. The PET/CT showed a higher sensitivity of 95.6% than BMB 46.7% in detecting BMI in lymphoma. We found a moderate agreement between PET/CT and BMB results in the whole cohort using Cohen's *k* computation. It was found that 0.47 with *p* value less than 0.0001.

Conclusions: PET/CT can detect more bone marrow involvement in lymphoma compared with BMB. It can replace the routine invasive BMB in many cases, especially those showing multifocal uptake in both Hodgkin and non-Hodgkin lymphoma. PET/CT can also help to guide the site of the biopsy in some cases. Iliac crest BMB is still needed in cases showing diffuse FDG uptake to differentiate malignant uptake from reactive hyperplasia, and in those with limited FDG avidity and in some cases with negative uptake to exclude early infiltration if management will differ.

Keywords: PET/CT, Bone marrow biopsy, Hodgkin lymphoma, Non-Hodgkin lymphoma, Bone marrow infiltration

Background

The assessment of bone marrow involvement is important in management of lymphoma patients, as it is a sign of advanced disease [1].

Bone marrow infiltration is detected in approximately 5 to 14% of HL and 25 to 40% of high-grade NHL [2, 3].

Iliac crest bone marrow biopsy (BMB) has been traditionally used for marrow assessment. It is obtained from the posterior portion of iliac crest, as it is the most easily accessible approach [4].

However, results of bone marrow aspiration biopsy (BMAB) are subjected to sampling error, especially if the disease is focal or present in sites outside the pelvis

biopsy site. In addition, BMB may be an unpleasant experience for the patient, associated with pain, anxiety, bleeding, and infection [5].

In view of these data, BMB cannot be considered as the gold standard for assessing bone marrow infiltration in patients with HD or NHL [6].

PET/CT has become more frequently utilized in detecting lymphomatous bone marrow involvement. In contrast to bone marrow biopsy, the noninvasive procedure enables the assessment of the entire marrow cavity while concurrently evaluating the extra-medullary disease [7].

PET/CT proved to be more sensitive compared to CT at baseline for extra-nodal site detection, which can be determined as an increased FDG-uptake in otherwise normally structured organs [8].

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Within the last few years, various studies have shown the superiority of PET/CT over BMB in the assessment of bone marrow infiltration in Hodgkin lymphoma (HL) in terms of diagnostic accuracy [9, 10]. A number of studies have discussed this issue in the context of non-Hodgkin lymphoma (NHL), particularly in diffuse large B cell lymphoma (DLBCL) with differing results [11–14].

Until this moment, there are no definite international guidelines for the indication of PET/CT and BMB [15].

The aim of this study was to assess the sensitivity of PET/CT and BMB in detecting bone marrow infiltration (BMI) in lymphoma and determine agreement between both in assessing bone marrow in lymphoma patients and whether we can evaluate the bone marrow by PET/CT without the need of the routine BMB.

The PET/CT imaging findings and BMB results of lymphoma patients were collected, analyzed, and correlated with each other, and with one or more of the following: follow up changes, local biopsy, targeted MRI, associated CT changes not explained by other benign findings.

Methods

This prospective study was done for 145 patients with a diagnosis of lymphoma and was approved by the Institutional review board. All subtypes of NHL and HL were included. Most of the patients with a new diagnosis of lymphoma underwent bone marrow biopsy as staging criteria. To be included in this study, patients must have had a PET/CT within 2 weeks of the bone marrow biopsy at either initial staging or relapse. Imaging may have been performed either before or after the biopsy, and must have been performed prior to the initiation of any form of therapy. Some of the relapsed cases underwent bone marrow biopsy and PET/CT imaging prior to a new line of therapy were included in this study.

Bone marrow biopsy

Preparation

The patient was placed on the procedure table (prone or lateral decubitus for posterior superior iliac crest and the iliac crest exposed). Any topical ointment was removed and skin cleaned. The iliac crest was palpated and the site of aspiration or biopsy determined. The puncture site was cleaned with antiseptic solution using a circular motion from the inner to the outer area; sterile drapes were placed over the biopsy site. Anesthetizing the marrow site with 1 to 2 mL of local anesthetic (1 to 2% lidocaine without adrenaline) was done.

Technique

All BMB were acquired one sided from the posterior iliac crest. The needle was held with the proximal end in the palm and the index finger against the shaft close to

the tip. With the stylet secured, the needle is presented through the skin pointing toward the anterior iliac spine. By gentle pressure, the needle was progressed with a slight turning movement until it feels anchored to the bone; the stylet was expelled, then using exchanging clockwise and counterclockwise. The needle was rotated with three turns to one side and afterward to one side without progressing; repeated once again, then the needle pulled back using a rotating movement. Utilizing a sterile gauze pad, manual pressure was applied to the site until the bleeding stops. The bone specimen was expelled from the biopsy needle by introducing a probe through the distal end. The specimen was dropped in formalin and labeled.

Interpretation of BMB

Trephine biopsy samples were then decalcified and stained with hematoxylin and eosin. They were interpreted by an expert hematopathologist for the presence of lymphomatous involvement, without knowledge of the imaging results.

FDG PET/CT acquisition

FDG-PET/CT was performed on an integrated PET/CT system with 16-slice CT (GE Discovery 710 PET/CT, AW 4.6, manufactured in Chicago, Illinois, USA). This dedicated system allowed the acquisition of co-registered CT and PET images in one session.

Patient preparation

All patients instructed that they should fast for at least 4–6 h before the study (to maintain low glucose and low insulin levels), but drink water to maintain good hydration.

The fasting blood glucose level was determined. The preferred fasting blood glucose is below 150 mg/dl.

CT imaging protocol

Whole-body CT study (neck, chest, abdomen, and pelvis), typical scanning parameters: 130 KV, 40 mAs, 2.5 mm slice thickness, pitch of 1.5, gantry rotation time of 0.8 second, and field of view of 50 cm.

PET imaging

PET performed on a dedicated PET scanner with approximately six to eight bed positions that planned in the three-dimensional acquisition mode for scanning from the head to the mid-thigh with 1–2 min acquisition at each bed in a cauda-cranial direction. Each bed position is 11.5 cm following acquisition of data at each bed position, there is approximately a 4-cm (25%) overlap between table stations. The maximum length of the patient that can be scanned with the current PET/CT scanner is 180 cm, then PET and CT images were

reviewed using a dedicated workstation and software (E.soft; GE medical solutions), which allowed three-dimensional displays (trans-axial, coronal, and sagittal) to be constructed using CT, PET, and PET/CT images and maximum intensity projection displays of the PET data. The CT data were used for attenuation correction for the PET data and for lung lesion screening as far as possible. For image construction, the images were constructed using the standard ordered subset expectation maximization (OSEM; two iterations, eight subsets) algorithm. The reconstructed PET image voxel size was 1.7 × 1.7 × 2.4 mm. Scanning started 45-60 min after intravenously administered 3 MBq/kg body weight of 18F-FDG, image acquisition was performed (the radiation effective dose from internally administered 18F-FDG for males was 0.002 mSv/MBq and for females was 0.025 mSv/MBq, and from the CT component was 6.8 mSv in males and 7.9 mSv in females).

Imaging interpretation

Qualitative (visual) assessment

PET/CT scans were interpreted as positive for BMI when the bone marrow 18F-FDG uptake was found superior to hepatic reference. The CT images were considered for corresponding CT changes.

Quantitative assessment

The maximum standardized uptake values (SUV max) were determined for the most active bony lesion after manual application of the volumetric regions of interest (ROI) on the trans-axial attenuation-corrected PET slices, around the areas showing the highest accumulation of 18F-FDG and away from any nearby overlapping activity. Another ROI was drawn over the normal liver where its SUVmax was considered a reference activity.

Data analysis

The different data used in this research methodology are demonstrated in Fig. 1.

Cases with concordant findings in both PET/CT and BMB (either positive or negative) were evaluated as true positive or true negative results. Non-concordance

between these two parameters was described as false negativity or false positivity as follow:

True positive PET/CT results

- Agreed PET/CT and BMB in the detection of BMI
- In patients with positive PET/CT and negative BMB results, we depended on one or more of the following:
 - > Regression or progression of lesions on follow-up PET/CT after chemotherapy
 - > Local biopsy or targeted MRI confirming PET/CT findings
 - > Presence of morphologic CT changes consistent with BMI not explained by other benign findings

False-positive PET/CT results

Patients with positive BMI in PET/CT study yet not meeting any of the previous criteria were considered as false positive.

True negative

If both BMB and PET/CT were negative for BMI.

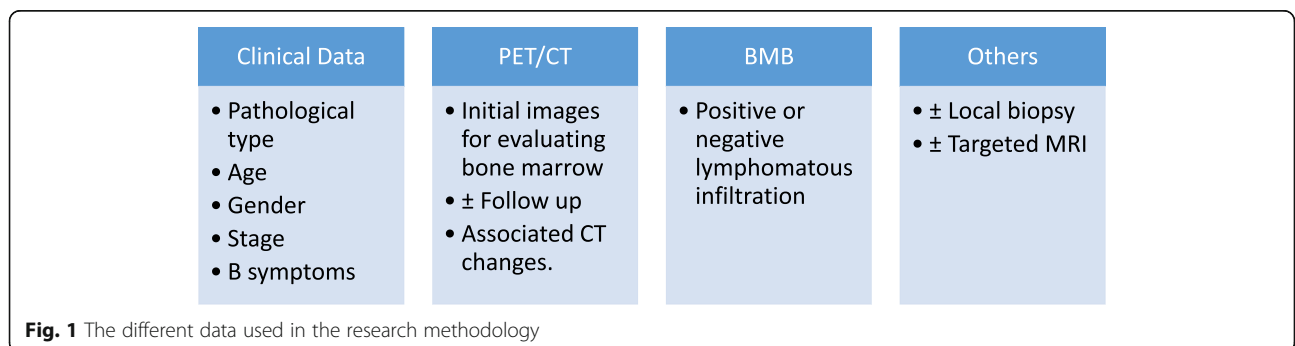
False negative

PET/CT was considered as false negative if BMB was positive and PET/CT was negative for BMI.

Statistical analysis

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPP), and accuracy with 95% confidence intervals for both PET/CT and BMB were calculated for the whole study, for Hodgkin and non-Hodgkin lymphoma then for the most common histological subtypes (nodular sclerosis, mixed cellularity, and DLBCL) in our study.

Agreement between 18F-FDG PET/CT and BMB findings was assessed using Cohen’s *k* computation for the whole study, for Hodgkin and non-Hodgkin lymphoma then for the most common histological subtypes in our study (nodular sclerosis, mixed cellularity, and DLBCL). SPSS version 23 was used in all the calculations.



Results

Patient characteristics

This prospective study was collected from a pathologically proven Hodgkin and non-Hodgkin lymphoma patients, 57 (39.3%) of them had NHL and 88 (60.7%) had HL.

The clinic-pathological characteristics are shown in Table 1. In the whole study, the frequency of B symptoms (temperature > 38 °C, night sweats, weight loss > 10% of normal body weight within a period of 6 months or less) was noted in 60 patients (41.4%). The different types of HL and NHL in the study are shown in Tables 2 and 3.

Impact of combined PET/CT and BMB findings on staging

Patients were staged according to Ann Arbor staging system. It is shown in Fig. 2.

Taking both techniques (PET/CT and BMB) into account in this study, there were 19 cases diagnosed as stage IV by both PET/CT and BMB by the presence of BMI. Thirteen cases were upstaged by PET/CT from stage III to stage IV, by detecting BMI not detected by BMB. Three cases were upstaged from stage I to stage IV by detecting BMI not detected by BMB. Eight cases were diagnosed as stage IV by PET/CT, by the presence of BMI and other extranodal lesions, with negative BMB results. Two cases were diagnosed as stage IV by BMB only, as no BMI was detected by PET/CT. Five cases were diagnosed as stage IV by PET/CT by the presence of other extranodal lesions, with no bone marrow infiltration.

Table 1 Clinico-pathological characteristics of the whole cohort ($n = 145$)

Clinical data	No.	(%)
Pathological types		
HL	88	60.7
NHL	57	39.3
Age		
Adult	98	67.5
Pediatric	47	32.4
Gender		
Male	100	69
Female	45	31
Stage		
I	20	14
II	44	30
III	31	21
IV	50	35
B symptoms		
Present	60	41.4
Absent	85	58.6

Table 2 Types of HD lymphoma in this study

HD	<i>n</i>	(%)
Total	88	60.7
Lymphocyte rich	3	2.1
Mixed cellularity	26	18
Nodular lymphocyte predominant	9	6.2
Nodular sclerosis	49	33.8
Lymphocyte depletion	1	0.7

Analysis of bone marrow involvement

Bone marrow infiltration was detected in 45 (31%) cases. Nineteen (13.10%) cases by both PET/CT and BMB, twenty-four (16.55%) cases by PET/CT only and two (1.3%) cases by BMB only. By dividing the positive cases according to their histological type, there were 17 HL positive cases and 28 NHL positive cases (Table 4).

Bone marrow infiltration detected by PET/CT was classified as either unifocal, bifocal, multifocal (more than two lesions), or diffuse infiltration (Table 5). However, within the diffuse involvement, eight (80%) cases showed positive infiltration in BMB and two (20%) cases were negative in BMB and therefore were considered as false positive in PET/CT (Fig. 3).

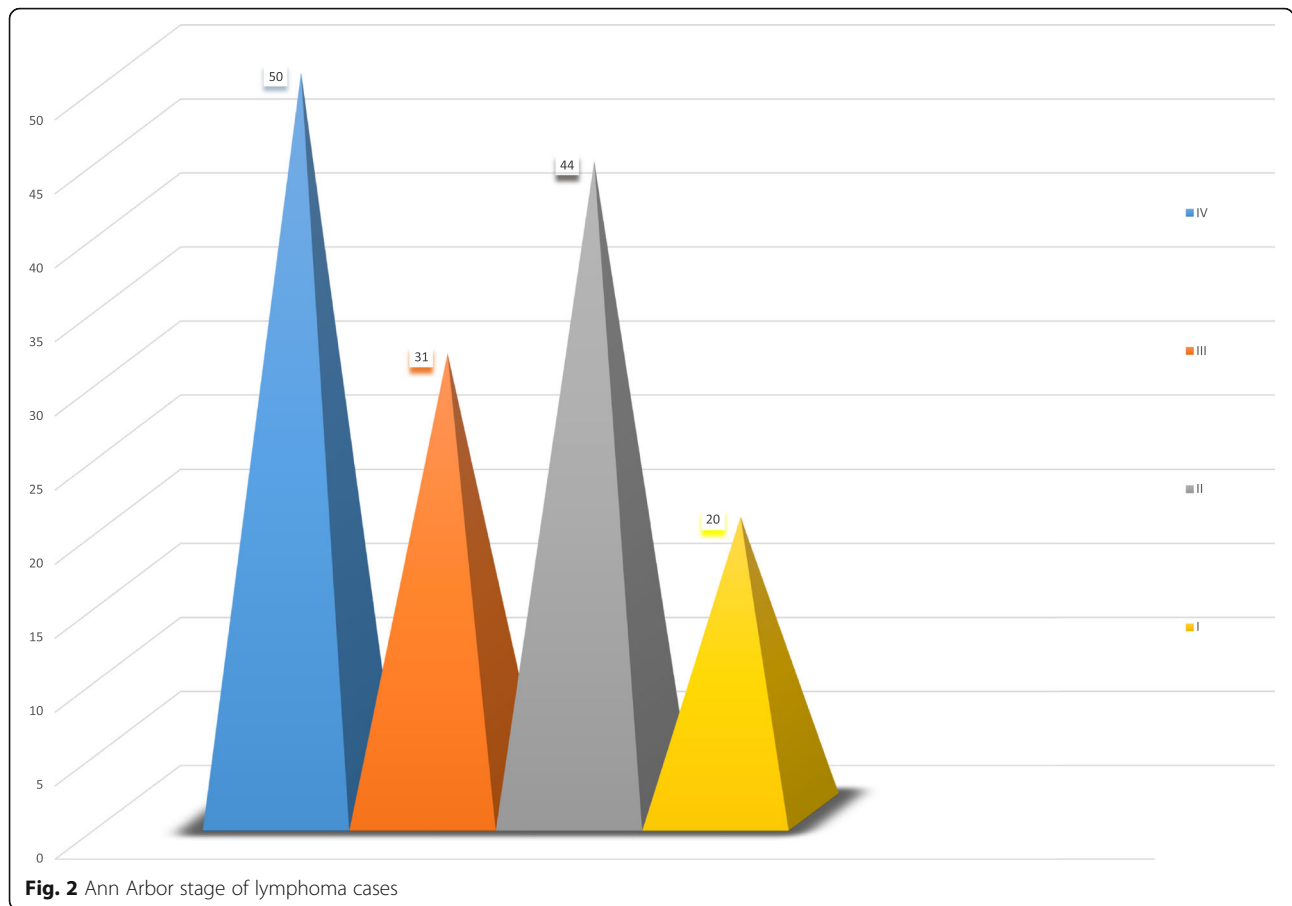
Semi-quantitative assessment of BMI in PET/CT by standardized uptake value (SUV) was found ranging from 3.5 to 33.7 with a mean of 11.66 ± 7.3 .

Within the 19 cases with positive BMB and PET/CT, 16 of them showed bilateral iliac crest involvement by PET/CT and three cases showed unilateral iliac crest involvement by PET/CT, and biopsy was taken from the affected side.

Within the 26 cases with positive PET/CT and negative BMB, two cases had HL and showed diffuse bone marrow uptake by PET/CT but BMB results were negative for infiltration, so they were considered as false positive. Four cases showed unilateral iliac crest involvement by PET/CT; however, BMB was taken from the contralateral side and 20 cases showed absent posterior iliac

Table 3 Types of NHL in this study

NHL	Frequency	Percent
Total	57	39.3
Burkitt	6	4.2
DLBC	27	18.6
Follicular	5	3.4
Large B cell	4	2.8
Lymphoplasmacytic lymphoma	1	0.7
MALT	2	1.4
Marginal zone b cell	2	1.4
Small lymphocytic lymphoma	1	0.7
T cell	8	5.5



crest involvement by PET/CT on either side, the uptake was present in other regions of the skeleton. The pattern of iliac crest involvement in positive PET/CT is illustrated in Fig. 4.

Diagnostic performance of PET/CT compared with BMB in the whole study

The PET/CT was reported as negative for BMI in 100 cases. Of these 100 patients, two patients were interpreted as positive for BMI because of positive findings on BMB. Therefore, the 18F-FDG PET/CT was considered as truly negative for 98 patients and falsely negative in 2 patients for BMI. The 18F-FDG PET/CT was

reported as positive for BMI in 45 patients, two of these patients showed diffuse FDG uptake in PET/CT; however, BMB results were negative for infiltration and revealed reactive hyperplasia, so they were considered as falsely positive in PET/CT and PET/CT was considered as truly positive for 43 cases. The BMB results were positive in 21 patients. PET/CT detected BMI in 24 (16.5%) additional cases, which were not detected by BMB, so they were considered as falsely negative in BMB. In these 24 cases, one or more of the following confirmed the PET/CT findings: subsequent follow up, corresponding CT changes that cannot be explained by other benign findings, targeted magnetic resonance

Table 4 Lymphoma cases with BMI

Positive cases of Hodgkin lymphoma	Positive cases of non-Hodgkin lymphoma
9 Nodular sclerosis	15 DLBCL
7 Mixed cellularity	5 Follicular
1 Lymphocyte depletion	2 T cell
	2 Large B cell
	1 MALT
	1 Diffuse lymphocytic lymphoma small cell type
	1 Small lymphocytic lymphoma
	1 Lymphoplasmacytic lymphoma
Total no. 17	Total no. 28

Table 5 Patterns of uptake in positive PET/CT results

Positive PET/CT	Positive BMB	Negative BMB	Total
Diffuse	8 (2 HL, 6 NHL)	2 (HL)	10
Multifocal	11 (3 HL, 8 NHL)	14 (7 HL, 7 NHL)	25
Bifocal	0	2(1 HL, 1 NHL)	2
Unifocal	0	8 (3 HL, 5 NHL)	8
Total no.	19	26	45

imaging, and/or local biopsy. This is illustrated in Table 6. Twelve cases showed regression of the disease in the form of complete response or partial response in either the interim or end of treatment follow-up, four cases showed progression of the disease in either the interim or end of treatment follow-up, local biopsy was done for seven cases, targeted MRI was done for 5 other cases, associated CT changes were present in 14 cases. Eight cases had other extranodal lesions which indicate advanced disease.

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy with 95% confidence interval of PET/CT and BMB are illustrated in Table 7.

Agreement between PET/CT and BMB in the whole study

In this study, there were 117 (80.6%) cases with concordant results in both PET/CT and BMB but discordant results were 28 (19.3%) cases (Table 8 and Fig. 5). Agreement between the PET/CT and BMB findings was

assessed using Cohen’s *k* computation and was found 0.47 with *p* value less than 0.0001, which indicate moderate agreement.

Diagnostic performance of PET/CT compared with BMB in HL

Regarding HL, there were 88 cases. The PET/CT was reported as negative for BMI in 70 cases, of these 70 patients, one patient was interpreted as positive for BMI because of positive findings on BMB. Therefore, the 18F-FDG PET/CT was considered as truly negative for 69 patients and falsely negative in one patient for BMI. The 18F-FDG PET/CT was reported as positive for BMI in 18 patients, two of these patients showed diffuse FDG uptake in PET/CT; however, BMB results revealed reactive hyperplasia, so they were considered as falsely positive in PET/CT and PET/CT was considered as truly positive for 16 cases. The BMB results were positive in 6 patients. PET/CT detected BMI in 11 (12.5%) additional cases, which were not detected by BMB, so they were considered as falsely negative in BMB while BMB detected only one (1.1%) additional case not detected by PET/CT.

Agreement between PET/CT and BMB in HL

In this study, there were 74 (84.1%) cases with concordant results in both PET/CT and BMB but discordant results were 14 (15.9%) cases in HL.

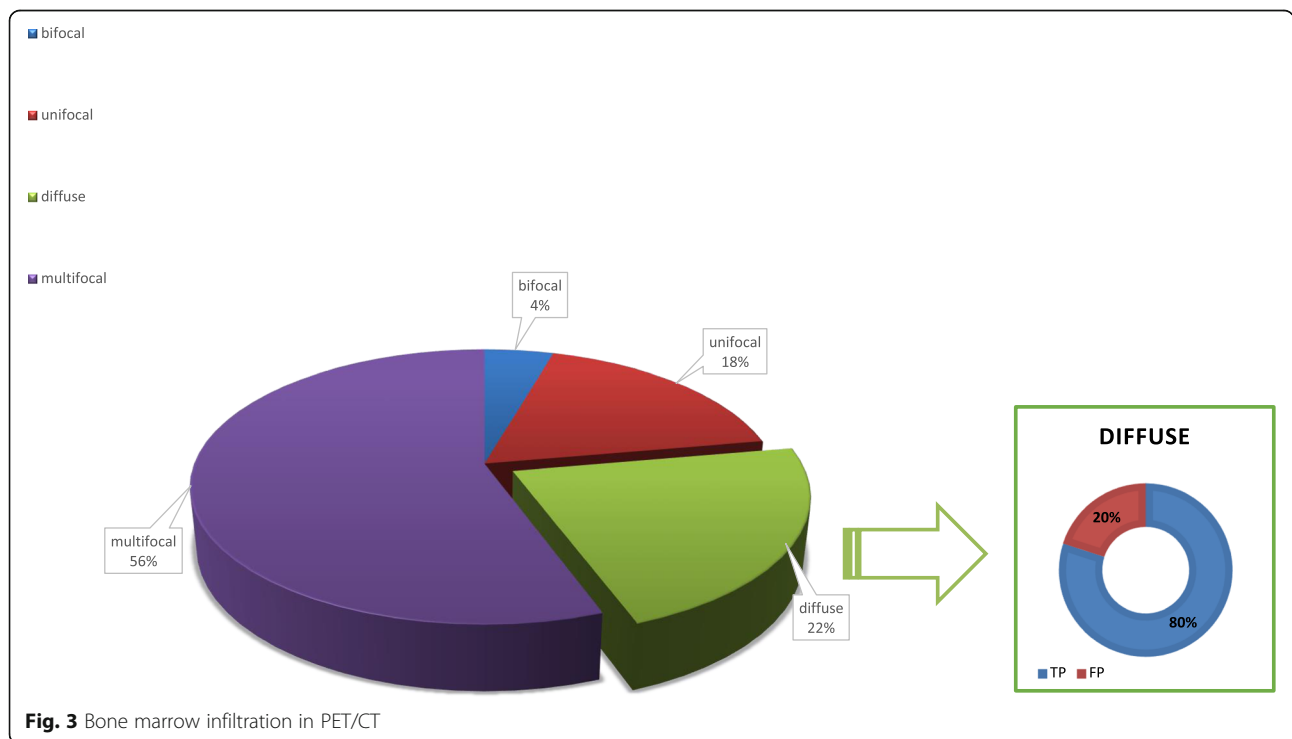


Fig. 3 Bone marrow infiltration in PET/CT

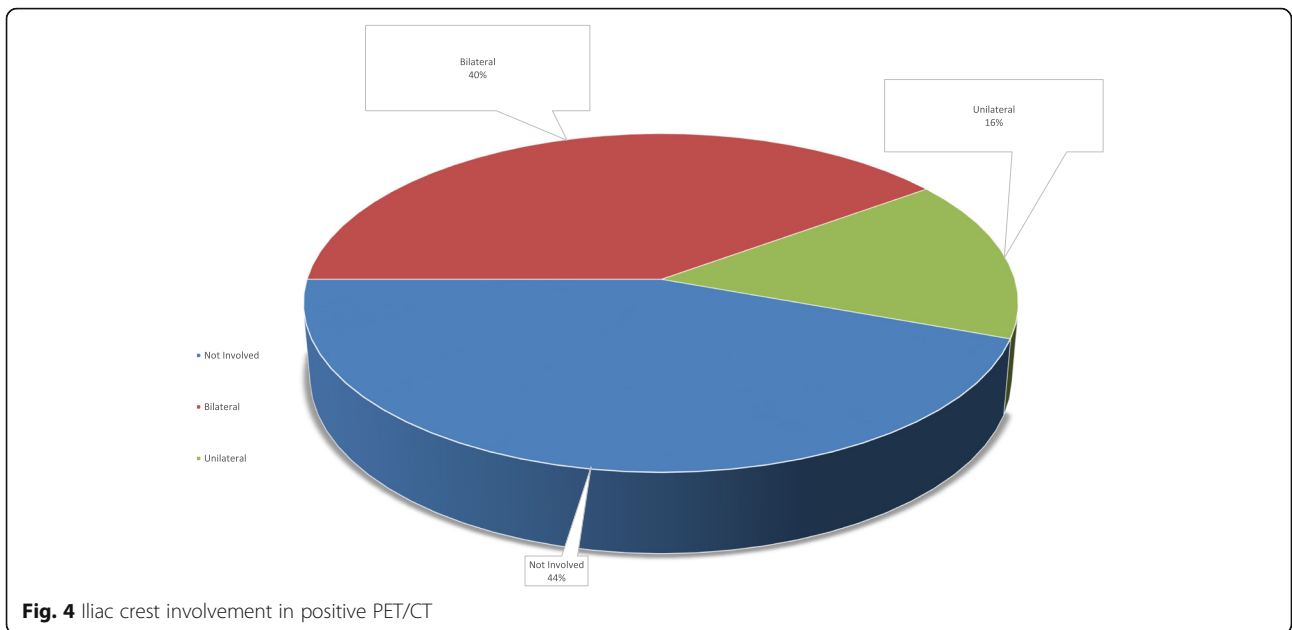


Table 6 Cases with true positive PET/CT and negative iliac crest BMB results

Patient	Type	MRI	Local biopsy	Follow-up interim and or EOT	CT changes	Other extranodal	Pattern	Iliac crest	B sym.
1	Mixed cellularity	ND	ND	CR (interim)	-	-	Multifocal	-	+
2	T cell	+	ND	SD (interim)	-	-	Multifocal	-	+
3	follicular	+	ND	CR (EOT)	+	-	Multifocal	-	-
4	Mixed cellularity	ND	ND	PD (interim)	+	+	Multifocal	Unilateral	+
5	Nodular sclerosis	ND	ND	PD (EOT)	+	-	Bifocal	-	+
6	Lymphocyte depletion	+	ND	CR (EOT)	+	-	Multifocal	Unilateral	+
7	Nodular sclerosis	ND	ND	PD (EOT)	+	-	Unifocal	-	-
8	DLBC	ND	ND	CR (interim)	+	-	Multifocal	-	-
9	DLBC	ND	+	CR (EOT)	+	-	Multifocal	Unilateral	+
10	Nodular sclerosis	ND	ND	PR (interim& EOT)	+	+	Unifocal	-	+
11	Large B cell	ND	+	lost	-	-	Multifocal	-	+
12	Nodular sclerosis	ND	+	CR (EOT)	+	+	Unifocal	-	+
13	follicular	ND	+	lost	+	-	Unifocal	-	-
14	DLBC	ND	ND	CR (interim-EOT)	-	-	Multifocal	Unilateral	-
15	DLBC	ND	+	lost	-	-	Unifocal	-	-
16	DLBC	ND	ND	Died after 4 month	+	+	Multifocal	-	+
17	Mixed cellularity	+	ND	lost	-	+	Multifocal	-	+
18	DLBC	ND	+	lost	+	-	Unifocal	-	-
19	follicular	+	ND	PR (EOT)	-	-	Unifocal	-	-
20	DLBC	ND	ND	CR (EOT)	-	-	Unifocal	-	-
21	MALT	ND	+	PR (interim)-CR (EOT)	-	-	Bifocal	-	+
22	Mixed cellularity	ND	ND	SD (interim)-PD (EOT)	+	+	Multifocal	-	+
23	Nodular sclerosis	ND	ND	PD (interim-EOT)	+	+	Multifocal	-	-
24	Nodular sclerosis	ND	ND	PR (interim)	-	+	Multifocal	-	+

Abbreviations: ND not done, CR complete response, SD stationary disease, PD progressive disease, PR partial response, EOT end of treatment

Table 7 Sensitivity, specificity, PPV, NPV, and accuracy of PET/CT and BMB

		Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI	Accuracy 95% CI
Whole study	PETCT	95.6 (89.3-100)	98 (95.2-100)	95.6 (89.3-100)	98 (95.2-100)	97.2 (94.5-99.9)
	BMB	46.7 (31.5-61.8)	100	100	80.6 (73.6-87.7)	83.4 (77.3-89.6)
HD	PETCT	94.1 (81.6-100)	97.2 (93.2-100)	88.9 (72.8-100)	98.6 (95.7-100)	96.6 (92.7-100)
	BMB	35.3 (10-60.6)	100	100	86.6 (79.1-94.1)	87.5 (80.5-94.5)
NHL	PETCT	96.4 (89.1-100)	100	100	96.7 (89.8-100)	98.2 (94.7-100)
	BMB	53.6 (33.9-73.3)	100	100	69.0 (54.5-83.6)	77.2 (66.0-88.4)
Nodular sclerosis	PETCT	88.9 (63.3-100)	95 (87.9-100)	80 (49.8-100)	97.4 (92.2-100)	93.9 (86.9-100)
	BMB	33.3 (0.0-71.8)	100	100	87.0 (76.8-97.1)	87.8 (78.2-97.3)
Mixed cellularity	PETCT	100	100	100	100	100
	BMB	42.9 (0.0-92.3)	100	100	82.6 (65.8-99.4)	84.6 (69.8-99.5)
DLBCL	PETCT	100	100	100	100	100
	BMB	53.3 (24.7-81.9)	100	100	63.2 (39.3-87.0)	74.1 (56.4-91.7)

Agreement between PET/CT and BMB in HL cases was calculated using Cohen’s kappa computation and was found 0.350 with *p* value less than 0.0001, which indicates fair agreement between both PET/CT and BMB (Table 9).

In our study, agreement between PET/CT and BMB was also done for nodular sclerosis and mixed cellularity subtypes (Tables 10 and 11). For nodular sclerosis type cases, it was found 0.236, with *p* value 0.040, which indicates fair agreement between both PET/CT and BMB results in nodular sclerosis cases.

For mixed cellularity type cases, it was found 0.523, with *p* value 0.002, which indicates moderate agreement between both PET/CT and BMB results in mixed cellularity cases.

Diagnostic performance of PET/CT compared with BMB in NHL

Regarding NHL, there were 57 cases. The PET/CT was reported as negative for BMI in 30 cases. Of these 30 patients, one patient was interpreted as positive for BMI because of positive findings on BMB. Therefore, the 18F-FDG PET/CT was considered as truly negative for 29 patients and falsely negative in one patient for BMI. The 18F-FDG PET/CT was reported as positive for BMI

in 27 patients but BMB results were positive in 15 patients. PET/CT detected BMI in 13 (22.8%) additional cases, which were not detected by BMB, so they were considered as falsely negative in BMB while BMB detected only one (1.8%) additional case not detected by PET/CT.

Agreement between PET/CT and BMB in NHL

In this study, there were 43 (75.4%) cases with concordant results in both PET/CT and BMB but discordant results were 14 (24.5%) cases in NHL.

Agreement between PET/CT and BMB in NHL cases was calculated using Cohen’s kappa computation and was found 0.496, with *p* value 0.040, which indicates moderate agreement between both PET/CT and BMB (Table 12).

In our study, agreement between PET/CT and BMB was also done for DLBCL (Table 13). It was found 0.236, with *p* value 0.040, which indicates fair agreement between both PET/CT and BMB results in DLBCL cases.

Discussion

Assessment of BMI in lymphoma plays an important role in staging as its presence upstage the disease to stage IV.

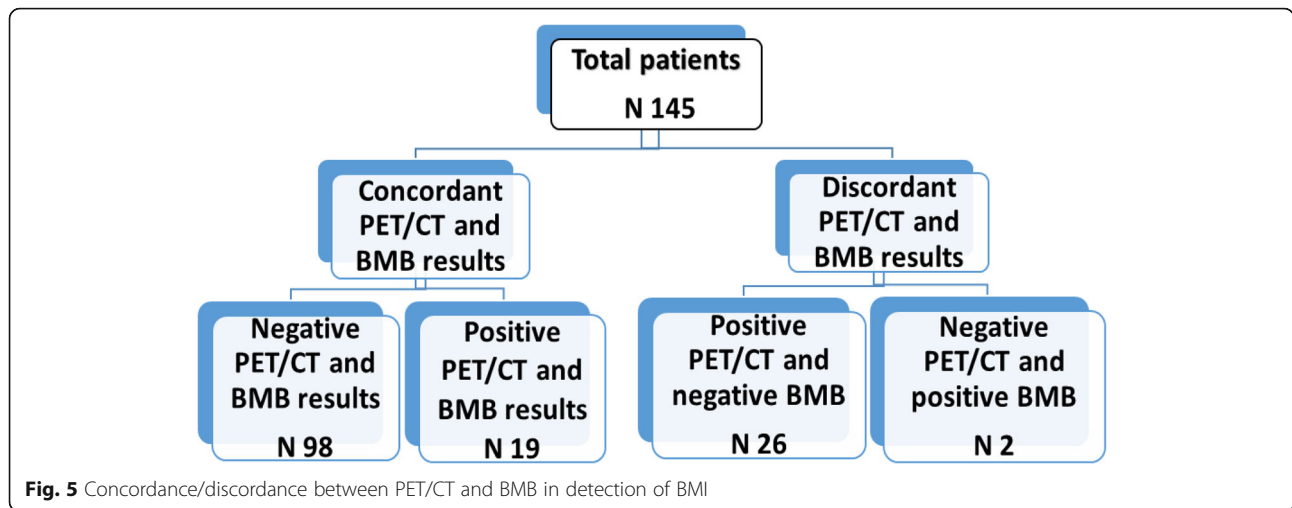
This study compares 18F-FDG PET/CT and BMB in evaluating bone marrow in 145 lymphoma patients, 88 cases were HL, and 57 cases were NHL.

BMB is an invasive technique that allows histologic examination for only a small bone marrow sample from the posterior iliac crest. This is in contrast to 18F-FDG PET/CT, which is a noninvasive technique that allows visualization of the entire bone marrow.

The blind BMB does not exclude BMI when infiltration is present in sites other than the posterior iliac crest [16].

Table 8 Agreement between PET/CT and BMB in the whole study

		BMB		Total	
		Negative	Positive		
PET/CT	Negative	Count	98	2	100
		% of total	67.6%	1.4%	69.0%
	Positive	Count	26	19	45
		% of total	17.9%	13.1%	31.0%
Total		Count	124	21	145
		% of total	85.5%	14.5%	100.0%



When BMB is only used as the reference standard, the sensitivity of PET/CT declines [5]. This is why we used follow-up findings, CT changes, and local biopsy and or MRI findings in patients with negative BMB results as an additional standard for these patients.

Diffuse uptake is considered a controversial area in most of the studies. Most studies found that diffuse uptake in bone marrow in HL cases is associated with a negative BMB, while in most DLCL cases with diffuse bone marrow uptake, positive BMB were found [11, 17]. Others found a diffuse pattern in HL with BMI in a small percentage of cases [18, 19]. In our study, we found 2 cases with HL having diffuse bone marrow uptake and positive BMB results (Fig. 6). This is consistent with the study done by Chen-Liang et al. [20], who also detected 2 cases of HL having diffuse uptake and positive BMB findings. In our study, all the six cases of NHL with diffuse uptake had positive BMB results (Fig. 7). This is consistent with the study done by Khan et al. [12], who found five cases with diffuse uptake, all had positive BMB results. However, in the study done by Cortés-Romera et al. [16], four cases only out of nine cases with diffuse uptake pattern had positive BMB results. Also, in the study done by Cerci et al. [21], 4 cases

only out of 18 cases with DLBCL had positive BMB results, so it was concluded that cases with diffuse FDG uptake should be biopsied to establish etiology.

PET/CT detected 24 (16.5%) cases with positive BMI that were missed by BMB. Local biopsy was done guided by PET/CT in seven cases (Fig. 8) and targeted MRI was done in five other patients, both confirmed bone marrow infiltration. Twenty cases had absent posterior iliac crest involvement in either side or four cases had unilateral posterior iliac crest involvement. It was interesting that we found the site of the biopsy taken was from the normal posterior iliac crest (Fig. 9).

PET/CT can detect infiltration in any region of the skeleton compared to the confined site of the posterior iliac crest by BMB. It can also guide the site of the biopsy in clinically warranted cases when management will differ.

The PET/CT showed a higher sensitivity of 95.6% (95% CI, 89.3-100%) than BMB 46.7% (95% CI, 31.5-61.8%) in detecting BMI and good specificity of 98% (95% CI, 95.2-100%) compared to that BMB 100%. The accuracy of PET/CT was 97.2% (95% CI, 94.5-99.9%) while that of BMB was 83.4% (95% CI, 77.3-89.6%).

Table 9 Agreement between PET/CT and BMB in HD lymphoma cases

		BMB		Total	
		Negative	Positive		
PET/CT	Negative	Count	69	70	
		% of total	78.4%	1.1%	79.5%
	Positive	Count	13	18	
		% of total	14.8%	5.7%	20.5%
Total		Count	82	88	
		% of total	93.2%	6.8%	100.0%

Table 10 Agreement between PET/CT and BMB in nodular sclerosis cases

		BMB		Total	
		Negative	Positive		
PET/CT	Negative	Count	38	39	
		% of total	77.6%	2.0%	79.6%
	Positive	Count	8	10	
		% of total	16.3%	4.1%	20.4%
Total		Count	46	49	
		% of total	93.9%	6.1%	100.0%

Table 11 Agreement between PET/CT and BMB in mixed cellularity cases

			BMB		Total
			Negative	Positive	
PET/CT	Negative	Count	19	0	19
		% of total	73.1%	0.0%	73.1%
	Positive	Count	4	3	7
		% of total	15.4%	11.5%	26.9%
Total	Count	23	3	26	
		% of total	88.5%	11.5%	100.0%

This is consistent with the meta-analysis done by Wu et al. [22], who included 32 studies and found that PET/CT sensitivity and specificity were 91.6% (95% CI, 85.1, 95.9) and 90.3% (95% CI, 85.9, 93.7) respectively. PET/CT was found highly sensitive and specific modality in detecting bone marrow involvement in lymphoma.

This is against the meta-analysis study done by Pakos et al. [23], who included 587 patients, 18F-FDG PET/CT results did not show excellent concordance with that of BMB for detecting bone marrow infiltration. The sensitivity and specificity of PET/CT were found 51% (95% CI, 38–64%) and 91% (95% CI, 85–95%) respectively. BMB was only used as the gold standard in this meta-analysis, so 18F-FDG PET/CT was not recommended for replacing the routine BMB in this meta-analysis.

In our study, we found moderate agreement between PET/CT and BMB results in assessment of bone marrow in the whole study using Cohen’s *k* computation. It was found 0.47 with *p* value less than 0.0001. As 117 (80.7%) patients showed concordant results between PET/CT and BMB and 28 (19.3%) showed discordant result. This is consistent with the previous studies in which the discordant rate was found ranged from 13.3 to 22.9% [1, 14, 16, 24–27].

In our study, there were 88 patients with Hodgkin lymphoma, 17 (19.3%) of them had BMI. BMB detected only 1 (1.1%) case that was not detected by PET/CT, but PET/CT detected 11 (12.5%) additional cases with bone marrow infiltration presented outside

Table 12 Agreement between PET/CT and BMB in NHL cases

			BMB		Total
			Negative	Positive	
PET/CT	Negative	Count	29	1	30
		% of total	50.9%	1.8%	52.6%
	Positive	Count	13	14	27
		% of total	22.8%	24.6%	47.4%
Total	Count	42	15	57	
		% of total	73.7%	26.3%	100.0%

Table 13 Agreement between PET/CT and BMB in DLBCL cases

			BMB		Total
			Negative	Positive	
PET/CT	Negative	Count	12	0	12
		% of total	44.4%	0.0%	44.4%
	Positive	Count	7	8	15
		% of total	25.9%	29.6%	55.6%
Total	Count	19	8	27	
		% of total	70.4%	29.6%	100.0%

the site of the biopsy and therefore were missed by the BMB.

Our results showed a higher sensitivity of PET/CT 94.1% (95% CI, 81.6-100) in detection of BMI compared to BMB 35.3% (95% CI, 10-60.6). This is consistent with the study done by Cistaro et al. [28], the sensitivity of 18F-FDG PET/CT was found 96% (95% CI, 89-100%) while that of BMB was found 38% (95% CI, 20-57%). This is also consistent with the study done by Büyüksimşek et al. [29], who included 110 patients with HL and found PET/CT sensitivity was 91.3% (95% CI, 71.96-98.93) compared to that of BMB which was 56.52% (95% CI, 34.49-76.81).

In the study done by Agrawal et al. [30], who included 38 patients with HL, all were pediatrics, PET/CT detected BMI in 3 (8%) additional patients not detected by BMB. The calculated sensitivity, specificity, PPV, and NPV of FDG PET/CT for detection of BMI were 87.5%, 100%, 100%, and 96% respectively and the sensitivity, specificity, PPV, and NPV of BMB for BMI were 62.5%, 100%, 100%, and 88.4% respectively.

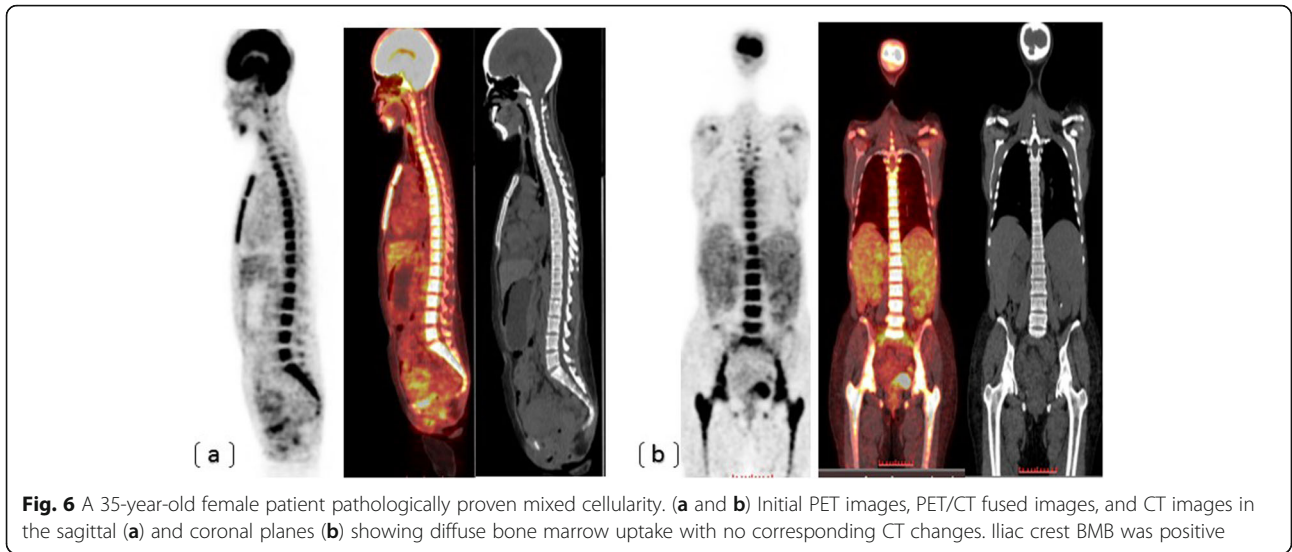
In the study done by Cheng et al. [1], who included 31 cases of pediatric HL. PET/CT detected BMI in 2 (6.5%) additional patients not detected by BMB.

Purz et al. [31] compared the difference between BMB and F-18 FDG PET/CT in the detection of BMI in 175 HL pediatric patients all with stage more than IIA. They found that F-18 FDG PET/CT detected 22% of positive cases not detected by BMB and concluded that F-18 FDG PET may replace BMB in routine staging procedure.

This is also consistent with previous studies, which recommended preclusion of the routine use of BMB for staging in these patients [8, 17, 32, 33].

In our study, we found a fair agreement between PET/CT and BMB in HL cases by using Cohen’s *k*, it was found 0.350 with *p* value less than 0.0001. This is consistent with the study done by Cistaro et al. [28], who found also fair agreement between PET/CT and BMB findings as Cohen’s *k* was found 0.398 with *p* value less than 0.001.

In our study, there were 57 patients with non-Hodgkin lymphoma, 28 (49%) of them had BMI. Only one (1.8%)



case was positive by BMB and was not detected by PET/CT but pathology of this patient was lymphoplasmacytic lymphoma, which is known to have limited and variable FDG avidity (Fig. 10). PET/CT detected 13 (22.8%) additional cases with positive BMI and negative BMB results. The sum of the concordant result of PET/CT and BMB was 43 (75.4%), and the discordant results were 14 (24.5%). This is consistent with the study done by Vishnu et al. [5], who included 99 cases of DLBCL, there were 38% of cases that had BMI. PET/CT was positive for BMI in 24 cases but BMB was positive in 14 cases. Two (2%) cases only were detected by BMB and were not detected by PET/CT while 12 (12%) patients were detected by PET/CT and were negative by BMB. The concordant results between PET/CT and BMB were 85 (86%). The discordant results between PET/CT and BMB were 14 (14%) patients.

Our results showed a higher sensitivity of PET/CT in NHL cases 96.4% (95% CI, 89.1-100) compared to BMB 53.6 (95% CI, 33.9-73.3) and perfect specificity 100% in

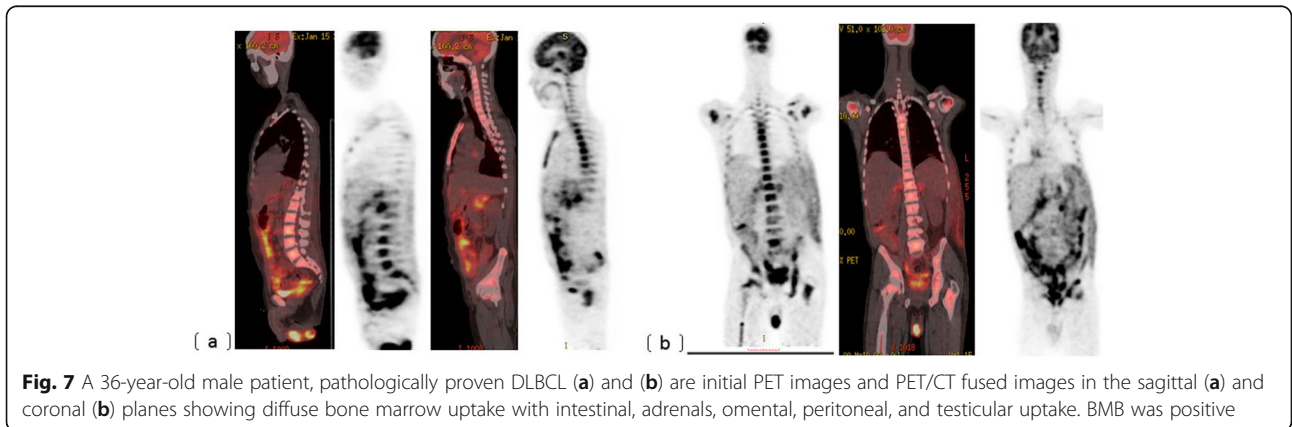
both. The accuracy of PET/CT was 98.2% (95% CI, 94.7-100) while that of BMB was 77.2% (95% CI, 66-88.4).

This is consistent with the study made by Badr et al. [34], who included 27 patients with NHL and found the sensitivity of PET/CT was 100% while that of BMB was 42.9% and the specificity was 100% in both.

In the meta-analysis done by Adams et al. [11], who included seven studies assessing PET/CT for detection of BMI in DLBCL. They found that the PET/CT sensitivity was 78.4% (95% CI, 69.9-85.5%) and specificity was 99.7% (95% CI, 98.3-100%) when both focal and diffuse uptake were considered positive for bone marrow involvement as in our study.

This is against the study done by Adams and Kwee [35], who compared PET/CT and BMB of the posterior iliac crest and showed that PET/CT may be negative in the posterior iliac crest in up to 80% of cases with a positive BMB.

The role of both PET/CT and BMB in the assessment of BMI is complementary [25]. PET/CT can be used to



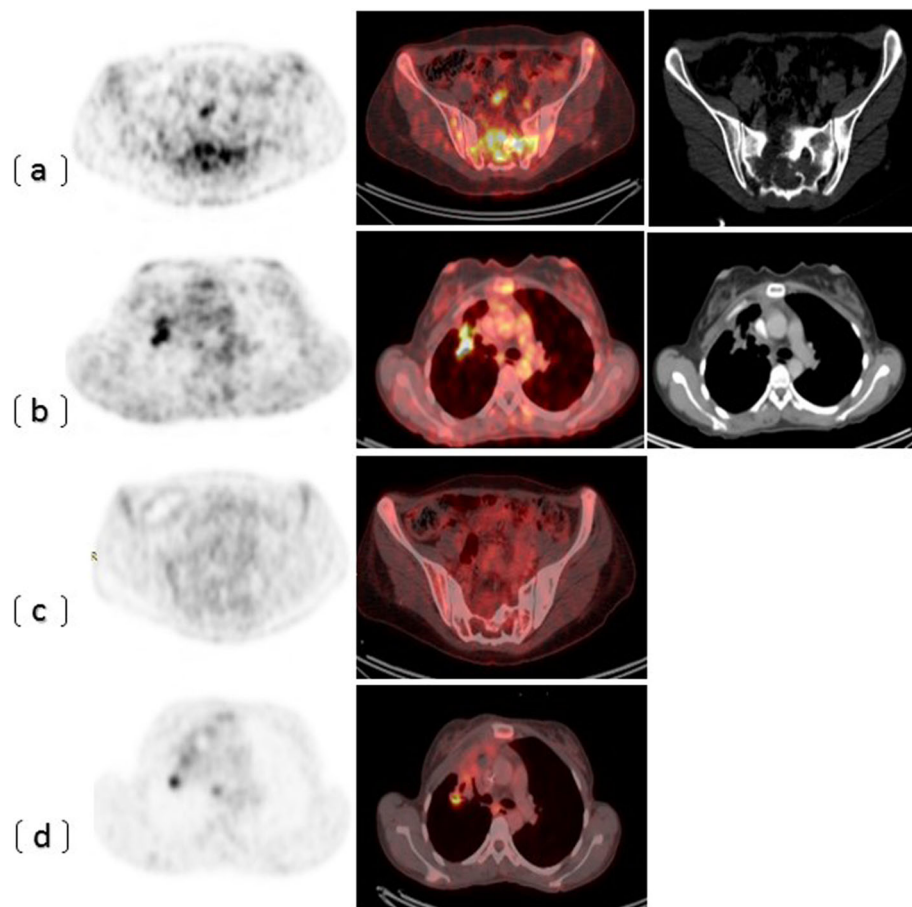


Fig. 8 A 27-year-old female patient with pathologically proven nodular sclerosis. Iliac crest BMB was negative. **(a and b)** Initial PET images, PET/CT fused images, and CT images in the axial plane showing FDG uptake at the sacrum with soft tissue component and associated CT infiltrative lytic lesion **(a)**. There is also pulmonary FDG uptake **(b)**. Local biopsy from the sacrum was taken and confirmed BMI. **(c and d)** The post-treatment images showing complete metabolic resolution of the sacral lesion and the pulmonary nodule showed partial response with decrease in its activity

guide the site of biopsy by the FDG uptake when lesions are present outside the routine iliac bone marrow sampling sites. Some studies suggest that routine BMB is still necessary in cases with a negative PET/CT scan result as PET/CT may miss early limited infiltration of the bone marrow, which can be detected by the BMB [16].

Limitations

The number of patients in our study was relatively small. We included a heterogeneous group of patients of HL and NHL. This has made our results for the separate calculation of the sensitivity, specificity, accuracy of PET/CT, and BMB in nodular sclerosis, mixed cellularity and DLBC types not accurate and should be evaluated with a larger sample size.

Most of the previous studies were done retrospectively, so local biopsy or targeted MRI were not done. From the strengths in our study is that it was done prospectively so guided local biopsy or targeted MR imaging

were done in 12 (50%) patients with positive PET/CT and negative iliac crest BMB results. This helped to confirm the positive uptake detected by PET/CT. However, this was not done for all patients, as it was not possible to take another biopsy from another site in all patients, as it is an invasive technique accompanied by pain and anxiety. Also, not all cases could undergo further targeted MRI, as it should be recommended by the multidisciplinary team for special cases, who will really benefit from it and not to take the place of other patients with different diseases who are really in need for it.

Conclusions

PET/CT showed greater sensitivity than posterior iliac crest BMB in both HL and NHL for evaluating BMI and can detect BMI that is missed by BMB, as uptake may be present in other sites of the skeleton away from the

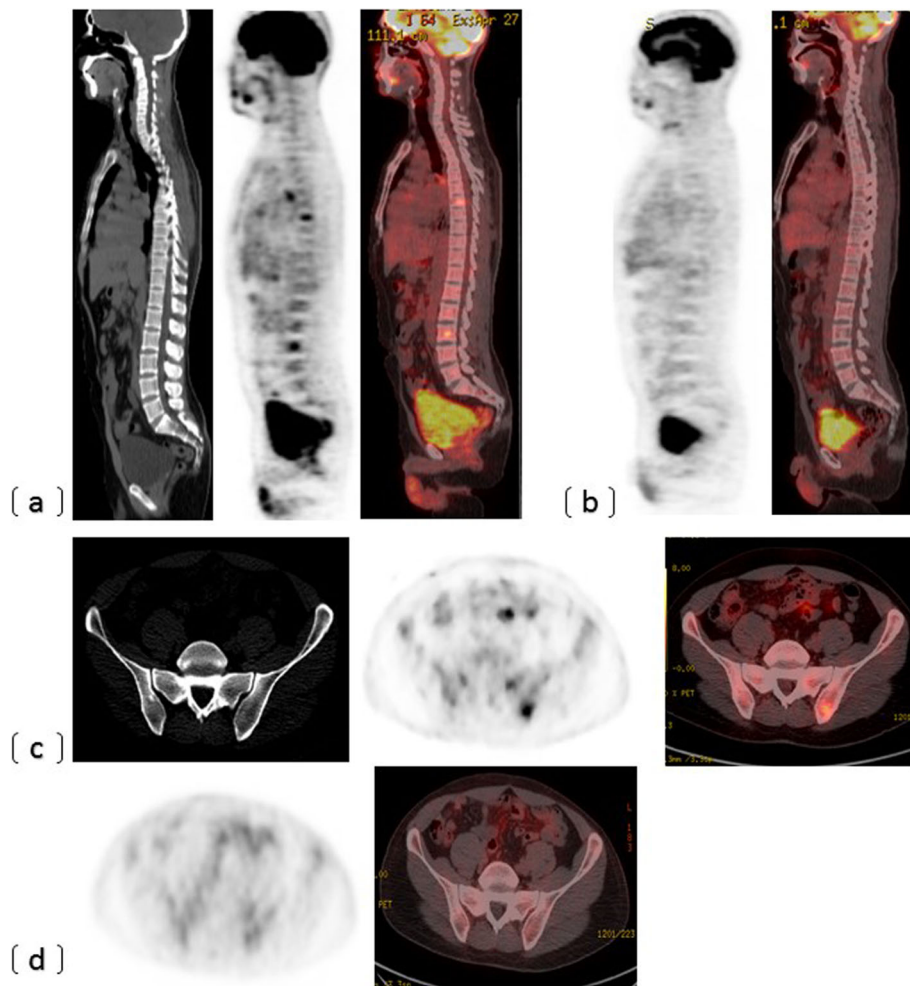


Fig. 9 A 37-year-old male patient with pathologically proven DLBCL (a) are initial CT image, PET image, and PET/CT fused images in the sagittal plane showing FGD uptake at the dorsal and lumbar spine with no corresponding CT changes. (c) Initial CT image, PET image, and PET/CT fused image in the axial planes showing uptake in left posterior iliac crest with no corresponding CT changes. (b and d) The post-treatment images showing complete resolution of the previous lesions. BMB was taken from the right posterior iliac crest, which is not involved and was negative

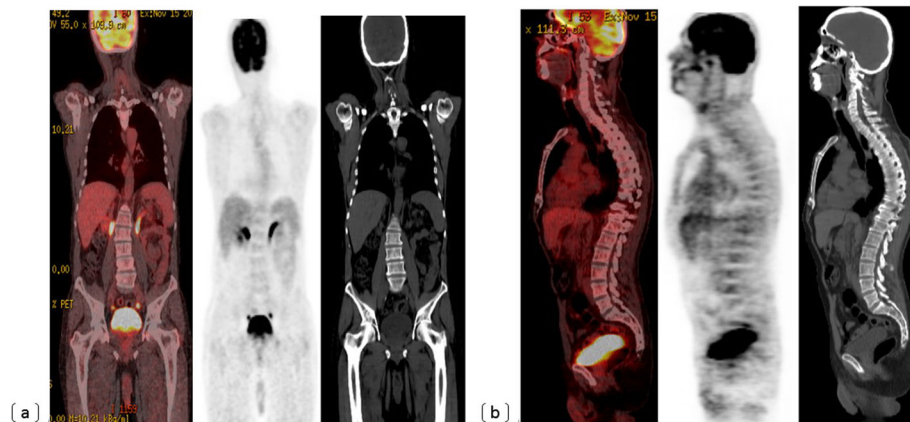


Fig. 10 A 56-year-old male patient pathologically proven lymphoplasmacytic lymphoma (a) and (b) are initial PET/CT fused images, PET images, and CT images in the coronal (a) and sagittal (b) planes showing no metabolically active lesions. BMB was positive for infiltration

iliac crest biopsy site. PET/CT also showed moderate agreement with BMB results.

PET/CT should precede the BMB as it can replace BMB in many cases, especially those showing multifocal uptake in both HL and NHL. PET/CT can help to guide the site of the biopsy in suspected infiltration, especially in unifocal FDG uptake. Iliac crest BMB is still needed in cases with diffuse FDG uptake to differentiate uptake from reactive hyperplasia, in certain types of lymphoma with known limited FDG avidity, and in some cases with negative uptake to exclude early infiltration if management will differ. The main limitation of this study is the small sample size, for which we recommend more studies with larger sample size.

Abbreviations

PET: Positron emission tomography; FDG: Fluorodeoxyglucose; CT: Computed tomography; MRI: Magnetic resonance imaging; BMB: Bone marrow biopsy; BML: Bone marrow infiltration; HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma; DLBCL: Diffuse large B cell lymphoma; MALT: Mucosa-associated lymphoid tissue; PPV: Positive predictive value; NPV: Negative predictive value; ROI: Region of interest; SUV: Standardized uptake value

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Authors' contributions

YEW, MSS, ASO, and HFE selected the patients and reviewed the images of them. YEW analyzed and interpreted the patient data and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

National Cancer Institute, Cairo University Institutional Review Board approval was taken before conducting this prospective study; March 2018—IRB number: IRB00004025. Approval number: 201617078.3
Written consent was obtained from patients or their authorized representatives.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old, deceased, or unconscious when consent for publication was requested, written informed consent for the publication of this data was given by their parent or legal guardian.

Competing interests

The authors declare that they have no competing interests.

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