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Utility of ^{18}F-fluorodeoxyglucose PET-CT scan in detecting bone marrow involvement in lymphoma

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***Background & objectives*: Evaluation of bone marrow infiltration in lymphoma is usually done by bone marrow biopsy (BMB). This study analyzed the utility of ^{18}F-fluorodeoxyglucose positron emission tomography/computerized tomography (^{18}F-FDG PET/CT) to detect bone marrow involvement (BMI) compared to BMB.**

***Methods*: Treatment-naïve lymphoma patients underwent both ^{18}F-FDG PET/CT scan and BMB before treatment initiation. BMI detected on PET/CT was compared with BMB.**

***Results*: The study population consisted of 80 patients and comprised 37 Hodgkin's lymphoma (HL) patients, 30 aggressive non-HL (NHL) and 13 indolent NHL patients. The majority of the aggressive NHLs were diffuse large B-cell lymphoma (20/30) and major indolent lymphoma was follicular lymphoma (5/13). When compared to BMB, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of focal (±diffuse) marrow FDG uptake on ^{18}F-FDG PET/CT were 100, 61.3, 33.3 and 100 per cent, respectively, for HL; 100, 65.4, 30.8 and 100 per cent, respectively, for aggressive NHL and 75, 80, 85.7 and 66.7 per cent, respectively, for indolent NHL. When comparing marrow involvement on ^{18}F-FDG PET/CT to baseline BMB and/or resolution of bone marrow FDG uptake at interim/end-of-treatment ^{18}F-FDG PET/CT, the sensitivity, specificity, PPV and NPV were 100 per cent each for HL and aggressive NHL and 77.3, 100, 100 and 66.7 per cent, respectively, for indolent NHL.**

***Interpretation & conclusions*: ^{18}F-FDG PET/CT has a good sensitivity and NPV for detecting BMI in HL and aggressive lymphoma. The low specificity and PPV improved if marrow uptake pattern on interim or end-of-treatment ^{18}F-FDG PET/CT scan was analyzed. In patients with HL who are staged with ^{18}F-FDG PET/CT at baseline and followed up with an interim/end-of-treatment PET/CT, baseline BMB may be avoided. For all other lymphoma subtypes, BMB may be essential if there is no marrow FDG uptake on PET/CT scan performed at baseline.**

Key words Bone marrow involvement - ^{18}F-FDG PET/CT - lymphoma - trephine biopsy

Lymphoma is diagnosed by cell morphology and immunophenotyping of the primarily involved tissue. Before starting treatment, the patient is staged with the Ann Arbor staging system for prognostication and

treatment planning[1]. Pre-treatment staging is done by contrast-enhanced computerized tomography (CECT) of the neck, thorax, abdomen, pelvis or combined positron emission tomography/CT (PET/CT) of the whole body. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT is the preferred staging modality for FDG-avid lymphoma[2]. Assessment of bone marrow involvement (BMI) is an essential component in staging which is done with a bone marrow biopsy (BMB) and this is invariably performed, even when the likelihood of involvement is low. BMB is an invasive, painful and time-consuming procedure with a relatively long turnaround time. Considering the high sensitivity of ^{18}F-FDG PET/CT in the detection of marrow involvement, the absolute indication of BMB in some of the histological subtypes has been questioned[3].

In Hodgkin lymphoma (HL), given the high sensitivity of ^{18}F-FDG PET/CT in detecting marrow infiltration, BMB is avoided for patients who are staged with ^{18}F-FDG PET/CT[4]. In diffuse large B-cell lymphoma (DLBCL), PET/CT is more sensitive than BMB, but it may miss low-volume (10 to 20% of the marrow) or diffuse involvement of the marrow and involvement of the marrow by a discordant low-grade lymphoma if present. Thus, marrow involvement on ^{18}F-FDG PET/CT scan is usually sufficient to designate advanced-stage disease, but if the scan is negative, a BMB is indicated[3,5,6]. Data are inconsistent concerning other aggressive non-HLs (NHLs) and indolent NHL where the utility of ^{18}F-FDG PET/CT in detecting BM involvement is not clear. This study was planned to assess the utility of ^{18}F-FDG PET/CT in detecting bone marrow involvement in all lymphoma subtypes.

Material & Methods

A prospective study was conducted in the department of Hematology, Nil Ratan Sircar Medical College and Hospital, Kolkata, from March 2017 to September 2018. Institutional ethical clearance was obtained before the initiation of the study. Written informed consent was obtained from each patient and/or their legal guardians at the time of enrolment into the study. Newly diagnosed, treatment-naïve patients of all ages with a histological diagnosis of lymphoma were included. The patients underwent staging with ^{18}F-FDG PET/CT and unilateral iliac crest BMB. ^{18}F-FDG PET/CT was performed before BMB, and the maximum time gap between the two procedures was four days. Patients who had received any form of chemotherapy or steroid before the staging, who required immediate cytoreduction due to aggressive presentation before staging was complete, patients in whom ^{18}F-FDG PET/CT was contraindicated and those staged with CECT were excluded. A total of 136 patients were clinically suspected as lymphoma during the study period, of whom 80 patients met the inclusion criteria and were enrolled in the study. The Figure shows the flow diagram of the study showing reasons for exclusion.

^{18}F-FDG PET/CT acquisition: All ^{18}F-FDG PET/CT scans were performed using the Siemens Biograph mCT (Erlangen, Germany) PET/CT scanner. Intravenous ^{18}F-FDG was administered at a dose of 10 mCi for adults and 0.21 mCi/kg for children (dose range was 2.73 mCi to 10 mCi or 101 MBq to 370MBq). The radiotracer uptake period was 45-60 min. All patients fasted for six hours before the scan procedure and the fasting blood glucose before the procedure was less than 150 mg/dl. A low-dose whole-body CT scan was performed followed by a PET scan from the base of the skull to mid-thigh, with special acquisition of the brain in all cases. PET images were reconstructed using ordered subset expectation maximization reconstruction algorithms.

^{18}F-FDG PET/CT interpretation (qualitative): FDG uptake more than that of the liver, localized in the marrow, was considered positive. Focal pattern (at least one) with or without diffuse involvement of marrow was considered as positive. Isolated diffuse involvement of the marrow was not considered positive for lymphoma infiltration. ^{18}F-FDG PET/CT marrow involvement was considered as true positive if there was marrow involvement on histology and/or the FDG uptake in the marrow resolved post-therapy as evaluated by interim or end-of-treatment ^{18}F-FDG PET/CT scan. Patients where ^{18}F-FDG PET/CT either showed no marrow involvement or showed diffuse marrow involvement along with a negative BMB were considered as true negative. No marrow uptake on ^{18}F-FDG PET/CT and a positive BMB was a false negative. A negative BMB with a positive focal (±diffuse) lesion on ^{18}F-FDG PET/CT which failed to show resolution on follow up interim or end-of-treatment PET/CT scan (in the event of complete metabolic response of all other nodal or extranodal sites involved by the lymphoma at baseline evaluation) was considered false positive.

^{18}F-FDG PET/CT interpretation (semi-quantitative): The standardized uptake value (SUVmax) normalized for body weight was calculated in patients with positive FDG uptake in marrow from the most intense area. When there was no abnormal FDG uptake in the

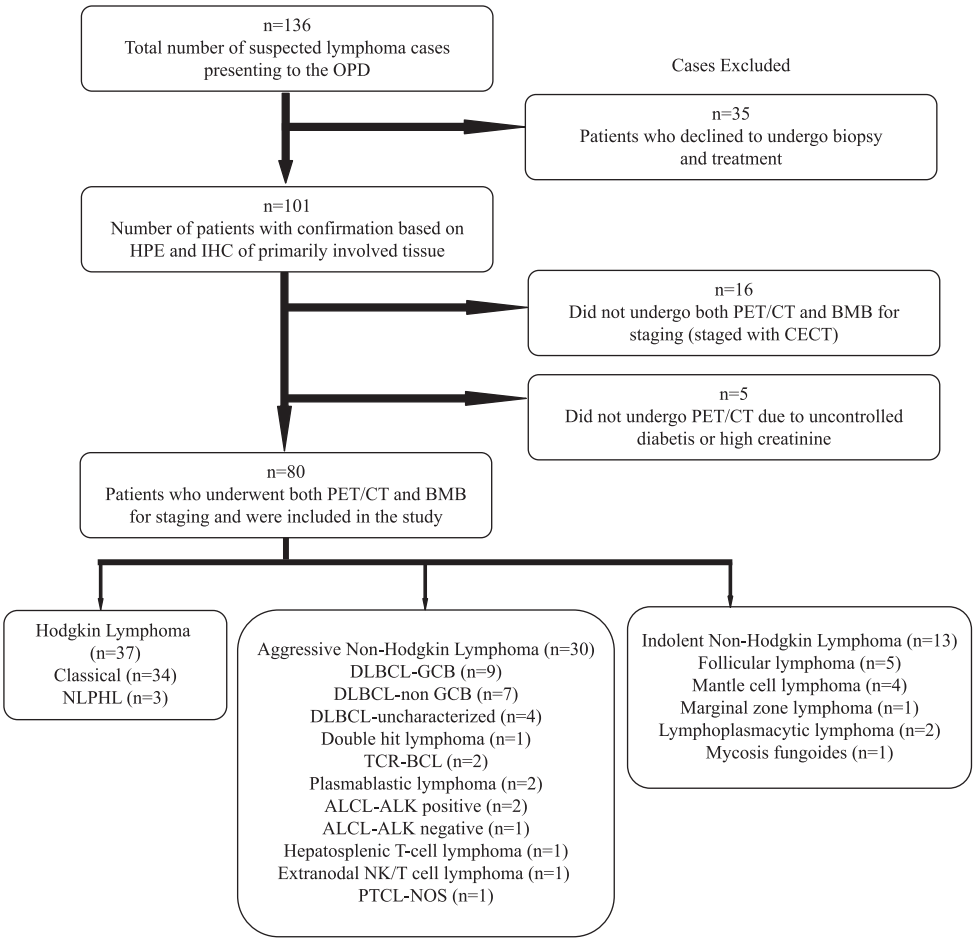

Figure. Consort diagram of the study. ALCL: anaplastic large cell lymphoma; BMB: bone marrow biopsy; DLBCL: diffuse large B-cell lymphoma; GCB: germinal centre B-cell; NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; PET/CT: positron emission technology/computerized tomography; PTCL-NOS: peripheral T-cell lymphoma not otherwise specific; TCR-BCL: T-cell-rich B-cell lymphoma; CECT, contrast-enhanced computerized tomography; ALK, anaplastic lymphoma kinase.

marrow, reference SUVmax was measured from the posterior superior iliac spine on both sides and the mean of these values was taken for analysis.

Bone marrow biopsy (BMB): The bone marrow procedure was performed after the PET/CT in all patients. Unilateral iliac crest bone marrow aspirate (BMA) and BMB (at least 2 cm length) were obtained under local anaesthesia. The BMB sections were processed and stained with haematoxylin and eosin stain. The pattern of infiltration and cell morphology was assessed in comparison with the morphology of the tissue of primary diagnosis. Immunohistochemistry with an appropriate and adequate panel was used whenever necessary to confirm the marrow involvement.

Statistical analysis: Measures of diagnostic performance of ^{18}F-FDG PET/CT were estimated by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) along with the corresponding confidence intervals (CI). Differences between groups for the continuous variable were compared using the Mann–Whitney U test and for categorical variables using the Chi-square test and Fisher's exact test. Statistical analysis was done using Prism version 7.05 (GraphPad Software, San Diego, USA).

Results

The demographic profile of the patients included in the study is shown in Table I. Of the 80 patients included, there were 37 HL cases, of whom majority 34 (91.9%) were classical HL and rest 3 (8.1%) were nodular lymphocytic predominant HL. Among the 43 NHL patients, 30 were aggressive NHL and 13 were indolent NHL. The majority of the aggressive NHLs were of B-cell origin (n=24), and DLBCL (n=20) was the most common histological

Table I. Demographic details of the patients included in the study (n=80)

Details of patients	HL, n (%)	Aggressive NHL, n (%)	Indolent NHL, n (%)
Total number of cases	37	30	13
Median age (yr)	23	47	55
Range (yr)	3-62	7-85	40-79
Sex			
Male	26 (70.3)	22 (73.3)	9 (69.2)
Female	11 (29.7)	8 (26.7)	4 (30.8)
B-symptoms			
Fever	21 (56.8)	17 (56.7)	5 (38.5)
Weight loss	16 (43.2)	17 (56.7)	5 (38.5)
Night sweats	18 (48.6)	13 (43.3)	5 (38.5)
Clinical organ involvement			
Lymphadenopathy	37 (100)	23 (76.7)	11 (84.6)
Hepatomegaly	15 (35.1)	6 (20)	3 (23.1)
Splenomegaly	11 (29.7)	7 (23.3)	3 (23.1)
Site of involvement			
Nodal	28 (75.7)	15 (50)	7 (53.8)
Extranodal	0	6 (20)	1 (7.7)
Nodal/extranodal	9/37 (24.3)	9/30 (30)	5/13 (38.5)
Ann Arbor stage			
I	2 (5.4)	6 (20)	1 (7.7)
II	9 (24.3)	1 (3.3)	1 (7.7)
III	6 (16.2)	5 (16.7)	1 (7.7)
IV	20 (54.1)	18 (60)	10 (76.9)
Cell type			
B-cell	37 (100)	24 (80)	12 (92.3)
T-cell	0	5 (16.7)	1 (7.7)
NK/T-cell	0	1 (3.3)	0

HL, Hodgkin lymphoma; NHL, non-HL

subtype. Among the indolent NHL, 12 were B-cell lymphoma cases and the common subtypes were follicular lymphoma (5/13) and mantle cell lymphoma (4/13).

^{18}F-FDG PET/CT showed marrow infiltration in 18 patients of HL and 13 and seven of aggressive and indolent NHLs, respectively. This was in contrast with marrow infiltration on BM histology where HL showed infiltration in six and aggressive NHL in four patients. Eight patients with indolent lymphoma showed marrow involvement on histology which was higher as opposed to ^{18}F-FDG PET/CT.

When marrow infiltration on ^{18}F-FDG PET/CT was compared with the BMB, there was 67 per cent concordance between the two modalities in HL compared to 72 per cent in NHL. Indolent NHL showed a higher concordance than aggressive NHL (77 *vs*. 70%). ^{18}F-FDG PET/CT showed excellent sensitivity and NPV in both HL (LR+ 2.58; 95% CI: 1.66-4.02) and NHL (LR+ 2.58; 95% CI: 1.46-4.57). The specificity and PPV of ^{18}F-FDG PET/CT were low in both the subtypes. Among the NHL subtypes, the sensitivity and NPV (LR+ 2.89; 95% CI: 1.6-4.9) were higher in the aggressive subtype compared to the indolent subtype while the specificity and PPV (LR+ 3.75; 95% CI: 0.62-22.64) were higher in the indolent subtype compared to the aggressive subtype. When ^{18}F-FDG PET/CT was compared with the gold standard BMB, the sensitivity, specificity, PPV and NPV were 100, 61.3, 33.3 and 100 per cent, respectively, for HL; 100,

Table II. Analysis of PET/CT in detecting bone marrow infiltration in cases showing marrow involvement in bone marrow biopsy at diagnosis

Type of lymphoma	BM histology showing lymphoma infiltration	BM status on PET		Percentage (95% CI)			
		PET+	PET−	Sensitivity	Specificity	PPV	NPV
HL	BMB positive	6	0	100 (54.1-100)	61.3 (42.2-78.2)	33.3 (24.3-43.8)	100
	BMB negative	12	19				
NHL	BMB positive	10	2	83.3 (51.6-97.9)	67.7 (48.6-83.3)	50 (36.2-63.9)	91.3 (73.7-97.5)
	BMB negative	10	21				
Aggressive NHL	BMB positive	4	0	100 (39.8-100)	65.4 (44.3-82.8)	30.8 (20.8-42.9)	100
	BMB negative	9	17				
Indolent NHL	BMB positive	6	2	75 (34.9-96.8)	80 (28.4-99.5)	85.7 (49.8-97.3)	66.7 (35.8-87.8)
	BMB negative	1	4				

PET+ and PET−, PET positive and negative for marrow infiltration by lymphoma. PET-CT, positron emission tomography–computed tomography; PPV, positive predictive value; NPV, negative predictive value; HL, Hodgkin lymphoma; NHL, non-HL; BM, bone marrow; BMB, BM biopsy; CI, confidence interval

65.4, 30.8 and 100 per cent, respectively, for aggressive NHL and 75, 80, 85.7 and 66.7 per cent, respectively, for indolent NHL (Table II). In all cases, a follow up ^{18}F-FDG PET/CT scan at the interim or end of treatment was done. In these interim or end-of-treatment scans, if there was a resolution of all nodal or extranodal FDG-avid lesions present at baseline, the marrow FDG uptake was analyzed. This analysis showed that there was a resolution of the FDG-avid marrow lesion seen at baseline in all cases (n=38), suggesting that the FDG avidity was probably due to lymphoma involvement. There were 22 cases where initial BMB showed no lymphoma infiltrate, but PET/CT showed the presence of focal (±diffuse) FDG-avid lesion at baseline which showed complete resolution after treatment of lymphoma. When the presence of marrow involvement on histology at baseline and/or disappearance of FDG uptake on follow up PET/CT scan were taken as the reference standard, the specificity and PPV of PET/CT improved to 100 per cent for all subtypes of lymphoma. However, for indolent lymphoma, the sensitivity (77.3%; 95% CI: 39.9-97.2%) and NPV (66.7%; 95% CI: 37.1-87.2%) remained low (Table III).

There was a significant difference in the mean SUVmax on PET/CT between those who showed marrow infiltration on BMB compared to those who did not 7.49 vs. 3.13; P<0.001).

Discussion

It has been a routine practice to perform BMB for staging in all cases of lymphoma. Most of the studies analyzing the utility of ^{18}F-FDG PET/CT in the evaluation of marrow infiltration are of retrospective design[7-9]. This study has a prospective design, similar to a few other published studies[10,11].

In this study, patients were staged simultaneously with both ^{18}F-FDG PET/CT and BMB. The marrow uptake results on ^{18}F-FDG PET/CT were analyzed with respect to the results of marrow histology on BMB. The presence of BMI on BMB alone (approach A) was considered for evaluating sensitivity, specificity, PPV and NPV. Alternatively, several studies[10,12,13] have taken data of positive BMB at diagnosis together with the resolution of FDG PET uptake on treatment as determined by follow up PET scan (interim or end of treatment) (approach B) as the standard for calculations of the utility of ^{18}F-FDG PET/CT in detecting marrow infiltration in lymphoma staging.

In HL using approach (A), the sensitivity, specificity, PPV and NPV were 100, 61.3, 33.3 and 100 per cent, respectively, which improved to 100 per cent for each of the four parameters by approach (B). Retrospective analysis with approach (A), showed that ^{18}F-FDG PET/CT had a sensitivity, specificity, PPV and NPV of 93.6 to 99, 56, 53 and 99.4 to 99 per cent, respectively[7,11]. A meta-analysis showed that ^{18}F-FDG PET/CT had an excellent pooled sensitivity of 94.5 per cent in comparison to a poor pooled sensitivity of 39.4 per cent for BMB in detecting marrow infiltration[14]. A prospective study, reported a sensitivity and NPV of 100 per cent each. However, the specificity and PPV were 86 and 71 per cent, respectively[10]. From the

Table III. Analysis of PET/CT in detecting bone marrow infiltration in cases with bone marrow biopsy involvement at diagnosis and/or disappearance of marrow fluorodeoxyglucose uptake post-treatment

Type of lymphoma	BM infiltration at diagnosis (any modality)	BM status on PET		Percentage (95% CI)			
		PET+	PET-	Sensitivity	Specificity	PPV	NPV
HL	Positive	18	0	100 (81.5-100)	100 (82.4-100)	100	100
	Negative	0	19				
NHL	Positive	20	2	90.9 (70.9-98.9)	100 (83.9-100)	100	91.3 (73.7-97.5)
	Negative	0	21				
Aggressive NHL	Positive	13	0	100 (75.3-100)	100 (80.5-100)	100	100
	Negative	0	17				
Indolent NHL	Positive	7	2	77.3 (39.9-97.2)	100 (39.8-100)	100	66.7 (37.1-87.2)
	Negative	0	4				

BMB+ and BMB−, BMB positive and negative for marrow infiltration by lymphoma; PET+ and PET−, PET positive and negative for marrow infiltration by lymphoma. BM, bone marrow; BMB, BM biopsy; PET-CT, positron emission tomography–computed tomography; PPV: positive predictive value; NPV: negative predictive value; HL, Hodgkin lymphoma; NHL: non-HL; CI, confidence interval

data in the present study, a positive ^{18}F-FDG PET/CT marrow involvement in HL may be sufficient for staging if a follow up ^{18}F-FDG PET/CT is planned for response assessment.

There were 30 patients with aggressive NHL in this study. The sensitivity, specificity, PPV and NPV of PET/CT were 100, 65.4, 30.8 and 100 per cent, respectively, by approach (A), which improved to 100 per cent for all four parameters on approach (B). A study of high-grade B-cell NHL reported a sensitivity of 52.7 per cent and NPV of 81.7 per cent[7]. The inclusion of diffuse marrow FDG uptake as positive reduced the sensitivity and NPV in this study. A meta-analysis[6] showed that the sensitivity and specificity of ^{18}F-FDG PET/CT ranged from 70.8 to 95.8 and 99.0 to 100 per cent, respectively, with pooled estimates of 88.7 and 99.8 per cent, respectively. Using approach (A) in DLBCL, the sensitivity and NPV of PET/CT in detecting BMI were 86 to 100 and 98 to 100 per cent, respectively[15,16]. Chen *et al*[12] analyzed 93 patients with DLBCL, Burkitt's lymphoma, lymphoblastic lymphoma and ALCL by approach (B). There was a concordance of 76 per cent between PET/CT and BMB. The sensitivity, specificity, PPV and NPV of PET/CT were 95, 98, 97 and 96 per cent, respectively. In an evaluation of aggressive NHL cases, the sensitivity, specificity, PPV and NPV of PET/CT were 100, 94, 93 and 100 per cent, respectively[10]. In aggressive NHL like DLBCL, the marrow may show discordant involvement with low-grade histology or may have a low-volume marrow involvement (10-20% tumour load in the marrow) and ^{18}F-FDG PET/CT may be falsely negative in such cases[7,17]. This may result in false downstaging of the disease. Our study did not have any such case of aggressive NHL which led to better specificity and PPV. Based on these observations, patients of aggressive NHL who undergo baseline staging and treatment follow up by ^{18}F-FDG PET/CT scan, BMB may be avoided at baseline for staging. However, baseline BMB is justified in cases where marrow is not involved in ^{18}F-FDG PET/CT[3].

There were 13 patients with indolent NHL in the present study, of whom eight cases had marrow involvement on histology. The sensitivity, specificity, PPV and NPV were 75, 80, 85.7 and 66.7 per cent, respectively, with approach (A) and 88.9, 100, 100 and 80 per cent, respectively, with approach (B). Sengar *et al*[18] showed a sensitivity (43.7%) and NPV (50%) of the ^{18}F-FDG PET-using approach (A). The specificity (81.2%) and PPV (77.8%) were relatively higher for follicular lymphoma. In the same study, approach (B) showed that the specificity and PPV of ^{18}F-FDG PET/CT improved to 100 per cent each, but the sensitivity and NPV remained 43 and 50 per cent, respectively. In follicular lymphoma using approach (A), the PPV and NPV were 100 and 48.5 per cent[8] while the sensitivity and specificity were 67 and 85 per cent[9]. Mittal *et al*[10] prospectively analyzed 15 follicular lymphomas and two small lymphocytic lymphomas using approach (B). They also found that specificity and PPV of PET/CT were 100 per cent each, while the sensitivity and NPV were comparatively lower at 50 and 70 per cent, respectively. The excellent specificity

and PPV signify that in indolent lymphoma in general and follicular and mantle cell lymphoma in particular, BMB for staging may be avoided if there is positive FDG-marrow uptake on PET/CT. However, in the case of no marrow uptake on PET/CT, BMB should be done to exclude marrow involvement.

The pattern of FDG uptake in the marrow needs special consideration. In the present study, patients who were considered positive for marrow involvement on ^{18}F-FDG PET/CT had at least one focal uptake pattern, with or without diffuse marrow uptake. Isolated diffuse uptake was not considered as positive for marrow involvement. Focal involvement on PET/CT in HL and both diffuse/focal involvement in high grade B-cell NHL were predictive of bone marrow involvement on histology[7]. High concordance between focal pattern on ^{18}F-FDG PET/CT and marrow infiltration on BMB (86%) was seen in follicular lymphoma[13]. The isolated diffuse pattern on ^{18}F-FDG PET/CT may be due to benign and reactive conditions, more so in HL[19,20]. In the present study, patients with focal involvement on ^{18}F-FDG PET/CT that were missed by BMB showed involvement of marrow at sites other than the iliac crest, resulting in sampling error. Detection of such cases requires a PET/CT-guided targeted biopsy. These focal lesions, however, disappeared on follow up scan post-treatment signifying their true positive nature.

With regard to the optimal SUVmax cut-off, previous studies[10,21] showed that marrow involvement on histology was significantly associated with a higher SUVmax in all lymphoma subtypes. Considering histological subtypes, marrow SUVmax in patients with follicular lymphoma (5.4 vs. 1.8; $P<0.001$)[9] and HL (3.0 vs. 1.2; $P<0.001$)[12] were significantly higher in patients with marrow involvement on histology than in those in whom BM was not involved. In the present study, there were three cases of DLBCL, in whom PET/CT showed a SUVmax of more than 10, but BMB failed to identify marrow involvement. This may be because these cases either showed involvement at a site other than the iliac crest or showed focal lesions in the iliac bone which were not sampled in the blinded BMB procedure.

The strength of the study was its prospective nature. Each patient was followed up with a repeat ^{18}F-FDG PET/CT scan during/after treatment, and the disappearance of the marrow uptake helped in delineating the true positive nature of disease involvement. The limitation was the sample size, especially concerning indolent lymphoma which was under-represented in the study. Furthermore, unilateral BMB was performed in all cases. The performance of bilateral BMB would have possibly increased the diagnostic yield, but the same is seldom practically performed in clinical practice. A targeted ^{18}F-FDG PET/CT-directed BMB at baseline would have improved the sensitivity of the procedure and would have made our approach (B) of data analysis more evidence based and concrete. This could be a potential hypothesis for future studies[22]. A larger, preferably multicentric study would validate the results and add to the much-required data pool for better decision-making in clinical practice.

The choice of ^{18}F-FDG PET/CT or BMB for detecting BMI in lymphoma staging should be made primarily based on the histological subtype of lymphoma determined by lymph node/extranodal site biopsy. ^{18}F-FDG PET/CT should be the method of the first choice for staging HL and BMB may be avoided if a follow up ^{18}F-FDG PET/CT is planned. In aggressive (DLBCL) and indolent NHL (follicular lymphoma), if baseline and follow up ^{18}F-FDG PET/CT is performed, and if there is the presence of marrow FDG uptake, the need of a BMB may be precluded. However, if marrow FDG uptake on PET/CT is absent, then a BMB should be done. However, due to meagre data in lymphoma subtypes other than HL, DLBCL and follicular lymphoma, a BMB is indicated especially if there is a negative bone marrow FDG uptake on PET/CT until large-scale data are available to answer this question.

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***Conflicts of Interest*:** None.

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