The Role of Integrated Positron Emission Tomography/Computed Tomography (PET/CT) and Bone Marrow Examination in Staging Large B-Cell Lymphoma

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ABSTRACT

INTRODUCTION: In the era of routine use of positron emission tomography/computed tomography (PET/CT) for staging, it is not yet clear whether PET/CT can replace bone marrow biopsy for the assessment of bone marrow involvement in large B-cell lymphoma.

OBJECTIVES: To compare the clinical utility of bone marrow biopsy and PET/CT scanning in the staging of large B-cell lymphoma.

METHODS: This was a retrospective analysis of all patients who presented to single center over a 4-year period with large B-cell lymphoma who had concurrent PET/CT and bone marrow biopsy performed in the assessment and staging of the lymphoma.

RESULTS: Out of 89 patients, 24 had bone marrow involvement either by PET/CT, by bone marrow biopsy, or by both. Bone marrow biopsy identified 12 patients (sensitivity 50%, specificity 100%, negative predictive value 84%), whereas PET/CT identified 23 patients (sensitivity 96%, specificity 100%, negative predictive value 98%). No patients were upstaged by the bone marrow biopsy result, and no patients had their treatment plan changed based on the bone marrow biopsy result.

CONCLUSION: The results show that PET-CT is more sensitive and has better negative predictive value than bone marrow biopsy. This suggests that PET-CT could replace bone marrow biopsy in detecting bone marrow involvement for staging of large B-cell lymphoma.

KEYWORDS: NHL, LBCL, DLBCL, PET/CT, BM, bone marrow, staging, lymphoma

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Background

Bone marrow biopsy (BMB) has traditionally been part of the standard investigations for staging of large B-cell lymphoma (LBCL). A finding of a bone marrow (BM) that is involved with lymphoma has implications for staging, prognosis, and in some patients a change in initial treatment. However, BMB has potential side effects of pain, bleeding, and infection and is limited by the potential for sampling error if the biopsy is not taken from a part of the marrow that is involved.

^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) is an imaging technique that is recommended and now widely used in the staging of LBCL. It is a sensitive technique when used in LBCL. There has been recent interest in using the PET/CT findings to either supplement or even replace the BMB in the evaluation of BM involvement in LBCL. Similar progress has already been made in the staging of Hodgkin Lymphoma, where the PET/CT has now largely removed the need for a formal BMB.[1,2]

This study aims to present the findings for a single center where both PET/CT and BMB have been routine concurrent tests performed for staging LBCL over a 4-year period between January 2013 and January 2017.

Methods

This is a retrospective study, in which data were collected on all new patients over the age of 14 diagnosed with LBCL and staged at the National Center for Cancer Care and Research (NCCCR) in Doha, Qatar, between January 2013 and January 2017. The NCCCR is the only cancer treatment center in Qatar and is part of the government-funded national health system. Only patients who had simultaneous PET/CT and BMB as part of pre-therapy staging were included. When we say simultaneous, we mean that the period between performing PET/CT and bone marrow biopsy is maximum 30 days and without lymphoma treatment between the studies. The electronic reports for BMB and PET/CT were extracted and reviewed individually by hematopathologists and dedicated PET/CT physicians, respectively. The original PET/CT images were reviewed and then categorized as having a normal, diffuse, focal or inhomogeneously positive BM. Baseline clinical, relevant

laboratory and pathological characteristics, staging, and patient outcome were obtained by review of patient records and the lymphoma multidisciplinary team (MDT) records.

Patient cases were excluded from the study if they had received corticosteroids or chemotherapy prior to the BMB or PET/CT. Patients with known concomitant malignancy were excluded. Patients who had received hematopoietic growth factor injections less than 48 hours before the PET/CT were excluded. Patients with a previously known and treated lymphoma were excluded.

Routine staging over this period involved unilateral bone marrow aspirate and trephine collected from the posterior iliac crest. BMB were analyzed following the standard procedures, including acetic acid, zinc, formalin (AZF) fixing, paraffin embedding, and staining with hematoxylin and eosin. Hematoxylin-eosin stained sections were morphologically evaluated together with the bone marrow aspirate and other relevant ancillary tests by experienced hematopathologists. The slides of each bone marrow were reviewed by 2 hematopathologists including correlation with immunohistochemistry and or flow cytometry immunophenotyping. As a rule, pan T (CD3) and Pan B (PAX5 and CD20) were performed in all cases, and a second panel of Immuno-stains was performed according to the case as appropriate. Flow cytometry immunophenotyping was performed on all cases. Fluorescent in situ hybridization was performed according to the institutional guidelines or if deemed necessary by the hematopathologist. The period of review spanned the introduction of the new World Health Organization (WHO) classification of lymphoid neoplasms. The original diagnostic result was retained, as seen in Table 1.

All FDG PET/CT scans were performed as routine whole-body scans from vertex to midthighs after at least 6-hour fasting. Patients underwent blood glucose test prior to administering FDG, received adequate pre-hydration and remained recumbent and silent to ensure fewer artifacts and to minimize FDG uptake in muscles. A cutoff for blood glucose of 11 mmol/L was used in accordance with European Association of Nuclear Medicine guidelines for routine FDG/PET studies. Emission data were acquired for 2-3 minutes per bed position depending on body habitus starting 60 ± 5 minutes after intravenous injection of lean body mass adapted FDG dose. Images were obtained on a Siemens mCT 64 scanner. Quality control procedures were carried out at regular intervals with strict adherence to local protocols, manufacturer, and international guidelines. The low-dose CT component of the PET/CT was used for both co-localization and attenuation correction of the PET emission data.

Coronal, sagittal, and transverse PET/CT projections were reconstructed by iterative methods as well as maximum intensity projection images and analyzed using the manufacturer's software. The image interpretation was through qualitative (visual) analysis by an experienced nuclear medicine consultant who was blind to the BMB result. Findings were divided into positive and negative categories with normal or diffusely increased bone marrow uptake considered negative by PET. Intense focal (solitary, oligo, or multiple) uptake(s) and inhomogeneous FDG distribution over the bones were considered positive by PET (Figure 1).

As a bone marrow biopsy itself has poor sensitivity, it could not be used as the gold standard comparator. For the purpose of this study, a "true positive bone marrow involvement" and a "true negative bone marrow involvement" were defined as in Table 2.

Table 1. Patient characteristics.

PARAMETER	N (%) OR MEAN/MEDIAN [RANGE]
Age (y)	
Range	[18-77]
Mean ± SD	48.6 ± 13.6
Median (IQR)	48 (39-60)
Sex	
Male	64 (72%)
Female	25 (28%)
Nationality	
MENA region	40 (45%)
Other	49 (55%)
Time of PET/CT to BM (days)	
Range	[0-28]
Mean	7.2
Median	6
Stage	
I	23 (26%)
II	12 (13%)
III	10 (11%)
IV	44 (49%)
Lymphoma type	
DLBCL	9 (10%)
DLBCL AB	30 (34%)
DLBCL GC	40 (44%)
DLBCL /BL	4 (4%)
HGBCL	4 (4%)
TCHBCL	1 (1%)
DLBCL/CHL	1 (1%)

Abbreviations: AB, activated B-cell subtype; BL, Burkitt-like; BM, bone marrow; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; CHL, classical Hodgkin lymphoma; GC, germinal center B-cell subtype; HGBCL, high grade B-cell lymphoma; IQR, interquartile range; MENA, Middle East and North Africa; PET, positron emission tomography; SD, standard deviation; TCHBCL, T-cell or histiocyte rich B-cell lymphoma.

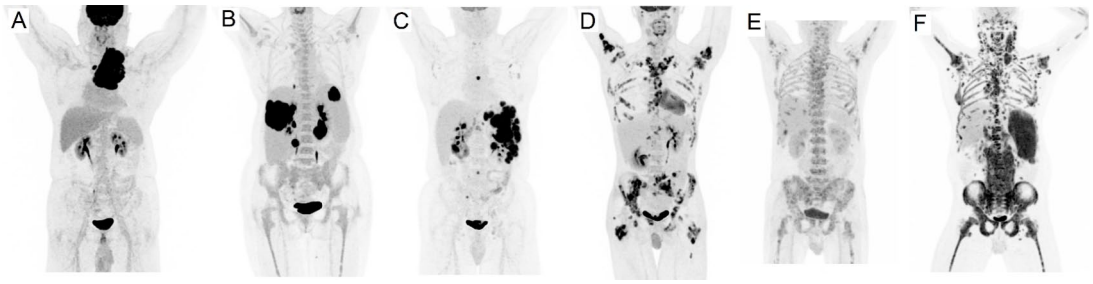

Figure 1. Patterns of bone marrow FDG-uptake in lymphoma—maximum intensity projection (MIP) whole-body PET images: (A) No significant uptake in bone marrow; bones cannot be identified. (B) Diffuse, mild uptake in bone marrow spaces—more likely representing reactive changes. (C) Small number of FDG-avid bone foci (in this example a D5 and L4 vertebral body focus). (D) Several FDG-uptakes are seen in multiple bones. (E) Mild to moderate inhomogeneous uptake all over the bone marrow. (F) Intense uptake nearly completely filling the bone marrow space. Various lymph nodal and liver/spleen involvements are also seen on the above images. FDG indicates fluoro-2-deoxy-D-glucose; MIP, maximum intensity projection; PET, positron emission tomography.

Table 2. Definitions for bone marrow involvement.

TRUE POSITIVE BONE MARROW INVOLVEMENT IF:		TRUE NEGATIVE BONE MARROW INVOLVEMENT IF:
1. There were positive pathologic findings in the bone marrow biopsy		1. There was diffuse uptake of ^{18}F-FDG in the bone marrow on PET/CT but the bone marrow biopsy was negative or
OR		OR
2. There was a positive ^{18}F-FDG PET/CT (unexplained by another etiology) which either-	a. Was confirmed by guided biopsy	2. An initially positive ^{18}F-FDG PET/CT that was invalidated by a guided biopsy or targeted MR imaging or
	OR	OR
	b. Was confirmed by targeted MRI imaging	3. Persistent focal bone marrow uptake on ^{18}F-FDG PET/CT reassessment despite the disappearance of uptake in other lymphoma lesions.
	OR	
	c. Was a focal bone marrow uptake or inhomogeneous FDG distribution over the bones that disappeared concomitantly with the other lymphoma lesions upon ^{18}F-FDG PET/CT reassessment.	

Abbreviations: CT, computed tomography; ^{18}F-FDG, ^{18}F-fluoro-2-deoxy-D-glucose; MR, magnetic resonance; MRI, magnetic resonance imaging; PET, positron emission tomography.

This research was reviewed by the Institutional Review Board and classified as "exempt" according to the Qatar Supreme Council of Health guidelines. The need for informed consent is waived for exempt studies. HMC ID number MRC/0508/2017.

Statistics

The diagnostic and predictive accuracy of BMB and PET/CT including sensitivity, specificity, positive predictive value, negative predictive value and accuracy (along with their corresponding 95% confidence limits), and the negative likelihood ratios were calculated. Continuous data were expressed as mean (+SD) and qualitative data were expressed as number and percentages. *P* values less than .05 were considered significant. Statistical analysis was performed using the statistical package SPSS for Windows version 21 (SPSS Inc, Chicago, IL, USA).

Results

Ninety patients with LBCL had both PET/CT and bone marrow biopsy results available. One patient with negative PET/CT and BMB was excluded as more than 30 days separated the PET/CT and BMB. Eighty-nine patients thus met the inclusion criteria and were included in the analysis. The main characteristics of the study population are shown in Table 1. A total of 24 patients were considered to have bone marrow involvement (BMI). Within that group, 12 patients were positive according to the bone marrow biopsy, and 23 were positive according to PET/CT. Only 1 patient was positive by BM biopsy but negative using PET/CT (Table 3). This patient had DLBCL, GC subtype. The BM biopsy had been performed 7 days after the PET/CT. The patient was categorized as stage IV disease due to other lesions outside of the bone marrow on PET/CT and so the BM

Table 3. Bone marrow involvement, comparing PET/CT with BMB.

	PET/CT POSITIVE	PET/CT NEGATIVE	TOTAL
BMB positive	11	1	12
BMB negative	12	65	77
Total	23	66	89

Abbreviations: BMB, bone marrow biopsy; CT, computed tomography; PET, positron emission tomography.

biopsy did not change the stage for the patient. The BM biopsy itself showed a hypercellular aspirate although the lymphoid cells were not increased. The trephine biopsy was also hypercellular with 90% cellularity and was infiltrated by numerous B-lymphoid cells in both an interstitial pattern and with a few small para-trabecular and one large inter-trabecular lymphoid aggregate composed mostly of B-cells. Flow cytometry on the aspirate showed a small (3%) population of monoclonal B-cells with kappa light chain restriction.

All patients who had a positive PET/CT suggesting BM involvement were confirmed to have such involvement either by concomitant BM biopsy, targeted magnetic resonance imaging (MRI) scanning, or resolution of positivity on subsequent PET/CT imaging in keeping with the other lymphoma lesions. There were no false positive PET/CT scans in relation to bone marrow status.

PET/CT was more sensitive than BMB (96% vs 50%), with greater diagnostic accuracy (99% vs 87%) and greater negative predictive value (98% vs 84%) (Table 4).

Discussion

These data show that PET-CT imaging has a high sensitivity and specificity for the detection of BM involvement in patients with LBCL and can detect BM involvement missed by BMB. No patients had their lymphoma stage changed by the results of the BMB if PET/CT had been performed (Table 5). No patients had their treatment plan changed by the results of the BMB.

Only 1 patient had a negative PET/CT with a positive BMB, but in this case the patient was already stage IV by other criteria and so staging, prognosis, and treatment were not changed by the BMB. Notably in this patient, the BMB had "discordant" findings in that it showed small cells, not large. Such small cells may have reduced avidity for FDG and therefore missed by PET/CT. Such "discordant" BMB findings have been seen to have less prognostic significance.[3-7]

The high sensitivity of 96% and high NPV (98%) of PET/CT in this cohort indicates that patients do not require bone marrow biopsy if the PET/CT results are negative for bone marrow involvement. There are rare cases described in the literature whereby patients with a negative PET/CT scan have been found to have extensive BM involvement with a concordant large cell lymphoma[8] but such cases are exceptional and may not justify continuing to perform routine BMB on all LBCL patients, particularly as such findings are unlikely to change the treatment plan for the patient.[9]

Table 4. Test characteristics for PET/CT and BMB.

STATISTIC	ESTIMATE	95% CI
Prevalence		
PET/CT	26.97%	18.10% to 37.42%
BMB	26.97%	18.10% to 37.42%
PET/CT + BMB combined	26.97%	18.10% to 37.42%
Sensitivity		
PET/CT	95.83%	78.88% to 99.89%
BMB	50.00%	29.12% to 70.88%
Specificity		
PET/CT	100.00%	94.56% to 100.00%
BMB	100.00%	94.48% to 100.00%
Diagnostic accuracy		
PET/CT	98.88%	93.90% to 99.97%
BMB	86.52%	77.63% to 92.83%
Positive predictive value		
PET/CT	100%	82.94% to 100%
BMB	100%	71.41% to 100%
Negative predictive value		
PET/CT	98.48%	90.51% to 99.77%
BMB	84.42%	78.40% to 88.99%
Negative likelihood ratio		
PET/CT	0.04	0.01 to 0.28
BMB	0.5	0.34 to 0.75

Abbreviations: BMB, bone marrow biopsy; CI, confidence interval; CT, computed tomography; PET, positron emission tomography.

Table 5. Lymphoma staging, comparing PET/CT alone with PET/CT + BMB combined.

BMB + PET/CT					
PET/CT	I	II	III	V	TOTAL
I	23	0	0	0	23
II	0	12	0	0	12
III	0	0	9	0	9
IV	0	0	0	45	45
Total	23	12	9	45	89

Abbreviations: BMB, bone marrow biopsy; CT, computed tomography; PET, positron emission tomography.

Similarly, positive PET/CT findings may remove the need for BMB for the detection of bone marrow involvement in these patients. PET/CT had a specificity and positive predictive value of 100% in this study, although this number is likely

influenced by the definition of bone marrow involvement used. Eleven of 12 patients in this study who had a negative BMB but a positive initial PET/CT were eventually deemed to have had bone marrow involvement by subsequent posttreatment normalization of FDG uptake in the focal areas. The 12th of the 12 patients had BM involvement confirmed by a targeted MRI but did not have resolution of changes on subsequent PET/CT as the lymphoma remained refractory to treatment. None of the patients had targeted biopsies to confirm involvement histologically. It is reasonable to question if resolution of initial focal PET/CT change can really be used as a reliable surrogate for BMI if a targeted biopsy has not been performed to confirm as other processes may also resolve with time or treatment, such as inflammation or marrow stimulation. Chen at al. show that focal PET/CT positivity is an independent predictor of progression free survival (PFS) both in patients who are BMB positive and in those who are BMB negative,[10] suggesting that focal PET/CT positivity does indicate true BM involvement. Other studies confirm this prognostic impact[11,12] although for those patients who are stage IV by criteria other than BMI it seems that PET/CT-defined BM involvement loses its prognostic impact while BMB-defined BM involvement still predicts a worse outcome.[13,14]

In this study, diffuse BM change on PET/CT was not deemed to indicate BM involvement, as per the predetermined methodology. None of the patients with a diffuse increase in BM uptake of FDG had a positive BMB. Similarly, when all the patients who had a positive BMB were examined, none of them had diffuse BM change on PET/CT without also having focal lesions, thus giving internal validation for this approach to interpreting diffuse PET/CT change. This is in keeping with one study[15] from Berchet et al but is in contrast to others.[13,16,17] Adams et al,[16] eg, found that diffuse BM uptake in aggressive NHL often meant that the BMB was positive (5 out of 6 such patients). Such discrepancies are difficult to explain and, until a more definitive answer is available, should warrant caution in the interpretation of diffuse uptake in the bone marrow on PET/CT. However, when looking for the prognostic impact of diffusely increased BM uptake on PET/CT rather than the correlation with BMB, Chen et al[10] have shown that patients with a diffuse pattern have the same 3-year overall survival (OS) and PFS as those patients with a negative PET/CT, whereas patients with focally increased uptake have worse OS and PFS. As the question of BM involvement is more pertinent to prognosis than it is to treatment decisions, it might be that this is the most relevant data to be aware of at this point in time.

No patients were upstaged by BMB in this study although rare case descriptions have reported that this is a possibility.[8] Treatment for DLBCL, on the whole, is with 6 to 8 cycles of R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone), and changing the staging from stage III to stage IV by BMB would not change this treatment.[18] For those with limited stage disease by imaging that can be incorporated into one radiation field (stage I and some stage II), BM involvement has the potential to change the treatment from involved field radiation therapy (IFRT) plus 3 cycles of R-CHOP into 6 cycles of R-CHOP alone.[19] However, bone marrow involvement in this group is rare, particularly in those without cytopenias or bulky disease,[20] and PET/CT has a high sensitivity, implying that BMB gives additional useful information in very few such patients and could be omitted, or that BMB could be limited to a select group of early-stage DLBCL patients who are otherwise deemed eligible for abbreviated R-CHOP treatment combined with IFRT or abbreviated R-CHOP.[21,22] In this study, 34 patients were deemed to be stage I or II by PET/CT, and none of them had bone marrow involvement by BMB.

The limitations of this study include the retrospective nature of the data collection as well as the small number of patients who were positive by bone marrow biopsy, making statistical analysis less powerful. However, selection bias was minimized by including all eligible patients diagnosed with LBCL within the selected time frame and no patients were lost to follow-up, probably due to the short time frame required for either a single bone marrow biopsy or PET/CT or a follow-up PET/CT to confirm resolution. Future, larger studies may be able to include a greater number of cases with positive by bone marrow biopsy.

In conclusion, this study shows that PET/CT alone is sensitive and specific for BMI in the staging of LBCL and has a high negative predictive value in newly diagnosed patients. Additional BMB did not change the lymphoma stage for any patient. This suggests that PET-CT could replace bone marrow biopsy in detecting bone marrow involvement for staging of LBCL.

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Author Contributions

A.A.-S. performed research design, data review and formulated the paper; F.I. performed data collection; L.S. performed PET scan analysis; D.S.S. participated in data collection and submitted the manuscript; R.Y.T. participated in clinical data review and L.J.F. performed statistical analysis, reviewed clinical data and wrote the manuscript.

Ethics statement

The study was approved by Hamad Medical Corporation ethics committee on human research (Medical Research Centre-MRC/0508/2017).

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