Assessing bone marrow involvement in diffuse large B-cell lymphoma with 18F-FDG PET/CT: A preliminary experience at Hospital Pulau Pinang

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ABSTRACT

Background: Bone marrow biopsy (BMB) is the standard of care for detecting bone marrow involvement (BMI) in newly diagnosed diffuse large B-cell lymphoma (DLBCL). The role of 18F-FDG PET/CT has been explored as a non-invasive method for detecting BMI in newly diagnosed DLBCL. Due to limited evidence, this method has not been adopted as a mainstream investigation for BMI in Malaysia. The aim of this study was to identify the role of 18F-FDG PET/CT for the detection of BMI in newly diagnosed DLBCL patients at Hospital Pulau Pinang (HPP).

Methods: DLBCL patients at HPP who underwent 18F-FDG PET/CT and BMB were recruited between November 2016 to February 2018. Two reviewers, blinded to the BMB results, evaluated the 18F-FDG PET/CT scans to identify and characterize BMI. The diagnostic performance of 18F-FDG PET/CT was calculated using the BMB histopathological evaluation as the reference standard.

Results: A total of 21 DLBCL patients were enrolled. Seven patients demonstrated BMI on PET/CT (3 with multifocal uptake were concordant with BMB). Fourteen scans were negative for BMI and concordant with BMB. The sensitivity and specificity of 18F-FDG PET/CT scans for detecting BMI is 100% and 77.8%, respectively.

Conclusion: 18F-FDG PET/CT is excellent for ruling-out the presence of BMI. A negative 18F-FDG PET/CT scan for BMI can preclude the need for BMB in certain cases. Although 18F-FDG PET/CT can accurately detect BMI in multifocal pattern of infiltration, it cannot fully replace BMB, which is still considered as the gold standard for evaluating BMI in DLBCL.

KEYWORDS:
BMB, Deauville's criteria, DLBCL, Nuclear Medicine, Staging

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin's lymphoma (NHL) worldwide.[1] Two separate studies in Malaysia identified that DLBCL has a higher prevalence compared to other types of NHL.[2,3] DLBCL is a highly aggressive disease that needs to be detected and treated immediately. The clinical course of the disease is highly variable based on the various subtypes and most patients present late at Stage III or IV.[4] Furthermore, up to 40% of patients have been reported to have relapsing disease after the 1st line of chemotherapy.[5]

DLBCL is divided into concordant and discordant types based on the histology. Concordant histology refers to a worse overall survival and prognostic outcome which occurs when cancer cell histopathology is similar in the marrow and nodal site. Opposite to discordant histology, it refers to differing histopathology between the marrow and nodal site, however it carries lesser impact on overall prognosis of the patients.

Aggressive histopathology is described as a high number of lymphoproliferative cells and T-cell rich nodules. Whereas immunohistochemical features of aggressive disease include diffuse leukocyte common antigen (LCA) and CD20 positivity as well as the presence of MIB, a proliferation marker index that is more than 80%.[6]

The clinical practice guideline by the European Society of Medical Oncology (ESMO) is commonly utilised as the standard of care for diagnosing DLBCL.[7] Additionally, the International Prognostic Index (IPI) was introduced to determine the prognostic factors for DLBCL patients. Based on the IPI, five characteristics were used to score and classify the disease prognosis, among which included bone marrow involvement (BMI).[1] The treatment given for DLBCL is based on the age and IPI index score of the patients, whereby the classification is (i) young low-risk without bulky disease (IPI=0), (ii) young low-risk with bulky disease (IPI=0), (iii) young low-intermediate risk (IPI=1), (iv) young high and high-intermediate risk (IPI=2), (v) patient aged 60-80 years old, and (vi) patient >80 years old with CNS involvement.[8]

Until recently, bone marrow biopsy (BMB) has been the undisputed standard of care for identifying BMI to stage the extra-nodal involvement of DLBCL.[9] A blind posterior iliac crest trephine biopsy and aspirate is routinely performed in newly diagnosed DLBCL. Subsequently, morphological and immunohistochemical evaluation are conducted on the BMB specimens to identify BMI using the Ann Arbor staging.[9] Ann Arbor Stage I is the presence of a single lymphatic region involvement or involvement of a single extra-lymphatic site

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involvement, Stage II is the involvement of ≥ 2 lymphatic regions or extra-lymphatic site(s) involvement on the same side of the diaphragm, Stage III is lymphatic involvement on both sides of the diaphragm, and Stage IV is diffuse or disseminated involvement of ≥ 1 extra-lymphatic organs with or without lymphatic involvement.[8]

Despite the widely acceptable practice of BMB, currently there is a move towards adopting less invasive means of evaluating BMI in DLBCL. In the latest consensus established by international working groups, the Lugano classification has been proposed to incorporate the role of 18-Fluorine-Fluorodeoxyglucose positron emission tomography / computed tomography (^{18}F-FDG PET/CT) scans in the staging and restaging of DLBCL.[8] ^{18}F-FDG PET/CT allows for a physiological response assessment based on the tumour metabolism itself, whereby it enters the tumour cells via sodium-independent glucose transporter receptors (GLUT-1, GLUT-3 and GLUT-12) by facilitated diffusion, and is then transported within the cells and phosphorylated, hence becoming trapped as FDG-6-phosphate.[10] The 18F-FDG PET/CT scans are evaluated based on the size and intensity of radiotracer uptake, where a visual assessment is conducted to identify patterns of abnormally high radiotracer uptake in the marrow.[11] Quantitative assessment using the maximum Standard Uptake Value (SUV_{max}) can also be employed to determine any abnormal FDG accumulation in volumes of interests (VOIs) at pertinent sites of the whole body.[12]

Nevertheless, there is still much debate on the visual assessment of BMI (qualitative analysis) and SUVmax evaluation of uptake at VOIs (quantitative analysis) on the ability of ^{18}F-FDG PET/CT scans to fully replace BMB for the assessment of BMI in patients with DLBCL.13,14 The conflicting results, together with the limitations due to the cost and availability of ^{18}F-FDG PET/CT scans were the main reasons as to why BMB was still mandated for assessing BMI.[15] In Malaysia, there is no local data available regarding the potential role of ^{18}F-FDG PET/CT scans to preclude the need for BMB in excluding BMI among newly diagnosed DLBCL patients. Thus, the aim of this study was to conduct qualitative and quantitative assessment of ^{18}F-FDG PET/CT radiotracer uptake characteristics for the evaluation of BMI among DLBCL patients. We also aimed to identify the role of ^{18}F-FDG PET/CT, including its diagnostic accuracy, compared to BMB for the detection of BMI in newly diagnosed DLBCL patients at a northern region Malaysian hospital, i.e., Hospital Pulau Pinang (HPP).

MATERIALS AND METHODS

Ethical clearance, study design and subject recruitment

This study was approved by the Medical Research Ethics Committee (MREC) of the Kementerian Kesihatan Malaysia and registered with the National Medical Research Register (NMRR ID: NMRR-16-1950-32951). This study was also approved by the Jawatankuasa Etika Penyelidikan Manusia (JEPeM) of Universiti Sains Malaysia (USM JEPeM ID: USM / JEPeM / 17050261) A prospective study with universal sampling method was carried out in the Nuclear Medicine Department, HPP from November 2016 to February 2018. The study subjects were newly diagnosed pre-treated "chemo naïve", adult DLBCL patients in the northern region of Malaysia, who were referred to HPP for therapeutic management. All patients underwent diagnostic pre-chemotherapy ^{18}F-FDG PET/CT scan and BMB within an interval of 60 days apart between the two tests. A delay period interval of more than 60 days may result in morphological histopathological changes leading to invalidity of results.[16] Patients who had received haematopoietic growth factor injections as a prophylaxis prior to receiving chemotherapy,17 in a period of less than 48 hours prior to the first ^{18}F-FDG PET/CT scan, were excluded from this study because this could result in false positive findings caused by an inflammatory reaction in the bone marrow.

^{18}F-FDG PET/CT imaging protocol

The preparation for ^{18}F-FDG PET/CT scans, for a total of 28 subjects who fulfilled the inclusion and exclusion criteria and were initially enrolled into this study, were performed as per the HPP department protocol. Subjects were advised to be fasted for 4-6 hours before the scan to limit the impact of dietary glucose to compete with the glucose analogue, i.e., ^{18}F-FDG. The patients were also instructed to avoid any strenuous exercise for few days prior to the scan in order to reduce skeletal muscle uptake of the glucose analogue. The subjects with Type 2 diabetes mellitus were carefully scheduled in the morning before taking their insulin. Whereas the subjects on oral hypoglycaemia agents, i.e., metformin were advised to withhold medication on the morning of the scan to decrease bowel background activity caused by the drug. Before injecting ^{18}F-FDG intravenously, all the subjects were ensured that their blood glucose levels were less than 11 mmol/L as indicated by the department protocol. After injection, the subjects were kept rested in a dimly lit room to allow for the uptake time. Subsequently, PET/CT scanning was conducted at approximately 60 minutes post-injection. PET/CT scans were conducted using a GE Discovery scanner (General Electric Company (GE), Boston, USA). Scans were performed from mid femur to the vertex with duration of 3 minutes per bed position. A transmission date acquisition of 40-minutes attenuation data acquisition using a built-in CT scanner was done along with 1-hour attenuation data acquisition using radioactive sources with 2D mode (in septa) collimator and 30% energy window of 511kev. Low-dose CT data was used for attenuation correction and anatomical localization of the PET images. Images were reconstructed in axial, sagittal and coronal fused PET/CT images and viewed on a dedicated PET/CT GE workstation.

Interpretation of ^{18}F-FDG PET/CT scans

The ^{18}F-FDG PET/CT scans were evaluated by two experienced nuclear medicine physicians at HPP, who were blinded to the subsequent BMB results. Both readers evaluated the images qualitatively for the presence of BMI as evidenced by radiotracer uptake in the bone marrow that was of higher intensity than the liver. They then characterised the pattern of uptake into focal (one area of discrete uptake), multifocal (presence of two or more regions of well-circumscribed uptake), diffuse (widespread regions of uptake involving the whole bone marrow), or mixed focal and diffuse uptake (Figure 1 A, B, C). In the instance that there were no bone marrow regions with radiotracer uptake higher than the

Table I: Sociodemographic factors and clinical data of the study subjects

Patient factors	Number of patients (Percentage (%))
Gender	
Male	13 (61.9)
Female	08 (38.1)
Race	
Malay	12 (57.1)
Chinese	06 (28.6)
Indian	03 (14.3)
Others	Nil
Ann Arbor Stage	
I	02 (9.5)
II	06 (28.6)
III	05 (23.8)
IV	08 (38.1)

Table II: Qualitative and quantitative 18F-FDG PET/CT results in DLBCL subjects

Num.	Quantitative		Qualitative	Type of uptake	BMB
	BM SUVmax	L SUVmax	BMI		
1	6.32	1.27	+	MF	+
2	11.23	2.16	+	MF	+
3	12.8	2.2	+	MF	+
4	4.79	2.32	+	D	-
5	4.77	2.68	+	D	-
6	2.65	2.1	+	D	-
7	3.5	2.5	+	F & D	-
8	1.09	2.02	-	N	-
9	0.94	3.5	-	N	-
10	1.31	2.21	-	N	-
11	3.11	4.11	-	N	-
12	2.28	3.09	-	N	-
13	2.26	2.47	-	N	-
14	2.01	2.7	-	N	-
15	2.37	2.5	-	N	-
16	1.69	3.02	-	N	-
17	3.48	3.72	-	N	-
18	1.85	2.74	-	N	-
19	1.37	2.03	-	N	-
20	1.7	2.1	-	N	-
21	3.4	3.8	-	N	-

*BM = Bone marrow; L = Liver; BMI = Bone marrow involvement; BMB = Bone marrow biopsy; *MF = Multifocal; D = Diffuse; F&D = Focal & diffuse; N= Negative.

Table III: Pattern of uptake on 18F-FDG PET/CT scan correlated with bone marrow biopsy

		18F-FDG PET/CT				
		Negative	Positive			
			Multifocal	Diffuse	Mixed Focal & Diffuse	Total
BMB	Negative	14	0	3	1	18
	Positive	0	3	0	0	3
	Total	14	3	3	1	21

liver, the scan was considered negative for BMI (Figure 1D). Any disagreement in the results was resolved by a third reader, a senior consultant of Nuclear Medicine, to attain a consensus on the evaluation of the presence of BMI. The readers also placed VOIs at selected marrow uptake sites to record the automated SUV_{max} for the quantitative analysis. A similar VOI was also placed at in the liver at the region of highest SUVmax avoiding vascular territories. According to the 5-point Deauville's scoring criteria which was recommended for standardization of ^{18}F-FDG PET/CT method for quantitative approach, marrow uptake positivity is considered when the SUVmax within the marrow is higher than the SUVmax of the liver.[18] Moreover, the liver can be a surrogate of arterial radiotracer uptake for SUV normalization, enabling reliable measurements of background radiotracer uptake provided that a consistent volume of interest (VOI) site is utilised to achieve standardization.[19]

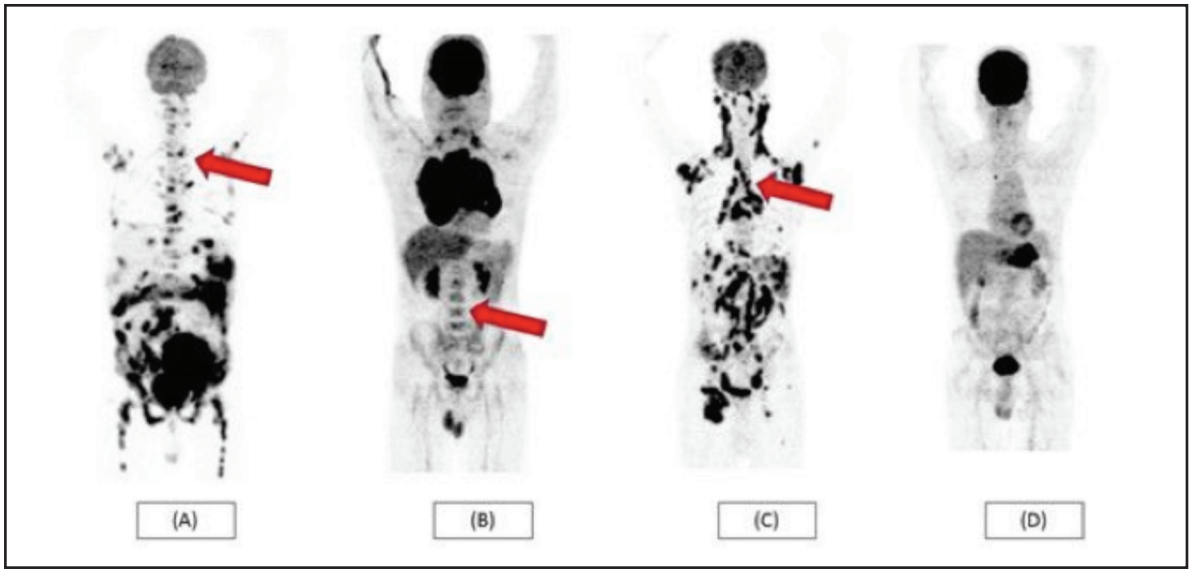

Fig. 1: Maximum Intensity Projection (MIP) images in coronal view showing various patterns of bone marrow uptake on 18F-FDG PET/CT scans. (A) Focal/multifocal uptake. (B) Diffuse uptake. (C) Mixed multifocal & diffuse uptake. (D) Negative study indicative of no bone marrow involvement.

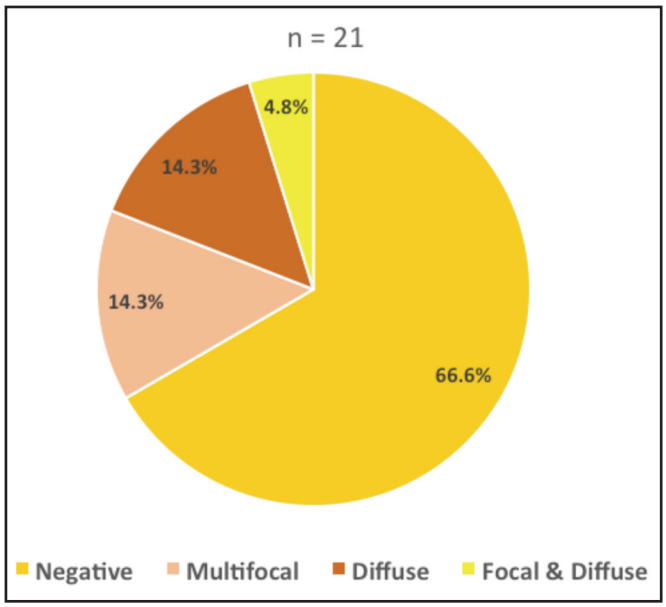

Fig. 2: Pattern of tracer uptake in ^{18}F-FDG PET/CT scans of the DLBCL subjects.

Equation 1:

SUV_{max} = Maximum tissue activity per volume of interest (millicurie/mL) / Total injected dose per body weight (millicurie)/gram)

Data analysis and statistical tests

The results of the ^{18}F-FDG PET/CT scan findings were then compared with the BMB results as the reference standard for the evaluation of BMI. Statistical analyses were performed using IBM Statistical Package for Social Science software version 24.0 for Mac (SPSS, 2016). Descriptive studies were expressed as frequency (percentage), mean ± standard deviation for normally distributed data or median (IQR) for skewed data. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy were calculated based on statistical formulas. A Cohen's kappa test was used to determine the validation and agreement between 18F-FDG PET/CT scan and BMB for BMI in DLBCL cases involving a statistical significance of $p<0.05$.

RESULTS

Subject demographics and clinical data

A total of 28 subjects who fulfilled the inclusion and exclusion criteria were initially enrolled in this study. However, only 21 subjects completed both 18F-FDG PET/CT scan and BMB within the time frame required. Thus, seven subjects had to be dropped out from this study due to the reason that the BMB and ^{18}F-FDG PET/CT scan were not conducted within a maximum period of 60 days apart. Seven subjects had to be dropped out due to the reason that BMB was not completed within the stipulated period after patients had their pre-chemotherapy ^{18}F-FDG PET-CT scan done.

The mean± standard deviation for the age of the 21 subjects was 45.6 ± 18.5 years old, ranging from 18 years old to 80 years old. Thirteen (61.9%) out of the 21 patients were males and the remaining 38.1% were females. The majority of these patients were Malays, followed by Chinese and Indians (Table I). As for the stage of disease, most of the subjects were in the category of Ann Arbour Stage IV disease (n=8, 38.1%) (Table I). There was a male preponderance for more advanced stage of DLBCL. All patients received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone chemotherapy (R-CHOP) regime.

Qualitative analysis determination of BMI

We detected radiotracer uptake that was higher than the liver uptake in seven out of 21 subjects (33.4%). The pattern of bone marrow uptake was variable among these patients; whereby three patients showed multifocal uptake, one

patient showed mixed focal and diffuse uptake, whereas another three patients showed diffuse uptake alone (Figure 2). The majority of the ^{18}F-FDG PET/CT scans were negative for BMI.

Quantitative analysis determination of BMI

Most ^{18}F-FDG PET/CT scans that were evaluated to be negative for BMI had bone marrow SUVmax of ≤ 2.0 g/mL. The commonest radiotracer uptake pattern that was positive for BMI was multifocal bone marrow uptake, which had SUV_{max} measurements of ≥ 6.0g/mL, with the highest recorded SUV_{max} uptake of 12.8 g/mL (Table II).

Diagnostic performance of 18F-FDG PET/CT scan compared to BMB

There was moderate agreement between ^{18}F-FDG PET/CT scan and BMB which showed significant concordance (kappa k-value: 0.500, p<0.008) By comparing ^{18}F-FDG PET/CT scans with BMB as the reference standard for detecting BMI, the results showed three truly positive scans and no falsely negative scans (Table III), thus giving a sensitivity of 100% (95%CI 29.2 - 100.0). There were 14 truly negative and four false positive scans (Table III), giving a specificity of 77.8% (95% CI of 52.4 - 93.6). The PPV is 42.9% (95% CI of 24.0 - 64.0) and the NPV is 100%. Therefore, the diagnostic accuracy of ^{18}F-FDG PET/CT for detecting BMI in DLBCL is 80.9% (95% CI of 58.1 - 94.6).

DISCUSSION

This study evaluated the role of ^{18}F-FDG PET/CT in determining the presence of BMI and uptake pattern in newly diagnosed DLBCL. The mean age of the subjects in this study was mid-40s, which is comparable to a study of DLBCL patients conducted in Sabah Malaysia, by Peh et al.[3]

Most of the subjects recruited in this study were in advanced Ann Arbor Stage IV disease. This is similar to another cohort study by Khan et al that had a high prevalence rate of 45% patients staged in Ann Arbor stage IV at presentation.[20] Our cohort study also showed that an advanced stage of DLBCL, i.e., Ann Arbor Stage III and IV, was more prevalent among the male gender. The higher mortality rate in the male gender compared to females, indicating that the majority of males were diagnosed at a late stage of disease has also been previously reported.[21]

On analysis of the pattern of marrow uptake on ^{18}F-FDG PET/CT scans, the commonest pattern of uptake was the multifocal type of uptake pattern (14.3%). compared to those with positive ^{18}F-FDG PET/CT scan and negative BMB study which showed 1 mixed focal and diffuse type of uptake (4.8%) and the remaining 3 (14.3%) showed only diffuse type of uptake. In the quantitative analysis, the bone marrow SUVmax for the 3 positive multifocal type of pattern of uptake in ^{18}F-FDG PET/CT scans showed a markedly high SUVmax uptake of 6.32-12.8 which is more than 70% of the mean liver SUVmax. Additionally, it has been reported that DLBCL with focal pattern of marrow uptake on ^{18}F-FDG PET/CT scans have a worse prognosis compared to the other patterns of uptake.[22] In fact Berthet et al identified that 2 of their study subjects had positive multifocal type of bone marrow uptake on the ^{18}F-FDG PET/CT scans with concordant BMB results. The subjects were then upstaged to Ann Arbor Stage IV and received intensified chemotherapy followed by autologous stem cell transplant, which improved their prognostic outcome.[1] Therefore, this may imply that multifocal type of bone marrow uptake may place these DLBCL patients in a more advanced disease stage.

There was one positive mixed focal and diffuse type detected, as well as 3 positive diffuse bone marrow uptake patterns seen on the ^{18}F-FDG PET/CT scans in this cohort study. The corresponding subjects were identified with a lower bone marrow SUVmax uptake of 2.65- 4.79 g/mL, which is less than 50% of the liver SUV_{max}. An explanation as to the reason for the diffuse uptake on ^{18}F-FDG PET/CT scans is likely due to the concurrent presence of other medical conditions such as anaemia (91.3%), elevated C-reactive protein levels (81.0%), leucocytosis (47.8%), thrombocytopenia (39.1%) and thrombocytosis (21.7%), as observed by Adams et al.[23] Furthermore, this medical manifestation is likely due to an alteration in the composition of the blood and reactive bone marrow processes besides a lymphomatous BMI.[1]

According to the Ann Arbor classification, the presence of BMI will automatically upgrade the patient to an advanced stage of the disease.[1] The subjects will then be subjected to additional more intensive treatment regimens such as doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisone (ACVBP); involved-field radiotherapy (IF-RT), or autologous stem-cell transplantation (ASCT).[8] Furthermore, as noted in this study all thee multifocal type of uptake pattern on ^{18}F-FDG PET/CT with concordant BMB results were noted to be at Ann Arbor Stage IV disease. This strongly agrees with a paper by Tilly et al which stated that a focal or multifocal pattern of uptake is usually seen in advanced stages of DLBCL disease.[8]

In this cohort study, all 14 out of 21 ^{18}F-FDG PET/CT scans were correctly assessed as negative for BMI. The average value of the liver SUV_{max} for all these negative scans was 2.5 g/mL and most patients had bone marrow SUV_{max} of ≤ 2.0 g/mL. A previous study by Chen et al revealed that there were 147 subjects that had ^{18}F-FDG PET/CT scans that were negative for BMI with concordant BMB results.[24]

Our cohort study showed a high NPV and a sensitivity of 100%, respectively. The findings from this study is in agreement with results from Berthet et al as their results reported negative BMI in ^{18}F-FDG PET/CT scans performed for 101 cases, 99 cases of which were concordant with negative BMB results, achieving a sensitivity and a NPV of 90.4% and 95.8%, respectively.[1] These results were also in line with a meta-analysis reported by Adams et al whereby the pooled sensitivity and specificity were 96.9% and 99.7%, respectively.[25]

In addition to that, our current cohort study has managed to prove a moderate agreement between our ^{18}F-FDG PET/CT scan and BMB with a significant p value of 0.008 and k-value of 0.500. Furthermore, a recent study done in 2017 by El Karak et al. had also demonstrated a weak but significant concordance between ^{18}F-FDG PET/CT scan and BMB using Receiver Operating Characteristic curve (kappa=0.391, with p=0.001).[26]

Many previous studies have recommended that BMB may be replaced by ^{18}F-FDG PET/CT in Hodgkin's lymphoma (HL).[14, 27] The low incidence rate of BMI and lack of treatment consequences in advanced HL disease makes it more permissible for BMB to be omitted in assessing for BMI provided that a pre-chemotherapy ^{18}F-FDG PET/CT scan is done.[15] In a recent study by Chen et al it is recommended that in view of BMB's unfavourable accuracy and limitation of predicting patient prognosis compared to ^{18}F-FDG PET/CT scans, the role of BMB is unnecessary in assessing BMI.[24]

Despite multiple studies done in assessing BMI with 18F-FDG PET/CT scan, the role of pre-chemotherapy ^{18}F-FDG PET/CT in assessing BMI in Malaysia has yet to be enforced in view of limited sources i.e., the limited availability of PET/CT scans, as well as the affordability and awareness of its role by primary physician teams. All lymphoma patients in Malaysia are still subjected to BMB despite many current reports recommending practitioners to be more selective in deciding which patients are suitable for BMB if the results of ^{18}F-FDG PET/CT are indeterminate. The motive of this study is to explore the complementary role of ^{18}F-FDG PET/CT as well as to collate the sensitivity and specificity between ^{18}F-FDG PET/CT scan and BMB in assessing BMI, specifically in DLBCL.

One of the limitations of our study is the relatively small sample size. Thus, we recommend a longer duration for patient recruitment to obtain larger datasets. The second limitation is the lack of follow-up scans, which can be rectified by conducting a future longitudinal study. Thirdly, no medical data regarding the anaemic status of our patients was included. Moreover, it is a challenge to diagnose BMI in anaemic patients considering that the SUVmax is not a reliable indicator of BMI in this group of patients. Additionally, when these patients have a diffuse pattern of ^{18}F-FDG uptake as opposed to focal, it gives rise to equivocal diagnostic accuracy. In the instance of a relatively lower BM SUVmax with diffuse pattern of uptake, a BMB becomes mandatory to exclude BMI. This will then allow for the assessment of progression free survival and overall survival of DLBCL patients in the northern region of Malaysia. Multicentre studies need to be considered, by including patients from all regions in Malaysia, which can truly represent the whole population in this country and reflect a more accurate clinical scenario.

In view of achieving a strong NPV and excellent sensitivity of ^{18}F-FDG PET/CT in excluding or detecting BMI respectively, we recommend that a negative bone marrow infiltration finding on an ^{18}F-FDG PET/CT scan should be able to preclude the need for BMB. However, in discordant histology i.e., aggressive tumour, the role of BMB may be crucial to be performed with the role of ^{18}F-FDG PET/CT being complementary.

CONCLUSION

^{18}F-FDG PET/CT is excellent for excluding the presence of BMI in DLBCL. A negative ^{18}F-FDG PET/CT scan for BMI can preclude the need for BMB in certain cases. Although ^{18}F-FDG PET/CT can accurately detect BMI in multifocal pattern of BM infiltration, it cannot fully replace BMB, which is considered as the gold standard for evaluating BMI in DLBCL.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1. Berthet L, Cochet A, Kanoun S, Berriolo-Riedinger A, Humbert O, Toubeau M, et al. In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. J Nucl Med 2013; 54(8): 1244-50.
2. Chang K, Lau N, Chew L, Tan S, Jameela S, Puru V. Incidence and Outcome of T-Cell Lymphomas in Malaysia. Blood 2006; 108(11): 4684.
3. Peh S, Shaminie J, Jayasurya P, Hiew J. Spectrum of malignant lymphoma in Queen Elizabeth Hospital, Sabah. Med J Malaysia 2003; 58(4): 546-55.
4. Hoefnagel J, Dijkman R, Basso K, Jansen P, Hallermann C, Willemze R et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood 2005; 105(9): 3671-8.
5. Johnson SA, Kumar A, Matasar MJ, Schöder H, Rademaker J. Imaging for Staging and Response Assessment in Lymphoma. Radiology 2015; 276(2): 323-38.
6. Ali AE, Morgen EK, Geddie WR, Boerner SL, Massey C, Bailey DJ, et al. Classifying B-cell non-Hodgkin lymphoma by using MIB-1 proliferative index in fine-needle aspirates. Cancer Cytopathol 2010; 118(3): 166-72.
7. Tilly H, Vitolo U, Walewski J, da Silva MG, Shpilberg O, André M, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 Suppl 7: vii78-82.
8. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26: v116-v25.
9. Alzahrani M, El-Galaly TC, Hutchings M, Hansen JW, Loft A, Johnsen HE, et al. The value of routine bone marrow biopsy in patients with diffuse large B-cell lymphoma staged with PET/CT: a Danish-Canadian study. Ann Oncol 2016; 27(6): 1095-9.
10. Farwell MD, Pryma DA, Mankoff DA. PET/CT imaging in cancer: Current applications and future directions. Cancer 2014; 120(22): 3433-45.
11. Adams HJ, De Klerk JM, Fijnheer R, Heggelman BG, Dubois SV, Nievelstein RA, et al. Bone marrow biopsy in diffuse large B-cell lymphoma: useful or redundant test? Acta Oncol 2015; 54(1): 67-72.

12. Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nuc Med Mol Im 2010; 37(1): 181-200.
13. Alzahrani M, El-Galaly TC, Hutchings M, Hansen JW, Loft A, Johnsen HE, et al. The value of routine bone marrow biopsy in patients with diffuse large B-cell lymphoma staged with PET/CT: a Danish-Canadian study. Ann Oncol 2016; 27(6): 1095-9.
14. Vishnu P, Wingerson A, Lee M, Mandelson MT, Aboulafia DM. Utility of Bone Marrow Biopsy and Aspirate for Staging of Diffuse Large B Cell Lymphoma in the Era of Positron Emission Tomography With 2-Deoxy-2-[Fluorine-18]fluoro-deoxyglucose Integrated With Computed Tomography. Clin Lymphoma Myeloma Leuk 2017; 17(10): 631-6.
15. El-Galaly TC, Hutchings M, Mylam KJ, Brown Pde N, Bukh A, Johnsen HE, et al. Impact of 18F-fluorodeoxyglucose positron emission tomography/computed tomography staging in newly diagnosed classical Hodgkin lymphoma: fewer cases with stage I disease and more with skeletal involvement. Leuk Lymphoma 2014; 55(10): 2349-55.
16. Dupas B, Augeul-Meunier K, Frampas E, Bodet-Milin C, Gastinne T, Le Gouill S. Staging and monitoring in the treatment of lymphomas. Diagn interv Imaging 2013; 94(2): 145-57.
17. Demetri GD. Hematopoietic growth factors. Defining the appropriate clinical role in multimodality cancer therapy. Chest 1995;107(6 Suppl):255s-60s.
18. Hasenclever D, Kurch L, Mauz-Körholz C, Elsner A, Georgi T, Wallace H, et al. qPET – a quantitative extension of the Deauville scale to assess response in interim FDG-PET scans in lymphoma. Eur J Nuc Med Mol Imaging 2014; 41(7): 1301-8.
19. Azmi NHM, Suppiah S, Liong CW, Noor NM, Said SM, Hanafi MH, et al. Reliability of standardized uptake value normalized to lean body mass using the liver as a reference organ, in contrast-enhanced 18F-FDG PET/CT imaging. Radiat Phys Chem 2018; 147: 35-9.
20. Khan AB, Barrington SF, Mikhaeel NG, Hunt AA, Cameron L, Morris T, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood 2013; 122(1): 61-7.
21. Nair R, Arora N, Mallath MK. Epidemiology of Non-Hodgkin's Lymphoma in India. Oncology 2016; 91(suppl 1)(Suppl. 1): 18-25.
22. Lee JW, Lee SC, Kim HJ, Lee SM. Prognostic value of bone marrow (18)F-FDG uptake on PET/CT in lymphoma patients with negative bone marrow involvement. Hell J Nucl Med 2017; 20(1): 17-25.
23. Adams HJA, Kwee TC, Fijnheer R, Dubois SV, Nievelstein RAJ, de Klerk JMH. Diffusely increased bone marrow FDG uptake in recently untreated lymphoma: incidence and relevance. Eur J Haematol 2015; 95(1): 83-9.
24. Chen Y, Zhou M, Liu J, Huang G. Prognostic Value of Bone Marrow FDG Uptake Pattern of PET/CT in Newly Diagnosed Diffuse Large B-cell Lymphoma. J Cancer 2018; 9(7): 1231-8.
25. Adams H, Kwee T, De Keizer B, Fijnheer R, de Klerk J, Littooij A, et al. Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary? Ann Oncol 2014; 25(5): 921-7.
26. El Karak F, Bou-Orm IR, Ghosn M, Kattan J, Farhat F, Ibrahim T, et al. PET/CT Scanner and Bone Marrow Biopsy in Detection of Bone Marrow Involvement in Diffuse Large B-Cell Lymphoma. PloS One 2017; 12(1): e0170299.
27. Elamir Y, Elazab M, Owis AS, Elsayed HF. PET/CT and bone marrow biopsy (BMB) in evaluating bone marrow in lymphoma. Egypt J Radiol Nucl Med 2020; 51(1): 201.