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**Use of FDG PET/CT in identification of bone marrow
involvement in diffuse large B cell lymphoma and follicular
lymphoma: comparison with iliac crest bone marrow biopsy**

Abstract

Background: Non-Hodgkin's lymphoma (NHL) accounts for around 4% of new cancer cases annually. Bone marrow involvement is important for staging and management. FDG PET/CT is used increasingly to identify this, in addition to bone marrow biopsy (BMB), which is seen as 'gold' reference standard.

Purpose: To compare determination of bone marrow involvement by FDG PET/CT against BMB in Diffuse Large B-cell Lymphoma (DLBCL) and Follicular Lymphoma (FL).

Material and Methods: This was a retrospective study of patients with histologically confirmed NHL at a single UK cancer center undergoing pre-treatment FDG PET/CT and BMB between June 2010 and February 2013. Information was collected from patient notes, cancer registry, histological and imaging reports. Diagnostic accuracy of FDG PET/CT was determined, compared to BMB as the reference standard.

Results: Twenty-four patients with DLBCL and 12 with FL were included. Five DLBCL patients had bone marrow involvement on PET/CT; all were confirmed on BMB. Three FL patients had marrow involvement on PET/CT but not on BMB; one FL patient had positive BMB but negative PET/CT. Using BMB as the reference standard, the sensitivity and specificity of FDG PET/CT for detecting bone marrow involvement in DLBCL were 100% and 100%, respectively, and in FL were 0% and 72.7%, respectively.

Conclusion: FDG PET/CT is accurate for detection of bone marrow involvement in newly diagnosed DLBCL, but not FL. In DLBCL, positive FDG PET/CT may negate the need for routine BMB, although BMB in addition or combination may be appropriate if this would influence management or prognosis.

Keywords: Diffuse large B-cell lymphoma; Follicular lymphoma; Bone marrow examination; Lymphoma, Non-Hodgkin/radionuclide imaging; Positron-Emission Tomography;

Introduction

Non-Hodgkin Lymphoma (NHL) is a common malignancy in the developed world, accounting for around 4% of new cancers annually (1). NHL is subtyped, with indolent and aggressive forms. Identifying bone marrow involvement is essential as it affects staging and clinical management (2). Bone marrow biopsy (BMB) is well-established and seen as gold standard for this. However, it is invasive, may have adverse events, can be distressing for patients (3), and may miss marrow involvement if infiltration is patchy (4). 2-Deoxy-2-[¹⁸F] fluoro-D-glucose positron emission tomography/computed tomography (FDG PET/CT) is used increasingly in lymphoma for staging prognostication, performing favorably compared to other imaging modalities (5). A meta-analysis of detection of bone marrow involvement in Diffuse Large B-cell Lymphoma (DLBCL) with FDG PET/CT versus BMB found that the former exhibited a high specificity (6). The European Society for Medical Oncology guidelines have recently been updated to reflect the growing evidence (7), however, it remains controversial (8). Other studies have shown that the sensitivity and specificity of FDG PET/CT is lower in other – particularly indolent – subtypes (9).

This study compares determination of bone marrow involvement by FDG PET/CT against BMB in one high-grade and one low-grade NHL subtype: DLBCL and Follicular Lymphoma (FL), respectively.

Material and Methods

This was a retrospective study of patients with histologically confirmed NHL at a single UK cancer center, who had had baseline (pre-treatment/staging) FDG PET/CT and BMB between June 2010 and February 2013. This also identified additional patients who underwent pre-treatment investigations in 2008-2009.

Information was collected from patient notes and the local Cancer Register, plus histological and imaging reports. Characteristics including disease stage (Ann Arbor classification (10)), age, sex, and days between PET/CT and BMB were recorded.

Patients with Hodgkin's Lymphoma (HL) were excluded, due to different biological and pathophysiological characteristics to NHL. NHL types with fewer than 15 patients were excluded due to small sample size. Patients with relapsed disease were excluded, due to different biological/pathological behavior. Patients were excluded if PET/CT or BMB results were inconclusive, non-diagnostic, or showed an alternative pathological process (Fig. 1).

All PET/CT scans were carried out at a single site. The FDG dose administered per PET/CT was 400 MBq, as per Administration of Radioactive Substances Advisory Committee (ARSAC) guidance. Time between FDG administration and scanning, as per local protocol, was approximately 60 minutes. All scans were dual-reported by Consultants in Nuclear Medicine/Radionuclide Imaging. Bone marrow FDG avidity was assessed visually, as staging of FDG-avid lymphomas is recommended to be done by visual assessment, with PET-CT images scaled to a fixed SUV display and color table. Focal uptake in HL and aggressive NHL is sensitive for bone marrow involvement (11). PET/CT was reported as positive where focal or multifocal bone marrow or bony uptake was identified at any anatomical location.

Bone marrow trephines were carried out at a single hospital. Biopsies were taken from a unilateral iliac crest. Samples were analyzed by Consultants in Histopathology.

All patients gave written consent for their anonymized nuclear imaging to be used for research and teaching purposes. According to the Medical Research Council Health Research Authority tool (<http://www.hra-decisiontools.org.uk/research/>), our study falls

under clinical audit/service evaluation and is therefore not considered research requiring NHS approval.

Cases were classed as either PET/CT positive or negative for bone marrow involvement (11), and BMB positive or negative for bone marrow involvement. Results were compared to calculate sensitivity, specificity, positive and negative predictive values for PET/CT in predicting bone marrow involvement in DLBCL and FL, using BMB as the reference standard. 95% confidence intervals were calculated by statistical software (www.medcalc.org), using the Clopper-Pearson interval method.

Results

In total 567 PET/CT scans were retrieved from 242 patients with Lymphoma, of which 187 were NHL (Table 1). DLBCL and FL were the commonest subtypes, consistent with population prevalence. For this reason, we assessed PET/CT in DLBCL and FL, and excluded other subtypes with very small numbers (fewer than 15 patients). Some patients with DLBCL and FL lacked baseline PET/CT and/or BMB, due to the urgent need for treatment at time of diagnosis; these patients were excluded due to lack of baseline investigations.

In the DLBCL group 40 patients out of 92 had a baseline scan. Of these, 27 had a baseline BMB. One patient was excluded as BMB was reported as suspicious but non-diagnostic, and 2 patients were excluded as PET/CT scans identified direct bone invasion, but no marrow involvement (Fig. 1). In these excluded patients, one had DLBCL of the orbit with direct invasion of the adjacent bone (iliac crest BMB was negative); the other had direct infiltration of the femoral neck by DLBCL, but PET/CT did not identify any areas of bone involvement

aside from this hip (bone biopsy from the femur at the FDG-avid site was positive; iliac crest biopsy was not done).

In the FL group 19 patients out of 34 had a baseline scan. Of these, 13 had a baseline BMB. One patient was excluded (Fig. 1) as PET/CT was reported as showing probable stage I disease, but with low-grade focal uptake of uncertain significance in a well-circumscribed sclerotic lesion in the left posterior ilium. Iliac crest BMB in this case was negative. Inconclusive scans were reviewed by the study investigators before exclusion.

Finally, 24 patients with DLBCL and 12 patients with FL were included. Patient characteristics are shown in Table 2.

Five DLBCL patients (20.8%) had bone marrow involvement on BMB and PET/CT, and 19 (79.2%) had no marrow involvement on both modalities. PET/CT and BMB results did not differ in any cases (Table 3). All cases of DLBCL in which bone marrow uptake was reported on PET/CT involved focal FDG uptake by the marrow (Fig. 2), except one case which showed multifocal uptake in the bones (Fig. 3).

One FL patient (8.3%) had bone marrow involvement on BMB but not PET/CT; 3 patients (25.0%) had bone marrow involvement on PET/CT but not BMB; 8 patients (66.7%) had negative BMB and PET/CT (Table 4). The three positive PET/CT scans were all reported as Stage IV disease with at least one focus of FDG uptake in the bone marrow. In all three cases, unilateral iliac crest BMB was negative, showing “no morphological (examined at multiple levels) or immunohistochemical (CD3 and CD20) evidence of lymphomatous infiltration” with no alternative pathologies demonstrated. An example of a positive PET/CT in FL is shown in Fig. 4.

Using BMB as the reference standard, PET/CT had sensitivity and specificity of 100% (95% CI 47.8-100%) and 100% (95% CI 82.4-100%), respectively, in detecting bone marrow involvement in DLBCL. Positive predictive and negative predictive values in DLBCL were 100% (95% CI 47.8-100%) and 100% (95% CI 82.4-100%), respectively.

In FL, PET/CT had sensitivity and specificity of 0% (95% CI 0-97.5%) and 72.7% (95% CI 39.0-94.0%), respectively, compared to BMB. Positive predictive and negative predictive values in FL were 0% (95% CI 0-70.8%) and 88.9% (95% CI 51.8-99.7%), respectively.

Discussion

This retrospective study demonstrates excellent accuracy of FDG PET/CT in detection of bone marrow involvement in patients with newly diagnosed DLBCL but poor accuracy in this context in FL when using BMB as the reference standard. Bone marrow involvement in NHL is clinically relevant, as it indicates stage IV disease (Ann Arbor staging classification (10)), and contributes to revised International Prognostic Index (IPI) score (12), both of which have prognostic implications.

Our results suggest that PET/CT is at least as accurate as BMB for detection of bone marrow involvement in DLBCL. Our findings support those of a recent meta-analysis of seven studies, which demonstrated a pooled sensitivity and specificity of FDG PET/CT of 88.7% and 99.8%, respectively, in newly diagnosed DLBCL (6). Individual studies have found sensitivity of PET/CT in this setting of 70.7%-95.8%, with specificity of 99.0-100% (Table 5) (4,13-17).

The meta-analysis by Adams et al. (6) discussed the issue of reporting diffuse bone marrow uptake on PET/CT, as diffuse uptake is more likely to be due to an alternative process. They

reported that of 14 patients (across 4 studies) with diffuse bone marrow uptake on PET/CT, BMB was positive in 12. However, in our study, all DLBCL patients with positive BMB had focal (or, in one case, multifocal) uptake on PET/CT. Low grade homogeneous diffuse bone marrow uptake could suggest a reactive pattern, and was double reported by two experienced PET-CT clinicians as negative PET/CT in our study; in all these cases, BMB was negative.

BMB assesses only a small sample of bone marrow, and is prone to false negative results (18). BMB is an invasive, potentially painful procedure, with complications in up to 0.07% of procedures (3), including hemorrhage, collapse, anaphylaxis, fracture at the biopsy site (3), and seeding of lymphoma cells into soft tissue (19). Histological analysis is time consuming and may delay diagnosis. FDG PET/CT, on the other hand, is readily available, non-invasive, with few complications, and images can be reported promptly. Our results suggest that routine BMB for all NHL patients is unnecessary in cases of negative PET/CT in DLBCL, as BM involvement may be ruled out.

Adams et al. (20) determined the additional value of staging BMB of patients with newly diagnosed DLBCL. BMB results changed IPI score in 8% of patients, but this did not alter management. They concluded that BMB could be omitted in routine staging of DLBCL (20). Other studies have shown that FDG PET/CT identification of bone marrow involvement led to upstaging to stage IV in almost one in ten patients (4,13,21), and to a change in treatment for 36-71% of those upstaged (13,21), whereas BMB did not upstage any cases to stage IV (13). Furthermore, detection of bone marrow involvement on PET/CT has been shown to be of use in predicting overall survival (OS) and progression-free survival (PFS) (4,13,15,22), with IPI score and bone marrow findings on PET-CT being independently predictive of PFS on multivariate analysis (4). In a large multi-center study, patients with bone marrow involvement on both BMB and PET/CT had poorer prognosis, whilst there was no significant difference in survival for those with BM involvement on a single modality, suggesting a role

for combined diagnostics (22).

Evidence for use of FDG PET/CT in follicular lymphoma (FL) is less definitive. There is a relative scarcity of evidence compared to DLBCL, reflecting the more widespread use of PET/CT in DLBCL than FL. PET/CT is more accurate in FL than conventional imaging, detecting up to 51% more nodal disease and 89% more extra-nodal lesions (23), and post-treatment PET/CT negativity may predict increased survival (23). Most studies have included patients with mixed lymphoma subtypes, or mixed subtypes of indolent lymphoma, but few have studied FL only. In a meta-analysis by Pakos et al. (2) of a pooled heterogeneous group of aggressive and indolent lymphomas, sensitivity of PET/CT was significantly greater in detecting bone marrow involvement in aggressive lymphoma types (including DLBCL) compared to indolent types (including FL) (76.2% vs. 30.2%; $p < 0.001$) (2).

Quantitative analysis of PET/CT in FL is not done in routine clinical practice, and so did not form part of our (retrospective) analysis. However, some studies have shown that this may improve diagnostic accuracy (24,25).

Patterns of marrow involvement may explain the differing detection accuracy of bone marrow involvement in FL compared to aggressive lymphomas. FL shows a predominantly paratrabeular pattern in 76-90% of cases (26,27), whereas in more aggressive lymphomas such as DLBCL, diffuse and nodular patterns are more frequent (26).

In our study, all three FL cases with positive PET/CT had negative BMB (i.e. PET/CT was 'falsely positive' if using BMB as the reference standard). These BM trephine biopsies were taken from a standard biopsy site (iliac crest), which in all three of these patients was PET negative. If PET/CT did not demonstrate uptake at the iliac crest, then BMB from this site

(as is standard) would not yield a positive result. In these three cases, BM biopsies were not taken from BM positive sites on PET/CT and it is therefore not known if those sites were true positive disease. It's possible to hypothesize that due to a patchy BM involvement the iliac site was not involved but sites other than this were, and therefore BMB at a unilateral iliac crest missed it. In view of this, we reviewed the subsequent follow-up post-treatment imaging of these three patients, that had taken place after treatment. Two of the three had had post-treatment follow-up PET/CT. In both cases this demonstrated complete metabolic response *including* sites of bone and lymph node uptake identified on their staging scans, and indicating that they had bone disease, which resolved after their treatment. This in turn suggests that they did have bone marrow disease that was correctly identified on staging PET/CT, but BMB was not taken from the site of uptake and was therefore negative and discrepant to the PET/CT result. In the third case, only follow-up CT was done, which also demonstrated complete response with no CT bony lesions, whilst the original unenhanced CT component of the PET/CT was suggestive of involvement of the right scapula, again disease outside of the biopsied iliac crest.

Overall in FL, the evidence in favor of PET/CT in detection of bone marrow involvement is scarce and further larger prospective studies are required. In patients with FL, PET/CT could be used to guide biopsy from a PET-positive site, if amenable to biopsy.

This study has several limitations, notably the small sample size, particularly in the smaller FL group. However, the results within the DLBCL group are likely significant, particularly considering other studies echoing this. This study used BMB as the reference standard, which itself can be falsely positive or negative. Bone marrow disease may regress at follow-up post-treatment, so follow-up PET/CT as an alternative reference standard would be

unhelpful in determining true positivity or negativity of initial PET/CT. BMB alone has been used as the reference standard in other studies (28,29).

All biopsies in our cases were taken from a unilateral iliac crest, whereas PET/CT positivity/negativity was reported based on whole body appearances. Clearly, PET/CT detection of BM involvement at a site other than that sampled by BMB is unlikely to correspond with a positive BMB result at the iliac crest, and this limits comparison of the two modalities. A 'true 'gold standard' for detection of BM involvement does not exist and BMB was chosen as the reference standard because it is commonly used to search for bone marrow involvement in lymphoma, and our results are therefore readily applicable in clinical practice. This may be a benefit of PET/CT use in DLBCL, as it is able to assess the whole body bone marrow, rather than a single anatomical location (iliac crest): Adams et al. showed that although BMB may detect some cases of bone marrow involvement that PET/CT misses (3.1%), in many more cases (12.5%), PET/CT detects bone marrow involvement missed by BMB (6). This is, however, less definitive in FL, as discussed earlier.

All scans used in this study were dual reported by two Consultants in Nuclear Medicine and/or Radionuclide Imaging, in order to reduce the risk of interpreter-dependent discrepancies. In addition, there is difficulty in translation of a complex prose imaging report to a binary outcome (positive or negative PET/CT) for analysis. However, this is reflective of clinical practice, in which treatment decisions are based upon the same multifaceted imaging reports. In clinical practice, if PET/CT results were equivocal or not diagnostic for BM involvement, further investigations may be suggested or undertaken.

Recently updated guidance from the European Society for Medical Oncology (ESMO) on diagnosis and staging of DLBCL states that BMB is still required in cases of negative PET/CT but can be omitted where the scan is positive (7). ESMO recommends that BMB is

carried out in all cases of FL (30). By contrast, National Comprehensive Cancer Network (NCCN) guidance still denotes BMB in both diseases as “essential” (31). This study supports the new ESMO guidelines for DLBCL, while disputing NCCN.

In conclusion, FDG PET/CT is highly accurate for detection of bone marrow involvement in patients with newly diagnosed Diffuse Large B-cell Lymphoma when compared with bone marrow biopsy. In cases of DLBCL where PET-CT shows clear *positive* evidence of bone or bone marrow involvement indicating advanced stage IV disease, routine BMB may be omitted. This does remain a clinical decision, to be made on a case-by-case basis, and BMB may be appropriate in combination with PET/CT if the lymphoma multidisciplinary team considers that this would influence therapeutic management or prognosis. However, there is not sufficient evidence that *negative* PET/CT can safely exclude the need for BMB. In FL, prospective studies are needed to determine a role for PET/CT in identification of bone marrow involvement, and PET/CT could be used in FL to guide biopsy from a PET-positive site.

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Tables

Table 1. Patients that underwent PET/CT scanning for NHL in 2010-2013 divided by NHL subtype

Non-Hodgkin Lymphoma type	Number of patients
Diffuse Large B-cell Lymphoma	92
Follicular Lymphoma	34
Uncertain histology	13
Mantle Cell Lymphoma	11
Marginal Zone Lymphoma	7
T-cell Lymphoma	6
Angio-immunoblastic T-cell Lymphoma	6
Low grade B-cell Lymphoma	6
Plasmablastic Lymphoma	4
Primary Mediastinal Lymphoma	3
Intravascular Large B-cell Lymphoma	2
Chronic Lymphocytic Leukaemia	2
Castleman Disease	1
Total	187

Table 2. Baseline characteristics of patients included in the study

		Diffuse Large B-cell Lymphoma	Follicular Lymphoma
Age	Range	20-79	33-71
	Mean	53.1	56.6
	Median	58.0	59.0
Sex	Male	16	4
	Female	8	8
Time of PET/CT to BM trephine (days)	Range	0-104	1-19
	Mean	12.2	7.9
	Median	6.0	5.5
Stage (Ann Arbor classification)	I	4	2
	II	7	2
	III	7	5
	IV	6	3

Table 3. Patients with DLBCL assessed as positive or negative for bone marrow involvement by BMB and PET/CT

DLBCL	PET/CT negative	PET/CT positive	TOTAL
BMB positive	0	5	5
BMB negative	19	0	19
TOTAL	19	5	24

Table 4. Patients with FL assessed as positive or negative for bone marrow involvement by BMB and PET/CT

FL	PET/CT negative	PET/CT positive	TOTAL
BMB positive	1	0	1
BMB negative	8	3	11
TOTAL	9	3	12

Table 5: Sensitivity and specificity of PET/CT in detection of bone marrow involvement in DLBCL in previous studies. CI: 95% confidence interval. Obs: observational. Pros: prospective. Retros: retrospective.

Study (reference)	Teagle et al (present study results)	Berthet et al 2013 (4)	Adams et al 2014 (6)	Khan et al 2013 (12)	Cortes-Romera et al 2014 (13)	Hong et al 2012 (14)	Pelosi et al 2011 (15)	Ribrag et al 2008 (16)
Design	Obs, retros	Obs, retros	Meta-analysis	Obs, retros	Obs	Obs, retros	Obs	Obs, pros
Sensitivity (95% CI)	100% (47.8-100%)	93.9 (79.8-99.3)	88.7 (82.5-93.3)	94.3 (80.8-99.3)	95.8 (78.9-99.9)	70.8 (48.9-87.4)	84.0 (63.9-95.5)	88.9 (51.8-99.7)
Specificity (95% CI)	100% (82.4-100%)	99.0 (94.6-100)	99.8 (98.8-100)	100 (96.2-100)	100 (93.9-100)	100 (94.5-100)	100 (96.2-100)	100 (89.7-100)

Figure legends

Fig. 1. Flow diagram showing the patient selection process. Only pre-treatment (staging) investigations were included. Patients with Hodgkin's Lymphoma (HL) and those with relapsed disease were excluded, due to different biological and pathophysiological characteristics. NHL types with fewer than 15 patients were excluded due to small sample size. (HL: Hodgkin's lymphoma; NHL: Non-Hodgkin lymphoma; DLBCL: diffuse large B cell lymphoma; FL: follicular lymphoma).

Fig. 2. PET-CT in patient with DLBCL showing focal uptake within the left hemi-pelvis. Bone marrow biopsy in this patient was positive.

Fig. 3. PET-CT in patient with DLBCL, showing widespread FDG-avid disease, including multifocal inhomogeneous uptake within the axial and appendicular skeleton.

Fig. 4. PET-CT in patient with follicular lymphoma showing focal uptake in T7 vertebra, L2-L5 vertebrae, left iliac wing, and left sacroiliac joint.