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18F-Fluorodeoxyglucose Positron Emission Tomography Versus Bone Marrow Biopsy for the Evaluation of Bone Marrow Infiltration in Newly Diagnosed Lymphoma Patients

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ABSTRACT

Background: Bone marrow evaluation (BME) is crucial for establishing an accurate staging and prognosis in lymphoma patients. **Objective:** The objective of the study was to study the diagnostic performance of 18F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) against bone marrow biopsy (BMB) for BME. **Methods:** Five hundred patient files of newly diagnosed lymphoma patients treated at an academic medical center were reviewed for BME at diagnosis by BMB and FDG PET-CT. Diagnostic performance of FDG PET-CT for detecting bone marrow infiltration (BMI) was assessed, as well as clinical predictors for positive BMB and positive FDG PET-CT. **Results:** BMB was positive in 16.3% of all patients, and 28.7% had a positive FDG PET-CT for BMI. Overall, the sensitivity of FDG PET-CT was 74.1% and specificity 80.1%. As for predictors for BMB and FDG PET-CT positivity, B symptoms and thrombocytopenia were independent factors for BMI. Seventy-four patients had discordant results between BMB and FDG PET-CT, non-Hodgkin lymphoma (NHL) having the most significant discordance. This discrepancy did not affect treatment. **Conclusions:** FDG PET-CT shows excellent performance for the detection of BMI in Hodgkin lymphoma. For diffuse large B-cell lymphoma, we recommend performing BMB and FDG PET-CT as complementary tests. In all other NHL, a unilateral BMB is mandatory at diagnosis. (REV INVEST CLIN. 2021;73(2):79-86)

Key words: Bone marrow infiltration. Bone marrow biopsy. 18F-Fluorodeoxyglucose. Positron Emission Tomography. Lymphoma.

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INTRODUCTION

Accurate staging is essential for establishing the prognosis and management of patients with Hodgkin lymphoma (HL) and non-HL (NHL) as the presence of advanced disease, including involvement of an extralymphatic site like the bone marrow, is associated with inferior outcomes[1].

18F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) has excellent diagnostic performance for evaluating bone marrow infiltration (BMI) in patients with lymphoma. Still, it is expensive and not always available at low and middle-income health-care facilities[2]. Single bone marrow biopsy (BMB) is a more accessible test and has been the standard to identify lymphomatous BMI[3]. Unfortunately, it is an unpleasant procedure for the patient and can be limited by technical constraints. This single-center retrospective cohort study aimed to evaluate the diagnostic performance of FDG PET-CT in the detection of BMI among lymphoma patients, comparing it with BMB as the gold standard. Furthermore, we assessed for discordant results between both studies, along with its effect on patient treatment.

MATERIALS AND METHODS

For this single-center, retrospective study, newly diagnosed lymphoma patients evaluated at an academic medical center between July 2017 and December 2018 were identified from our institutional lymphoma database. Five hundred files were reviewed. The following parameters were analyzed: gender, age, type of lymphoma (according to the 2016 World Health Organization classification of hematopoietic and lymphoid tumors), lactate dehydrogenase (LDH), presence of cytopenias (hemoglobin <12 g/dl, <150,000 platelets/mm^3, <1500 neutrophils/mm^3), B symptoms (body temperature above 38°C, drenching night sweats or weight loss of 10% or more in the past 6 months), stage of disease (according to the Ann Arbor classification), results of BMB and FDG PET-CT, as well as treatment.

This study was approved by the Institutional Review Board at the National Cancer Institute, Mexico (REV 003/19), and carried out under good clinical practices and local and legal requirements.

ELIGIBILITY CRITERIA

Eligible patients were men and women 16 years of age and older, with a recent diagnosis of lymphoma (HL or NHL), with both FDG PET-CT and BMB performed and adequately reported at the institutional electronic health record. Patients who were not treatment-naive, those without an adequate report of both studies and patients without a diagnostic BMB were excluded from the analysis.

Evaluation of bone marrow infiltration

BMB was unilaterally performed, at the posterior iliac crest, with an appropriate bone needle (Jamshidi) to get a bone sample of 15-20 mm long. The specimen was set through fixation with 10% neutral buffered formalin. After that, it went through a decalcification process with formic acid, and finally, it was included in paraffin. Immunohistochemical analysis, according to histological characteristics, was performed and reported by an expert hematopathologist.

A positive BMB for marrow infiltration was defined as a lymphocytic infiltrate with either a nodular, interstitial, centrally located or diffuse pattern (depending on the type of lymphoma) and the respective immunohistochemistry with a panel of antibodies based on morphological findings.

A Biograph 16 PET-CT scanner was employed (Siemens, Erlangen, Germany). Patients fasted for at least 6 h to ensure a serum glucose level below 100 mg/d. Whole-body CT was performed 50-70 min after the IV injection of a ponderal dose of 5.5 MBq/kg (150 μCi/kg) of 18F-FDG. Transmission data were acquired using low-dose CT (120 kV, automated from 100 to 130 mA, a 512 × 512 matrix, a 50-cm field of view (FOV), 3.75-mm slice thickness, and a rotation time of 0.8 s), extending from the base of the skull to the proximal thighs. Immediately after CT acquisition, a whole-body PET was acquired in three dimensional (matrix 168 × 168). For each bed position (16.2 cm, overlapping scale 4.2 cm), we used 3-min acquisition time with a 15.5-cm FOV. The emission data were corrected for randoms, scatter, and

decay. Reconstruction was conducted with an ordered subset expectation maximization algorithm with three iterations/12 subsets and Gauss-filtered to a transaxial resolution of 6 mm at full-width at half-maximum. Attenuation correction was performed using the low-dose non-enhanced CT.

A workstation (Multimodality Workplace, Siemens) providing multi-planar reformatted images was also used for image display and analysis. The MTV and the SUVmax, of whole-body tumors, were measured with the isocontour tool of the TrueD Syngo software (Siemens, Erlangen, Germany) with manual adjustment. A positive FDG PET-CT for bone marrow infiltration was defined as increased focal 18F-FDG uptake in the bone marrow, given that diffuse uptake is considered non-specific. As the BMB is currently the gold standard for evaluating lymphomatous BMI, a positive FDG PET-CT with a negative BMB was deemed to be false positive. A negative FDG PET-CT, with a positive BMB, was defined as a false negative.

Statistical analysis

Fisher's exact and Pearson Chi-square tests were used to compare categorical variables. Comparisons of continuous variables were made using the Mann-Whitney U test. Results are expressed as median and interquartile ranges when numeric, or frequency and percent when categoric. Setting the BMB as the gold standard, the diagnostic performance of FDG PET-CT for detecting BMI was evaluated. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (LR) with 95% exact binomial confidence intervals were calculated for all cases (global), and the most common histological subtypes as subgroups. Confidence intervals (CI) for diagnostic LRs were calculated using a logarithmic transformation and the delta method (asymptotic distribution theory). A logistic regression model was used for univariate and multivariate analysis of predictors for positive BMB and positive FDG PET-CT for BMI.

For all analyses, $p < 0.05$ was considered statistically significant. All data were analyzed using the free software "R" (The R Foundation, version 3.1.1).

RESULTS

Patient characteristics

A total of 500 patients with lymphoma were retrieved from the database. We excluded 98 patients without a BMB and 36 patients without an FDG PET-CT performed. Furthermore, we excluded 11 patients with a non-diagnostic BMB. Only 355 patients met the inclusion criteria and were included for the analysis.

The most common histologic type was diffuse large B-cell lymphoma (DLBCL) in 43.4% of cases, followed by classical HL in 16.1%, and follicular lymphoma (FL) in 13.2% [Table S1 (supplementary material)]. The median age at diagnosis was 54 years, and 56.3% were male. B symptoms were present in 60.3% of cases, and 73% debuted with an advanced stage of disease according to the Ann Arbor classification (stages III and IV). Regarding laboratory values: 44.1% presented with anemia, 2.8% neutropenia, 6.2% thrombocytopenia, 3.7% any bicytopenia, 1.1% pancytopenia, and 43.1% with an elevated LDH. Bone marrow involvement was present in 16.3% of patients, and 28.7% had a positive FDG PET-CT for BMI. Of note, when comparing baseline characteristics between patients with HL and NHL, age was significantly different (median of 35 years versus 57 years, $p < 0.001$), as well as the presence of B symptoms (77.6% of HL patients vs. 56.9% of NHL patients, $p = 0.005$). The rest of the clinical and laboratory characteristics are summarized in Table 1.

Detection of bone marrow involvement

For the analysis of the diagnostic performance of FDG PET-CT for bone marrow involvement, only 355 patients with an FDG PET-CT study had a conclusive BMB. Distribution of positive and negative FDG PET-CT cases between patients with and without BMI is shown in Table 2. Prevalence of BMI was 16.3% in these 355 patients, 17.2% of HL (mostly classical HL), 12.3% of DLBCL, 29.8% of FL, and 15.6% of other types of lymphoma patients had a positive BMB.

Overall, estimated sensitivity of FDG PET-CT was 74.1%, specificity 80.1%, PPV 42.2%, NPV 94.1%, +LR 3.73, and −LR 0.32. Table 3 displays the diagnostic

Table 1. Patient characteristics

Clinical and laboratory characteristics	Total (n = 355)	HL (n = 58)	NHL (n = 297)	p-value†
Males, n (%)	200 (56.3)	34 (58.6)	166 (55.9)	0.812
Age (year), median (IQR)	54, (40-65)	37.5, (26-49)	57, (43-66)	< 0.001
B symptoms, n (%)	214 (60.3)	45 (77.6)	169 (56.9)	0.005
Anemia §, n (%)	156 (44.1)	37 (63.8)	119 (40.2)	0.002
Neutropenia §, n (%)	10 (2.8)	1 (1.7)	9 (3.0)	1.000
Thrombocytopenia §, n (%)	22 (6.2)	4 (6.9)	18 (6.1)	0.769
Bicytopenia §, n (%)	13 (3.7)	1 (1.7)	12 (4.1)	0.702
Pancytopenia §, n (%)	4 (1.1)	1 (1.7)	3 (1.0)	0.512
Elevated LDH, n (%)	153 (43.1)	23 (39.7)	130 (43.8)	0.664
Stage (Ann Arbor), n (%)				
I	32 (9.0)	1 (1.7)	31 (10.4)	0.012
II	64 (18.0)	13 (22.4)	51 (17.1)	
III	63 (17.8)	17 (29.3)	46 (15.4)	
IV	196 (55.2)	27 (46.6)	169 (56.9)	
Advanced stage (≥ III)	259 (73.0)	44 (75.9)	215 (72.4)	0.702
Bone marrow findings				
Positive BMB, n (%)	58 (16.3)	10 (17.2)	48 (16.2)	0.993
Positive FDG PET-CT (for BMI), n (%)	102 (28.7)	22 (37.9)	80 (26.9)	0.125

HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; LDH: lactate dehydrogenase; BMB: bone marrow biopsy; BMI: bone marrow infiltration; IQR: interquartile range.
†p value obtained by Mann–Whitney's U test for age, and by Pearson's Chi-square test for dichotomic categoric variables when expected values were higher than five or variable had more than two categories or by fisher exact test otherwise.
§ Laboratory results available in 354 individuals. FDG PET-CT: fluorodeoxyglucose positron emission tomography-computed tomography.

performance of FDG PET-CT in the subpopulations of HL, DLBCL, FL, and other types of lymphoma.

Predictors for bone marrow involvement

Clinical and laboratory characteristics at diagnosis were evaluated as predictors for bone marrow involvement, as described in Table S2 (supplementary material). After multivariate analysis, the presence of B symptoms, neutropenia, and thrombocytopenia was independent factors for BMI, with an adjusted odds ratio (OR) of 2.44, 95% CI (1.19, 4.99), 5.64, 95% CI (1.32, 24.08), and 4.12, 95% CI (1.66, 10.26), respectively.

Besides, baseline characteristics were also evaluated as predictors for a positive FDG PET-CT (for BMI) as summarized in Table S3 (supplementary material). Presence of B symptoms, thrombocytopenia, and an advance stage according to the Ann Arbor staging system remained significant in the multivariate analysis with adjusted OR of 2.96, CI 95% (1.73, 5.05), 2.75, 95% CI (1.17, 6.48), and 19.22, 95% CI (5.90, 62.66), respectively.

Factors related to discordant results

Seventy-four patients had discordant results between BMB and FDG PET-CT, 15 patients had a positive BMB, but a negative FDG PET-CT, and 59 had the opposite combination. After analyzing the baseline characteristics, the proportion of neutropenia and bicytopenia was significantly higher in the group of positive BMB and negative FDG PET-CT than to the contrary group (13.3% vs. 0% and p = 0.039 for both factors). The discrepancy between BMB and FDG PET-CT results for bone marrow involvement did not affect the proportion of therapy modification (40.0% vs. 44.1%, p = 1.000).

Table 2. Detection of bone marrow involvement in lymphoma patients

FDG PET-CT findings	BMB (+)	BMB (–)	Total
All cases			
FDG PET-CT (+)	43	59	102
FDG PET-CT (–)	15	238	253
Total	58	297	355
HL			
FDG PET-CT (+)	9	13	22
FDG PET-CT (–)	1	35	36
Total	10	48	58
DLBCL			
FDG PET-CT (+)	12	27	39
FDG PET-CT (–)	7	108	115
Total	19	135	154
FL			
FDG PET-CT (+)	11	7	18
FDG PET-CT (–)	3	26	29
Total	14	33	47
Other NHL			
FDG PET-CT (+)	11	12	23
FDG PET-CT (–)	4	69	73
Total	15	81	96

HL: Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; NHL: non-Hodgkin lymphoma; BMB: bone marrow biopsy; FDG PET-CT: fluorodeoxyglucose positron emission tomography-computed tomography.

Table 3. Diagnostic performance of FDG PET-CT for BMI in lymphoma patients

Measurement	All types (n = 355)	HL (n = 58)	DLBCL (n = 154)	FL (n = 47)	Other types (n = 96)
Classification probabilities					
Se (%), 95% CI	74.1, (62.9, 85.4)	90.0, (71.4, 100.0)	63.2, (41.5, 84.8)	78.6, (57.1, 100.0)	73.3, (51.0, 95.7)
Sp (%), 95% CI	80.1, (75.6, 84.7)	72.9, (60.3, 85.5)	80.0, (73.3, 86.7)	78.8, (64.8, 92.7)	85.2, (77.4, 92.9)
Predictive values					
PPV (%), 95% CI	42.2, (32.6, 51.7)	40.9, (20.4, 61.5)	30.8, (16.3, 45.3)	61.1, (38.6, 83.6)	47.8, (27.4, 68.2)
NPV (%), 95% CI	94.1, (91.2, 97.0)	97.2, (91.9, 100.0)	93.9, (89.5, 98.3)	89.7, (78.6, 100.0)	94.5, (89.3, 99.7)
Diagnostic LRs					
+LR, 95% CI	3.73, (2.84, 4.91)	3.32, (2.00, 5.52)	3.16, (1.95, 5.11)	3.70, (1.82, 7.55)	4.95, (2.70, 9.06)
–LR, 95% CI	0.32, (0.21, 0.50)	0.14, (0.02, 0.89)	0.46, (0.25, 0.83)	0.27, (0.10, 0.75)	0.31, (0.13, 0.73)

HL: Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; Se: sensitivity; Sp: specificity; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; +LR: positive likelihood ratio; –LR: negative likelihood ratio; FDG PET-CT: fluorodeoxyglucose positron emission tomography-computed tomography.

DISCUSSION

There is evidence that supports the use of FDG PET-CT for the evaluation of bone marrow involvement in patients with HL and DLBCL, but for all the other types of lymphoma, an FDG PET-CT-guided approach for this purpose is not so evident[4-7].

The principal limitations of the use of FDG PET-CT for the initial evaluation of BMI in lymphoma patients are the cost of the study and availability of the equipment. On the other side, a BMB is an invasive procedure that is often very painful for the patient and can present some variability in obtaining the sample. We also have to consider that it evaluates only a small region of the patient's bone marrow[8-11].

At present, for the initial evaluation of BMI in patients with HL and DLBCL is considered valid not to perform a BMB if there is a positive FDG PET-CT for bone marrow infiltration. On the contrary, BMB is reserved for those patients with cytopenias (HL) and in case of concordant/discordant bone marrow involvement might have an impact on prognosis or treatment (DLBCL)[1,6,7].

The vast majority of studies evaluating the diagnostic performance of FDG PET-CT for detecting bone marrow involvement had been retrospective in nature. They often confer different results for lymphomas other than HL and DLBCL. In a meta-analysis by Pakos *et al.,* which included 13 studies comprising 587 patients, FDG PET-CT utility in the evaluation of bone marrow for staging patients with lymphoma was evaluated. Compared with the BMB as the gold standard, sensitivity and specificity of FDG PET-CT were 51 and 91%, respectively. In the subgroup analysis, the BMB showed higher sensitivity in HL (76%) and aggressive NHL. At the same time, FDG PET-CT resulted in false negatives in more than 2/3 of patients with bone marrow infiltration by BMB in indolent lymphomas[3].

The incidence of bone marrow involvement by BMB (gold standard) in lymphoma patients reported at a cohort evaluated by Park *et al.* is very similar to the incidence of BMI by FDG PET-CT reported in our study, especially in the NHL subgroup of patients. In HL cases, we found a much higher incidence of BMI by FDG PET-CT (30%) than the one reported by Park *et al.* using BMB (10%); this can be explained by the large proportion of patients with advanced-stage HL (75.9%) in our cohort [Table S4 (supplementary material)][12].

In our study, globally, the diagnostic performance of FDG PET-CT was similar to other cohorts with sensitivity, specificity, PPV, and NPV of 74.1%, 80.1%, 42.2%, and 94.1%, respectively[2]. For patients with HL, the sensitivity of FDG PET-CT for BMI was the highest (90%) with specificity, PPV, and NPV of 72.9, 40.9, and 97.2%, respectively. These results, comparable to those reported by the international literature, support the recommendation of omitting the BMB in patients with an FDG PET-CT positive for BMI[13,14].

In this cohort, we also found that in patients with a negative FDG PET-CT and a positive BMB, some clinical variables resulted significant as the presence of cytopenias and B symptoms. These results suggest that the unilateral BMB is required for patients with HL with a negative FDG PET-CT and cytopenias (with or without B symptoms) at diagnosis.

Many authors had studied the utility of FDG PET-CT for BMI detection in patients with DLBCL. Most of them concluded that a unilateral BMB should be performed only if FDG PET-CT turns out negative for BMI and if the identification of discordant histology in the marrow might impact patient management (clinical trials)[15-20]. In our study, the proportion of DLBCL patients with BMI at diagnosis was low (12%), even in the advanced stage group. This finding can be explained by the heterogeneous infiltration that characterizes DLBCL in the marrow and because we take a "blind" BMB, always using de posterior iliac crest even without increased focal 18F-FDG uptake. We recommend performing a BMB for patients with a positive FDG PET-CT for BMI (Ann Arbor stage IV) that otherwise would qualify as early-stage (Ann Arbor stages I and II) and would benefit from less aggressive treatment.

About FL, in our study, the general diagnostic performance of FDG PET-CT for the detection of BMI was excellent, even better than the HL subgroup. These results have to be taken with caution, as the population with FL represented only 13.2% of the sample. An interesting observation is the diagnostic performance of FDG PET-CT for BMI in patients with FL was

also better than the one for DLBCL patients (contrary to that reported by the literature)[21-24]. Although the sample is small, these results invite us to research about FDG PET-CT utility for detecting BMI in FL so that we can extend a valid recommendation for this specific type. Performing bilateral BMB with morphologic evaluation has proven to be useful in evaluating patients with NHL and HL. Even though it is not a general recommendation, bilateral BMB can improve the yield for BMI detection in lymphomas with diffuse bone marrow infiltration[8].

Other types of lymphoma subgroup included: extranodal NK-/T-cell lymphoma, nasal type (7.6%), mantle cell lymphoma (3.9%), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (3.4%), Burkitt lymphoma (2.3%) and others (20 subtypes total). In this group of patients, the diagnostic performance of FDG PET-CT was outstanding. Nevertheless, it is difficult to recommend the substitution of BMB for FDG PET-CT in these patients because of the subgroup's heterogeneity and the size of the sample it represents. Furthermore, it is a fact that many of these types of lymphoma infiltrate the bone marrow in a non-focal fashion, and that FDG PET-CT can fail to detect BMI in this situation[25-27]. Therefore, for these patients, we recommend performing a unilateral BMB with immunohistochemical analysis.

It is well known that bone marrow FDG uptake strongly correlates with blood counts, especially white blood cell counts[28,29]. In our study, the presence neutropenia and thrombocytopenia were independent factors for BMI with OR of 5.64, 95% CI (1.32, 24.08) and 4.12, 95% CI (1.66, 10.26), respectively, after adjusting by the presence of other cytopenia, B symptoms, elevated LDH and advanced stage. Similarly, for positive FDG PET-CT, thrombocytopenia was also significant with OR of 2.75, 95% CI (1.17, 6.48) after adjusting by the same covariates; so, it is crucial to consider these factors and other clinical characteristics such as B symptoms, when we decide whether or not to skip the BMB at a patient's initial evaluation.

Seventy-four patients had discordant results between BMB and FDG PET-CT, with a discordance rate of 20%, similar to the 19% reported by Hong et al.[27]. The discrepancy in BMB and FDG PET-CT results did not affect treatment in our cohort, mainly because the vast majority of patients were already classified with an advanced stage (Ann Arbor stage III or IV), for the presence of another organ involvement.

This study has several limitations. First, the retrospective nature prevents us from controlling the sample's clinical variables and the quality of the FDG PET-CT reports, as the inability to perform a guided BMB to the sites with higher FDG uptake. Second, the high number of patients excluded from the analysis for not having both FDG PET-CT and BMB performed and adequately reported. Third, it appears that DLBCL, HL, and FL represented the majority of the population, so the other types of lymphomas individually comprised 1% or less of the total sample. For future studies, it would be interesting to evaluate the infiltration pattern in the bone marrow with FDG PET-CT (focal vs. diffuse) as well as the FDG uptake intensity (SUV-max) and its correlation with histopathological findings on the BMB.

In this single-center, retrospective study, we confirmed that FDG PET-CT shows excellent performance for detecting BMI in HL. For DLBCL, we recommend performing BMB and FDG PET-CT as complementary tests. In all other NHL, unilateral BMB with immunohistochemical analysis should always be performed at diagnosis.

SUPPLEMENTARY DATA

Supplementary data are available at Revista de Investigación Clínica online (www.clinicalandtranslationalinvestigation.com). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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