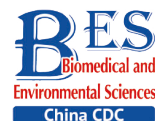## Original Article

Diagnostic Efficacy of ^{18}F-FDG PET/CT in Detecting Bone Marrow Infiltration in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma*

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Abstract

Objective   Diffuse large B-cell lymphoma (DLBCL) is often associated with bone marrow infiltration, and 2-deoxy-2-(18F) fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has potential diagnostic significance for bone marrow infiltration in DLBCL.

Methods   A total of 102 patients diagnosed with DLBCL between September 2019 and August 2022 were included. Bone marrow biopsy and ^{18}F-FDG PET/CT examinations were performed at the time of initial diagnosis. Kappa tests were used to evaluate the agreement of ^{18}F-FDG PET/CT with the gold standard, and the imaging features of DLBCL bone marrow infiltration on PET/CT were described.

Results   The total detection rate of bone marrow infiltration was not significantly different between PET/CT and primary bone marrow biopsy (*P* = 0.302) or between the two bone marrow biopsies (*P* = 0.826). The sensitivity, specificity, and Youden index of PET/CT for the diagnosis of DLBCL bone marrow infiltration were 0.923 (95% *CI*, 0.759–0.979), 0.934 (95% *CI*, 0.855–0.972), and 0.857, respectively.

Conclusion   ^{18}F-FDG PET/CT has a comparable efficiency in the diagnosis of DLBCL bone marrow infiltration. PET/CT-guided bone marrow biopsy can reduce the misdiagnosis of DLBCL bone marrow infiltration.

Key words: Diffuse large B-cell lymphoma; Bone marrow infiltration; Positron emission computed tomography (PET/CT); Bone marrow biopsy; Diagnostic efficacy

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a common malignant tumor that originates in the lymphoid hematopoietic system and constitutes 2.8% of all cancers and 2.6% of all cancer-related deaths worldwide per year[1]. Diffuse large B-cell lymphoma (DLBCL) represents approximately 33.37% of all lymphomas and is the most common subtype[2,3]. Bone marrow infiltration is considered stage IV, and its strong invasiveness, easy extranodal invasion, and high risk of recurrence make treatment difficult[4,5]. Routine bone marrow examinations (bone marrow smears, biopsy,

immunopathology, flow cytometry, cytogenetics, and molecular biology) are prone to misdiagnosis due to the limited location and quality of bone biopsy. In recent years, patients with DLBCL have been accurately diagnosed with systemic involvement due to the development and popularization of PET/CT examination; however, only a few studies on bone marrow are available[6-8]. Herein, we evaluated the efficacy and applicability of 2-deoxy-2-(18F) fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for the diagnosing of DLBCL bone marrow infiltration compared to bone marrow aspiration and biopsy and described the PET/CT imaging characteristics of bone marrow infiltration.

MATERIALS AND METHODS

Patients

This retrospective study evaluated 102 patients diagnosed at PLA General Hospital between September 2019 and August 2022. The inclusion criteria were as follows: primary DLBCL diagnosed by pathological histomorphology and immunohistochemistry according to the World Health Organization (WHO) classification system; age ≥ 18 years old; PET/CT examination and bone marrow biopsy (bone marrow smear, bone marrow biopsy and immunopathology, and bone marrow flow cytometry) were optimized at the first visit. The exclusion criteria were as follows: a second tumor (with or without bone metastasis); active inflammation or diffuse liver lesions during PET/CT examination; unstable blood glucose and fasting blood glucose ≥ 8.8 mmol/L during PET/CT examination; and patients who underwent treatment, such as radiotherapy, chemotherapy, or received granulocyte colony-stimulating factor (G-CSF), erythropoietin (EPO), and thrombopoietin (TPO) within 3 months.

PET/CT Imaging

A Discovery VCT PET/CT imager (GE Company) was used for detection. Before examination, patients were asked to fast for > 6 hours to bring their fasting blood glucose below 8.8 mmol/L. The intravenous injection dose of ^{18}F-FDG was 4–5 MBq/kg. The patients were asked to empty their bladders 1 h after injection and scanned from the top of the skull to the bottom of the plantar surface using PET/CT. During reconstruction, PET images are required for anatomical localization and attenuation correction using an ordered subset expectation maximization (OSEM) algorithm. The scan results were analyzed by at least two experienced nuclear medicine radiologists. The PET/CT diagnostic criteria for bone marrow infiltration were according to the European Society for Medical Oncology (ESMO) clinical guidelines: the presence of increased FDG metabolism in the liver with or without increased diffuse uptake in focal bone marrow.

Bone Marrow Aspiration and Biopsy

The anterior/posterior superior iliac spine was used as the entry point for the first biopsy. Bone marrow aspirates were examined using smear, biopsy, immunopathology, and flow cytometry. If the bone biopsy result was negative, but PET/CT detected abnormal metabolic signals, a second biopsy was performed. Hematologists performed bone marrow biopsy and flow cytometry, and the smear and biopsy immunopathology results were analyzed in the bone marrow morphology laboratory.

Statistical Analysis

The results of bone marrow aspiration and biopsy of lymphoma cells (bone marrow smear, biopsy, immunopathology, and flow cytometry) were used as the gold standard to calculate several PET/CT indices for the diagnosis of DLBCL bone marrow infiltration, including sensitivity, specificity, total accuracy, positive predictive value, negative predictive value, and Youden's index. All data were analyzed using SPSS 20.0. The McNemar's test was used to compare the diagnostic efficiency of the two inspection methods. Kappa tests were used to measure the agreement between the two methods, with kappa coefficients ≥ 0.75, 0.4 ≤ k < 0.75, and k < 0.4, indicating strong, moderate, and weak agreement, respectively. A two-tailed P < 0.05 indicated statistical significance.

Ethical Approval

The study design and protocols were approved by the Ethics Committee of Chinese PLA General Hospital. Written informed consent was obtained from all participants.

RESULTS

Clinical Baseline Characteristics of Patients

In total, 102 patients were included in this study, 56 males (54.9%) and 46 females (45.1%). The cohort comprised 88 (86.3%) patients with Ann Arbor stage

IV, 0 (0%) with stage III, and 14 (13.7%) with an international prognostic index (IPI) score of 4–5. The median and average ages at onset were 50 and 47 (range, 18–65) years, respectively. The clinical characteristics of the 102 patients with newly treated DLBCL are presented in Table 1.

Comparison of the Detection Rate of DLBCL Bone Marrow Infiltration between Biopsy and PET/CT

Among the 102 patients, 21 cases of bone marrow infiltration were detected by initial bone

Table 1. Clinical baseline characteristics of 102 diffuse large B-cell lymphoma patients

Clinical characteristics	N (%)
Age (year) ≥ 60	30 (29.4)
Sex	
Male	56 (54.9)
Female	46 (45.1)
Ann-Arbor stage	
I	10 (9.8)
II	4 (3.9)
III	0 (0)
IV	88 (86.3)
IPI Score	
3	15 (14.7)
4–5	14 (13.7)
B symptoms	85 (83.3)
ECOG score ≥ 3	38 (37.3)
LDH > 250 U/L	79 (77.5)
Hans subtype	
GCB	36 (35.3)
Non-GCB	66 (64.7)
Ki-67 ≥ 75%	34 (33.3)
Blood routine	
HGB < 100 g/L	48 (47.1)
WBC < 4.0×10^9/L	16 (15.7)
PLT < 100×10^9/L	27 (26.5)
Splenomegaly	32 (31.4)
Hepatomegaly	10 (9.8)
Lymphadenopathy	92 (90.2)

Note. IPI: International prognostic index; ECOG: Eastern cooperative oncology group performance score; LDH: Lactate dehydrogenase; GCB: Germinal center B cell-like; HGB: Hemoglobin; WBC: White blood cell; PLT: Platelet count.

marrow aspiration and biopsy (14 bone marrow smears, 21 immunopathology biopsies, and 18 flow cytometry results). The total detection rate was 20.6% (21/102); the detection rate of bone marrow smears was 13.7% (14/102), biopsy immunopathology was 20.6% (21/102), and flow cytometry was 17.6% (18/102).

Patients with negative bone biopsy results but abnormal metabolic signals on PET/CT underwent a second biopsy of the abnormal bone marrow metabolic sites (Figure 1). Consequently, eight cases of bone marrow infiltration were detected. In total, 29/102 cases of bone marrow infiltration were detected in patients with DLBCL by bone marrow bone marrow aspiration and biopsy (including 20 iliums, 28 biopsy immunopathology, and 24 flow cytometry). The total detection rate of bone marrow infiltration in the combination of the first and second bone marrow aspiration and biopsy was 28.4% (29/102), and the detection rates of bone marrow smear, biopsy immunopathology, and flow cytometry were 19.6% (20/102), 27.5% (28/102), and 23.5% (24/102), respectively.

A total of 26/102 (25.5%) cases of bone marrow infiltration were detected using PET/CT, and the detection rate was not significantly different from that of the first bone marrow aspiration and biopsy (P = 0.302) or the combination of the two procedures (P = 0.453) (Table 2). However, the detection rate of PET/CT was higher than that of the initial bone marrow smear examination (P = 0.002)
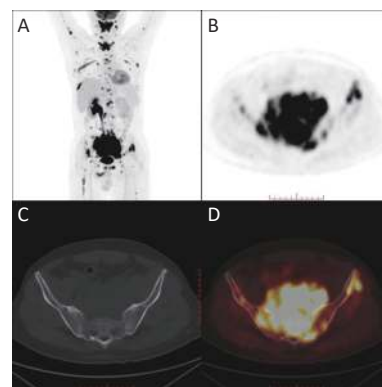
Figure 1. ^{18}F-FDG PET/CT image of a patient with diffuse large B-cell lymphoma. (A) Maximum intensity projection (MIP)-PET/CT shows an increased FDG uptake in the pelvic cavity and bones. (B) Coronal PET, (C) Coronal CT, (D) Coronal fused PET/CT images show high metabolism in the left anterior superior iliac spine.

([Table 2](#)). Moderate agreement was observed between PET/CT and the first DLBCL bone marrow infiltration (k = 0.587, P < 0.001), while strong agreement was detected between PET/CT and the combination of the two DLBCL bone marrow infiltrations (k = 0.826, P < 0.001).

Diagnostic Efficacy of PET/CT for DLBCL Bone Marrow Infiltration

Compared to standard first bone marrow aspiration and biopsy, the sensitivity of PET/CT in the diagnosis of DLBCL bone marrow infiltration was 0.615 [95% confidence interval (*CI*): 0.425–0.776], the specificity was 0.934 (95% *CI*: 0.855–0.972), and Youden's index was 0.549 ([Table 3](#)). When the first and second bone marrow aspiration and biopsy were combined as the gold standard, the sensitivity, specificity, and Youden's index of PET/CT were 0.923 (95% *CI*: 0.759–0.979), 0.934 (95% *CI*: 0.855–0.972), and 0.857, respectively ([Table 3](#)).

PET/CT Imaging Characteristics of DLBCL Bone Marrow Infiltration

A total of 26 patients were diagnosed with bone marrow infiltration by PET/CT according to the ESMO clinical practice guidelines: 23/26 (88.5%) showed focally increased [18]FDG uptake and 3/26 (11.5%) showed an increase in diffuse FDG metabolism in the bone marrow throughout the body. Among them, the top three incidence sites of increased focal metabolism were the ilium (21/26), 3–5 lumbar vertebrae (16/26), and femur (8/26), and the lower incidence sites were the sternum (1/26), humerus (1/26), and ribs (1/26). Of the three patients with diffuse FDG metabolism in the whole-body bone marrow, one patient was diagnosed with bone marrow infiltration by two bone biopsies and two patients were diagnosed without bone marrow infiltration ([Table 4](#)).

Among the 29 patients with DLBCL diagnosed by bone marrow infiltration, 23 showed only focally increased [18]FDG uptake, one showed focally increased [18]FDG uptake with increased systemic bone marrow diffuse FDG metabolism, two showed only increased systemic bone marrow diffuse FDG metabolism, and three did not show obvious abnormalities in bone marrow FDG metabolism.

DISCUSSION

Accurate staging of patients with DLBCL is a prerequisite to improve prognosis and treatment selection. In recent years, ^{18}F-FDG PET/CT has been used for the clinical staging of lymphoma due to its accurate assessment of systemic lymphoma involvement; however, the currently recognized gold

Table 2. Comparison of detection rate of DLBCL bone marrow infiltration between biopsy and PET/CT

Detection methods	S+T+	S+T-	S-T+	S-T-	P (McNemar test)	Kappa	P (Kappa)
Total of first bone marrow examination	16	5	10	71	0.302	0.587	< 0.001
Bone marrow smear	13	1	13	75	0.002	0.574	< 0.001
Bone marrow biopsy immunopathology	16	5	10	71	0.302	0.587	< 0.001
Bone marrow flow cytometry	14	4	12	72	0.077	0.541	< 0.001
Combination of the first and second bone marrow examination	24	5	2	71	0.453	0.826	< 0.001
Bone marrow smear	19	1	7	75	0.070	0.777	< 0.001
Bone marrow biopsy immunopathology	23	5	3	71	0.727	0.799	< 0.001
Bone marrow flow cytometry	20	4	6	72	0.754	0.735	< 0.001

Note. S+, Gold standard positive; S-, Gold standard negative; T+, PET/CT positive; T-, PET/CT negative. DLBCL: Diffuse large B-cell lymphoma.

Table 3. Diagnostic efficacy of PET/CT for DLBCL bone marrow infiltration

Variables	S+T+	S+T-	S-T+	S-T-	Sensitivity (95% *CI*)	Specificity (95% *CI*)	Youden's index
First bone marrow examination	16	5	10	71	0.615 (0.425–0.776)	0.934 (0.855–0.972)	0.549
Combination of the first and second bone marrow examination	24	5	2	71	0.923 (0.759–0.979)	0.934 (0.855–0.972)	0.857

Note. S: Diagnosis by DLBCL; T: Diagnosis by PET/CT; DLBCL: Diffuse large B-cell lymphoma.

standard for assessing bone marrow is still bone marrow aspiration and biopsy[6,7]. In addition, the presence of bone marrow infiltration is a key issue not only for lymphoma patients but also for patients with refractory leukemia, and PET/CT is also used to detect bone marrow involvement in leukemia[8]. However, the following limitations of bone marrow aspiration and biopsy should be considered. First, the common point for bone marrow aspiration was the anterior iliac/posterior superior iliac spine; however, common focal occurrences of DLBCL bone marrow infiltration were in the vertebral body, pelvis, and femur. Therefore, false-negative results are likely to occur without lymphoma infiltration at the entry site[9,10]. Second, the quality of the specimens significantly affects the accuracy of the results. Third, invasive bone marrow aspiration and biopsy are inconvenient, and patients who undergo multiple punctures experience great pain during diagnosis and treatment. Furthermore, PET/CT can replace bone marrow aspiration and biopsy to assess the occurrence of bone marrow involvement in most cases of DLBCL, according to the 2016 ESMO guidelines and the 2014 Lugano classification[11,12].

Previous studies have confirmed that FDG uptake rates vary significantly in pathological types of lymphoma on PET/CT examination and that DLBCL is a highly sensitive type of cancer[13-17]. A meta-analysis by Adams et al.[18] on the diagnosis of DLBCL infiltration using FDG PET/CT showed that the diagnostic sensitivity and specificity of PET/CT were 88.7% and 99.8%, respectively, similar to those of the present study. In this study, ^{18}F-FDG PET/CT had a high diagnostic efficiency for DLBCL bone marrow infiltration, in agreement with the gold standard (k = 0.826). Patients with a poor condition or poor bone marrow biopsy results due to age and mental state

Table 4. Distribution and characteristics of bone marrow infiltration sites detected by PET-CT (a total of 26 cases)

Site and characteristics	Cases (%)
Focal increased ^{18}FDG uptake	23 (88.5)
Focal and systematic diffuse bone marrow ^{18}FDG uptake	3 (11.5)
Ilium	2 (80.8)
Lumbar vertebra (L3–L5)	16 (61.5)
Femur	8 (30.8)
Sternum	1 (3.8)
Humerus	1 (3.8)
Ribs	1 (3.8)

and who could not provide a high-quality specimen could be assessed for bone marrow infiltration using noninvasive PET/CT. It could also be used as an examination option in follow-up patients to track and evaluate bone marrow involvement and has been recommended internationally[6,19-26]. In the present study, we found that another eight patients with negative bone marrow infiltration for the first bone penetration had a second bone penetration due to the positive results of PET/CT, suggesting that biopsy combined with PET/CT guidance increases the detection rate. For newly diagnosed patients, bone marrow aspiration and biopsy could be performed according to PET/CT results, which improved the sensitivity of the examination and avoided repeated bone penetration pain.

Previous studies have found that the incidence of bone marrow infiltration in DLBCL at the first diagnosis was 11%–34%[27,28], consistent with our results (28.9%). The International Atomic Energy Agency sponsored a prospective international cohort study to better define the use of PET in DLBCL in eight countries that contributed to 327 cases; the hazard ratios for PET-negative/biopsy-negative cases versus PET-positive/biopsy-positive cases were 2.67 for EFS and 3.94 for OS. This large study showed that positive iliac crest biopsy histology only confers a poor prognosis to patients with abnormal marrow ^{18}F-FDG uptake identified on the staging PET scan[29]. In this study, lymphoma cells detected using any method, including bone marrow smear, biopsy, immunopathology, and flow cytometry, were diagnosed as DLBCL bone marrow infiltration. When comparing the three methods, the sensitivity of bone marrow biopsy and immunopathology at the first diagnosis was higher than that of the smear, making it the first choice for patients with DLBCL. The current results suggest that the sites most likely for bone marrow infiltration on PET/CT examination were the iliac bone, lumbar spine (L3–5), and femur, consistent with most previous studies. Most patients with bone marrow infiltration[24,29] showed increased focal FDG uptake with or without increased systemic bone marrow diffuse FDG uptake on PET/CT instead of increased focal FDG uptake or tumor proliferation and invasiveness. Only two cases had elevated systemic bone marrow diffuse FDG uptake. Although some studies have noted that approximately 29% of newly diagnosed patients with lymphoma have diffusely elevated bone marrow FDG uptake, most have false-positive results. Therefore, diffuse uptake of FDG in the bone marrow is associated with bone marrow inflammation, systemic inflammation, and

hematopoietic activity. Shagera et al.[30-32] showed that only IPI and ^{18}F-PET/CT bone marrow status were independent factors for progression-free survival (PFS), as evaluated by multivariate analysis of newly treated DLBCL patients. Some studies[33,34] have shown that ^{18}F-PET/CT-related parameters are closely related to overall survival and PFS and are critical for predicting the prognosis of DLBCL. This showed that the stratification rate of ^{18}F-PET/CT was higher than that of bone marrow examination in patients with newly diagnosed DLBCL. Taken together, these studies suggest that PET/CT imaging should be combined with routine blood tests, C-reactive protein (CRP), and other results to evaluate the clinical correlation between increased FDG uptake and bone marrow infiltration. Meanwhile, as a single-center retrospective study, the sample size was acceptable compared to previous studies; however, some patients were in a relatively late stage, which could have resulted in selection bias. This is the main limitation of this study. Therefore, further studies with larger sample sizes and well-designed sampling methods are required.

In Summary, ^{18}F-FDG PET/CT can be an alternative method for assessing bone marrow infiltration in patients with DLBCL who cannot tolerate a bone biopsy due to its high diagnostic efficiency. Bone marrow aspiration and biopsy guided by PET/CT improve the sensitivity of the overall diagnosis and reduce the missed diagnosis rate. PET/CT-guided secondary puncture can reduce missed diagnosis rates according to the gold standard and has potential clinical significance.

AUTHORS' CONTRIBUTIONS

HUANG Wen Rong conceived and designed the study. GUO Bo, GU Zhen Yang, LI Yan Fen, and GAO Lei acquired the data. GUO Bo and QIN Ran analyzed the data. GUO Bo and QIN Ran drafted the manuscript. HUANG Wen Rong revised the manuscript. GUO Bo and QIN Ran acquired, analyzed, and interpreted the data and performed the statistical analysis. All authors have read and approved the final version of the manuscript.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study design and protocols were approved by the Ethics Committee of the Chinese PLA General Hospital. Written informed consent was obtained from all enrolled subjects.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

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