ORIGINAL ARTICLE

PET-CT scan can be a reliable alternative to bone marrow Biopsy? Comparison of PET CT scan and marrow biopsy finding in diagnosed cases of lymphoma for staging

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ABSTRACT

Objectives: To determine the diagnostic accuracy of ^{18}F-labeled fluoro-2-deoxyglucose (^{18}FDG) positron emission tomography/computed tomography (^{18}FDG-PET/CT) scan for identifying bone marrow involvement in diagnosed patients with lymphoma keeping bone marrow biopsy (BMB) as gold standard.

Study Design: cross-sectional study.

Setting: Department of Radiology, Armed Forces Institute of Radiological Imaging (AFIRI), Rawalpindi from April 26, 2021 to October 25, 2021.

Materials & Methods: A total of 128 cases of lymphoma of age 20-85 years and both genders were included. Patients who had taken treatment for lymphoma or were using bone marrow-stimulant factors or drugs before undergoing PET/CT scanning were excluded.

PET/CT imaging was done at AFIRI 6 HD True point PET/CT 1 hour after intravenous injection of 0.2 mCi/kg ^{18}FDG. PET acquisition was performed for 4 minutes per bed position for seven to eight bed positions. Bone marrow was classified into three types based on signal intensity and localization by FDG uptake on PT/CT as diffuse involvement, focal involvement, and normal bone marrow. Findings from ^{18}FDG PET/CT were compared with BMB results for determining the diagnostic accuracy of abdominal FDG PET-CT.

Results: Overall sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of ^{18}FDG-PET/CT scan for identifying bone marrow involvement in diagnosed patients with lymphoma keeping BMB as gold standard was 95.45%, 93.55%, 94.03%, 95.08%, and 94.53%, respectively.

Conclusion: This study concluded that the diagnostic accuracy of ^{18}FDG-PET/CT scan for identifying bone marrow involvement in diagnosed patients with lymphoma is very high.

Keywords: Lymphoma, positron emission tomography/computed tomography, sensitivity.

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Introduction

Lymphomas take place when cells of lymphatic system proliferate in an uncontrolled fashion [1] and can be divided into two main categories Hodgkin lymphoma (HL) and non-HL which are derived from immune cells like B-cells, T-cells, and natural killer (NK) cells [2]. Non-HL is seen as the sixth most common malignancy of both men and women with prevalence reported, respectively, about 9.6/100,000 and 7.2/100,000 [3]. In 2016, most common cancer cases of Pakistan are breast, leukemia, and HL and non-HL. The prevalence of HL is 4.9% and non-HL 4.7% [4]. High prevalence of lymphoma in any country is directed to increased frequency of extra nodal involvement. Pakistan and Saudi Arabia are presented in the lymphoma belt, extra nodal lymphoma in these countries is noted to be above 50% [5].

Even though bone involvement can occur as originating in progressive stage of lymphoma arising from other sites, lymphoma which initially arises in the bone than

any other place of body is known as primary bone marrow lymphoma (PBL). In our country patients of all age groups, diffuse large B cell lymphoma (DLBCL) is the most common type of PBL. Involvement of hip bone followed by femur is more commonly observed, with male pattern of predominance [6].

Proper therapy selection needs correct diagnosis and staging. More common staging system used for non-HL as well as HL is Ann Arbor staging system, Bone marrow involvement is not likely in initial stages (I and II) of HL therefore bone marrow biopsy (BMB) is not indicated for early stages, though it may be carried out in clinically advanced stages [7].

In non-HL, bone marrow involvement is seen in 18%-36% of aggressive lymphomas and 40%-90% of indolent lymphomas [2]. In HL, bone marrow involvement is detected in 5%-14% of cases [8]. Knowledge about bone marrow involvement plays a crucial role in deciding the treatment of the patient. Therefore, evaluation of bone marrow infiltration can upstage the disease process. BMB is routinely used in diagnostic and staging modality and is the most direct procedure as well, gold standard for detecting lymphoma infiltration, but it is an invasive method and is accompanied by complications such as pain and hemorrhage. Alternatively, ^{18}F-labeled fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is an imaging modality, being non-invasive and can comprehensively evaluate the initial staging of lymphoma patients and the state of bone marrow involvement with sensitivity of 98% and sensitivity of 95.6% [9].

Therefore, many clinical institutions put forward the suggestion of replacing BMB with PET-CT as the initial investigation in diagnosing bone marrow infiltration in lymphoma [10]. In this study, we compared the diagnostic accuracy of PET/CT scan with BMB for identifying bone marrow involvement in patients diagnosed with lymphoma and assessed whether it would be beneficial for the patients as it is a non-invasive and time-effective way for staging and initiation of treatment.

Methodology

The study was conducted at Armed Forces Institute of Radiology and Imaging (AFIRI), Rawalpindi from April 26, 2021 to October 25, 2021. Ethical approval was granted by ethical review committee via reference no. 0010. Sample size was calculated by using open epi calculator (https://www.openepi.com/SampleSize/SSPropor.htm) and having 98% confidence level. About 128 patients with mean age mean age of 54.62 ± 9.65 years (age range 20-85) presenting to AFIRI, Rawalpindi, fulfilling the inclusion criteria were selected by non-probability, consecutive sampling. Informed consent was taken from each patient. Prevalence of 67.58% [9] with 5% desired precision for sensitivity and specificity of ^{18}FDG PET CT in diagnosing bone marrow involvement in lymphoma as 95.6% and 98%, respectively.

Inclusion criteria

- Diagnosed cases of lymphoma.
- Age between 20 and 85 years.
- Both genders.

Exclusion criteria

- Patients who had started treatment for lymphoma or were using bone marrow stimulant factors or drugs before undergoing PET/CT scanning.
- Patients with sepsis or active infection during PET/CT scanning, as infection can affect the results.

Patients fulfilling the inclusion criteria were included in the study after obtaining well informed written consent. All the data collection was conducted by the researcher to maintain data quality and compliance with the study protocol. Both ^{18}FDG-PET/CT scan and BMB before treatment were included in this study. Patients were staged based on the Ann Arbor staging system and classified according to the World Health Organization (WHO). Bone marrow biopsies of all patients who underwent unilateral iliac crest biopsy were reviewed by faculty pathologists at armed forces institute of pathology. Lymphoma involvement is defined as the presence of abnormal lymphoid cells in the bone marrow and biopsy specimens were classified based on WHO classification. PET/CT imaging was done at AFIRI 6 HD True point PET/CT 1 hour after intravenous injection of 0.2 mCi/kg ^{18}FDG. PET acquisition was performed for 4 minutes per bed position for seven to eight bed positions. Bone marrow was classified into three types based on signal intensity and localization by FDG uptake on PET/CT as diffuse involvement, focal involvement, and normal bone marrow. Findings from ^{18}FDG PET-CT and BMB results were compared for determining the diagnostic accuracy of FDG PET-CT. All the acquired information was entered in the proforma. Data were entered on computer software Statistical Package for the Social Sciences version 22. Quantitative variables like age were measured as mean ± SD. Qualitative variables like Gender, true positive (TP), true negative (TN), false negative (FN), and false positive (FP) were measured as frequency and percentages. A 2 × 2 Table was constructed.

Results

Age range in this study was from 20 to 85 years with mean age of 54.62 ± 9.65 years.

Majority of the patients 79 (61.72%) were between 51 and 85 years of age as shown in Table 1. Out of 128 patients, 95 (74.22%) were males and 33 (25.78%) were females with male to female ratio of 2.9:1 (Figure 1). In FDG PET-CT positive patients, 63 (TP) had bone marrow involvement and 04 (FP) had no bone marrow involvement on BMB. Among 61, FDG PET-CT negative patients, 03

(FN) had bone marrow involvement on BMB whereas 58 (TN) had no bone marrow involvement on BMB (p = 0.0001). Overall sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of ^{18}FDG-PET/CT scan for identifying bone marrow involvement in diagnosed patients with lymphoma keeping BMB as gold standard was 95.45%, 93.55%, 94.03%, 95.08%, and 94.53%, respectively (Table 2). Receiver operative characteristic (ROC) curve is shown in Figure 2.

Discussion

^{18}F-FDG PET-CT is an important diagnostic tool for pre-treatment staging before start of treatment including radiotherapy/chemotherapy or surgery planning and afterward for treatment response assessment and is most commonly used for follow-up evaluation of head and neck squamous cell carcinomas [11]. Although ^{18}F-FDG is the most commonly used PET tracer for cancer staging, but it has limitation due to physiological uptake of ^{18}F-FDG by normal organs that may influence image interpretation. ^{18}F-FDG uptake is a normal process of uptake of glucose which is further metabolized to release energy in normal tissue with various normal pattern in brain, vocal cords, salivary glands, cervical muscles, lymphoid tissue, and brown fat. This uptake is also seen in various benign tumors, such as common pleomorphic adenoma [12]. Postoperative inflammatory process or radiotherapy may even give an FP increase uptake of ^{18}FDG-PET CT [13]. Limitation due to artifacts produces by metal implants or prosthesis limit the interpretation of images thus requiring non-attenuation corrected PET data evaluation software [14,15]. Recent introduction of whole-body PET-magnetic resonance imaging has offered greater functional-anatomical details and has revolutionized clinical management of oncological patients [16,17].

This study has been conducted to determine the diagnostic accuracy of ^{18}FDG-PET/CT scan for identifying bone marrow involvement in diagnosed patients with lymphoma keeping BMB as gold standard. In this study, sensitivity, specificity, PPV, NPV, and diagnostic accuracy of ^{18}FDG-PET/CT scan for identifying bone marrow involvement in diagnosed patients with lymphoma keeping BMB as gold standard was 95.45%, 93.55%, 94.03%, 95.08%, and 94.53%, respectively. This is consistent with the meta-analysis done by Wu et al. [18], who included 32 studies and found that PET/CT sensitivity and specificity

Table 1. *Age distribution of patients (n = 128).*

AGE (IN YEARS)	NO. OF PATIENTS	% AGE
20-50	49	38.28
51-85	79	61.72
Total	128	100.0

Mean ± SD = 54.62 ± 9.65 years.

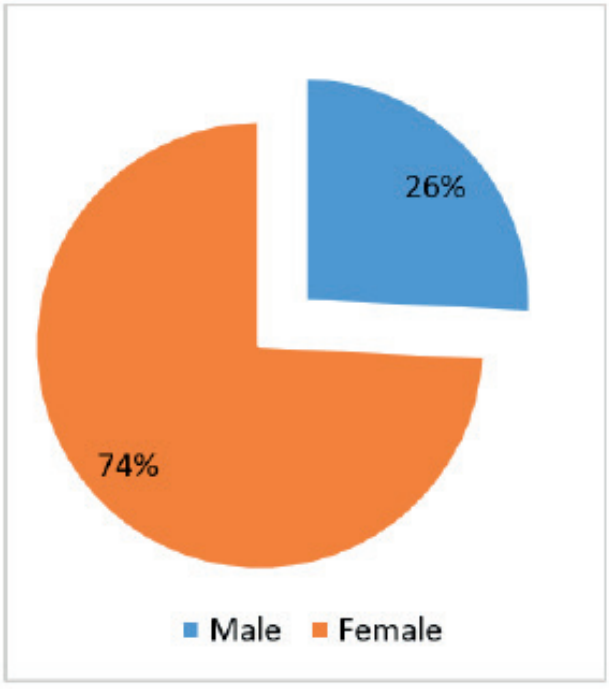

Figure 1. *Distribution of patients according to gender (n = 128).*

Table 2. *Diagnostic accuracy of ^{18}FDG-PET/CT scan for identifying bone marrow involvement in diagnosed patients with lymphoma keeping BMB as gold standard.*

	POSITIVE RESULT ON BMB	NEGATIVE RESULT ON BMB	*P*-VALUE
Positive on FDG PET-CT	63 (TP)[a]	04 (FP)[c]	0.0001
Negative on FDG PET-CT	03 (FN)[b]	58 (TN)[d]	

Sensitivity: 95.45%, Specificity: 93.55%, PPV: 94.03%, NPV: 95.08%, Likelihood ratio for positive test result: 14.80, Likelihood ratio for negative test result: 0.05, and diagnostic accuracy: 94.53%.
[a]TP = True positive; [b]FP = False positive; [c]FN = False negative; [d]TN = True negative.

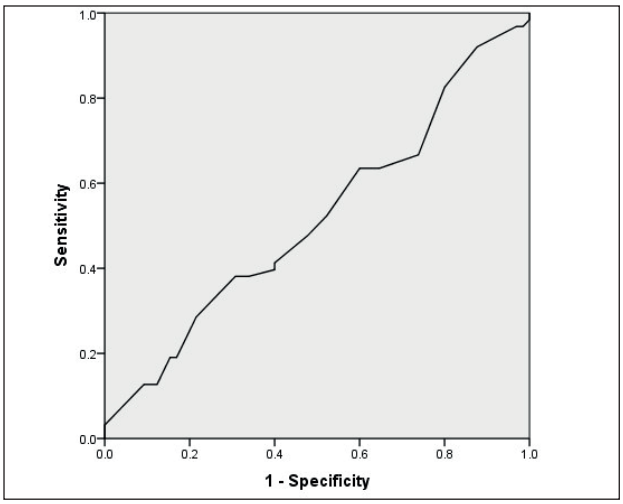

Figure 2. *ROC curve.*

were 91.6% (95% CI, 85.1, 95.9) and 90.3% (95% CI, 85.9, 93.7), respectively. PET/CT was found highly sensitive and specific modality in detecting bone marrow involvement in lymphoma.

A study done by Cistaro et al. [19] has shown the sensitivity of ^{18}F-FDG PET/CT was found 96% (95% CI, 89%-100%) while that of BMB was found 38% (95% CI, 20%-57%).

This is also consistent with the study done by Büyükşimşek et al. [20], who included 110 patients with HL and found PET/CT sensitivity was 91.3% (95% CI, 71.96-98.93) compared to that of BMB which was 56.52% (95% CI, 34.49-76.81).

Ruilong et al. [21] conducted a meta-analysis of 12 studies and suggested that the pooled sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of ^{18}F-FDG-PET were 0.82 (95% CI: 0.76-0.87), 0.81 (95% CI: 0.66-0.90), 4.30 (95% CI: 2.30-7.90), and 0.22 (95% CI: 0.16-0.30), respectively. Moreover, Zhang et al. [22] indicated that the pooled sensitivity, specificity, PLR, NLR, and diagnostic odds ratio of CT were 0.89 (95% CI: 0.88-0.91), 0.70 (95% CI: 0.68-0.73), 2.88 (95% CI: 2.46-3.37), 0.16 (95% CI: 0.12-0.21), and 23.83 (95% CI: 16.18-35.11), respectively.

Gordin et al. [23] reported sensitivity, specificity, PPV, NPV, and accuracy are 89%, 95%, 94%, 90%, and 92%, respectively, for PET/CT, compared with 92%, 18%, 51%, 71%, and 54%, respectively, for conventional cross sectional imaging. Purz et al. [24] compared the difference between BMB and ^{18}FDG PET/CT in the detection of BMI in 175 HL pediatric patients all with stage more than IIA. They found that F-18 FDG PET/CT detected 22% of positive cases not detected by BMB and concluded that ^{18}FDG PET may replace BMB in routine staging procedure. In the meta-analysis done by Adams et al. [25] who included seven studies assessing PET/CT for detection of BMI in DLBCL. They found that the PET/CT sensitivity was 78.4% (95% CI, 69.9%-85.5%) and specificity was 99.7% (95% CI, 98.3%-100%) when both focal and diffuse uptake were considered positive for bone marrow involvement.

Conclusion

This study concluded that diagnostic accuracy of ^{18}FDG-PET/CT scan for identifying bone marrow involvement in diagnosed patients with lymphoma is very high. So, we recommend that ^{18}FDG-PET/CT scan should be used routinely for identifying bone marrow involvement in diagnosed patients with lymphoma in order to take proper management steps for reducing the morbidity and mortality of our population.

List of Abbreviations

DOR	Diagnostic odds ratio
HL	Hodgkin lymphoma
NLR	Negative likelihood ratio
PBL	Primary bone lymphoma
PLR	Positive likelihood ratio
ROC	Receiver operative characteristic

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent to participate

Written consent was obtained from all the participants.

Ethical approval

Ethical approval was granted by ethical review committee via reference no. 0010.

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References

1. Word ZH, Matasar MJ. Advances in the diagnosis and management of lymphoma. Blood Lymphat Cancer. 2012;2(29):29–55.
2. Hosseini SA, Tahmoorespur M, Sekhavati MH, Nasiri MR. Construction and cloning of a recombinant expression vector containing human Cd20 Gene for antibody therapy in Non-Hodgkin Lymphoma. Mol Med. 2016:20:161–7.
3. Naseem SS, Nagi AH, Ashraf M, Bilal S, Akhlaq M, Henna N, et al. A pattern of lymphadenopathies seen in a tertiary care hospital in Lahore, Pakistan. Turk J Med Sci. 2011;41(2):353–8.
4. Sarwar MR, Iftikhar S, Saqib A. Availability of anticancer medicines in public and private sectors, and their affordability by low, middle and high-income class patients in Pakistan. BMC Cancer. 2018;18(1):14.
5. Bangash MH, Hussain I, Zakaria MP, Piracha MN. Pattern of extranodal involvement in non hodgkins lymphoma. Pak Armed Forces Med J. 2014;01(4):605.
6. Qureshi A, Ali A, Riaz N, Pervez S. Primary non-hodgkin's lymphoma of bone: experience of a decade. Indian J Pathol Microbiol. 2010;53(2):267–70.
7. Anwar RE, Iqbal UJ AN, Ahmad NA. Frequency of bone marrow involvement in hodgkin's lymphoma in patients presented at Shoukat Khanum Memorial Cancer Hospital Lahore. Pak J Med Heal Sci. 2015;9(4):1347–9.
8. Monabati A, Safaei A, Noori S, Mokhtari M, Vahedi A. Subtype distribution of lymphomas in South of Iran, analysis of 1085 cases based on World Health Organization classification. Ann Hematol. 2016;95(4):613–8.
9. 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):1–5.
10. Angelopoulou MK, Mosa E, Pangalis GA, Rondogianni P, Chatziioannou S, Prassopoulos V, et al. The significance of PET/CT in the initial staging of Hodgkin lymphoma: experience outside clinical trials. Anticancer Res. 2017;37(10):5727–36.

11. Oyen WJ, Marres HA, Kaanders JH. Progress in nuclear medicine procedures in head and neck oncology. Q J Nucl Med Mol Imaging. 2011;55(5):485–6.
12. Schwarz E, Hürlimann S, Soyka JD, Bortoluzzi L, Strobel K. FDG-positive Warthin's tumors in cervical lymph nodes mimicking metastases in tongue cancer staging with PET/CT. Otolaryngol Head Neck Surg. 2009;140(1):134–5.
13. Hentschel M, Appold S, Schreiber A, Abramyuk A, Abolmaali N, Kotzerke J, et al. Serial FDG-PET on patients with head and neck cancer: implications for radiation therapy. Int J Radiat Biol. 2009;85(9):796–804.
14. Wong RJ. Current status of FDG-PET for head and neck cancer. J Surg Oncol. 2008;97(8):649–52.
15. Burrell SC, Van den Abbeele AD. 2-Deoxy-2-[F-18] fluoro-D-glucose-positron emission tomography of the head and neck: an atlas of normal uptake and variants. Mol Imaging Biol. 2005;7(3):244–56.
16. Loeffelbein DJ, Souvatzoglou M, Wankerl V, Martinez-Möller A, Dinges J, Schwaiger M, et al. PET-MRI fusion in head-and-neck oncology: current status and implications for hybrid PET/MRI. J Oral Maxillofac Surg. 2012;70(2):473–83.
17. Buchbender C, Heusner TA, Lauenstein TC, Bockisch A, Antoch G. Oncologic PET/MRI, part 1: tumors of the brain, head and neck, chest, abdomen, and pelvis. J Nucl Med. 2012;53(6):928–38.
18. Wu LM, Chen FY, Jiang XX, Gu HY, Yin Y, Xu JR. 18F-FDG PET, combined FDG-PET/CT and MRI for evaluation of bone marrow infiltration in staging of lymphoma: a systematic review and meta-analysis. Eur J Radiol. 2012;81(2):303–11.
19. Cistaro A, Cassalia L, Ferrara C, Quartuccio N, Evangelista L, Bianchi M, et al. Italian multicenter study on accuracy of 18F-FDG PET/CT in assessing bone marrow involvement in pediatric Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2018;18(6):e267–73.
20. Büyükşimşek M, Kolsuz İ, Yetişir AE, Tohumcuoğlu M, Oğul A, Mirili C, et al. Performance of positron emission tomography-computed tomography and bone marrow biopsy in detecting bone marrow infiltration in lymphoma cases. Turk J Haematol. 2020;37(4):220–5.
21. Ruilong Z, Daohai X, Li G, Xiaohong W, Chunjie W, Lei T. Diagnostic value of 18F-FDG-PET/CT for the evaluation of solitary pulmonary nodules: a systematic review and meta-analysis. Nucl Med Commun. 2017;38:67–75.
22. Zhang CY, Yu HL, Li X, Sun YY. Diagnostic value of computed tomography scanning in differentiating malignant from benign solitary pulmonary nodules: a meta-analysis. Tumour Biol. 2014;35:8551–8.
23. Gordin A, Golz A, Keidar Z, Daitzchman M, Bar-Shalom R, Israel O. The role of FDG-PET/CT imaging in head and neck malignant conditions: impact on diagnostic accuracy and patient care. Otolaryngol Head Neck Surg. 2007;137(1):130–7. https://doi.org/10.1016/j.otohns.2007.02.001
24. Purz S, Mauz-Körholz C, Körholz D, Hasenclever D, Krausse A, Sorge I, et al. [18F]Fluorodeoxyglucose positron emission tomography for detection of bone marrow involvement in children and adolescents with Hodgkin's lymphoma. J Clin Oncol. 2011;29(26):3523–8.
25. Adams HJ, Kwee TC, de Keizer B, Fijnheer R, de Klerk JM, Nievelstein RA. FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2014;41(3):565–74.