



# The role of PET/CT in the evaluation of bone marrow involvement in lymphoma patients at the initial staging

Lenfoma hastalarında tanı anında evreleme amaçlı çekilen PET/CT'nin kemik iliği infiltrasyonunu göstermedeki yeri

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## ABSTRACT

**Objective:** Bone marrow (BM) involvement is one of the most important prognostic factors in lymphoma patients. Therefore, it is important to determine the presence of BM involvement in lymphoma patients at the time of diagnosis. Bone marrow biopsy (BMB) is still accepted as the gold standard for evaluating the marrow but it is painful and invasive. In this retrospective study, we aimed to evaluate the role of positron emission tomography combined with computed tomography (PET/CT) in evaluating the BM involvement in lymphoma patients at the initial staging.

**Patients and Methods:** The patients who were evaluated by PET/CT and bone marrow biopsy at time of diagnosis were enrolled in the study.

**Results:** The overall sensitivity of PET/CT in demonstrating BM involvement was 65.8%, and the specificity was 89.4%. In the subgroup analysis of 176 Hodgkin lymphoma (HL) patients, the sensitivity and specificity of the PET/CT were 81% and 84% respectively. Negative predictive value was 98%. In 201 diffuse large B cell lymphoma (DLBCL) patients, the sensitivity and specificity of the test were 91.3% and 94.3%, respectively. Negative predictive value was 98.8%.

**Conclusion:** PET/CT is an accurate and complementary modality with high specificity and sensitivity in detecting BM infiltration in HL and DLBCL patients.

**Keywords:** PET/CT, Lymphoma, Bone marrow infiltration

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## ÖZ

**Amaç:** Kemik iliği (Kİ) tutulumu, lenfoma hastalarında en önemli prognostik faktörlerden biridir. Bu nedenle, tanı anında Kİ tutulumunun gösterilmesi önemlidir. Kemik iliği biyopsisi (KİB) tutulumu göstermede altın standart kabul edilmesine rağmen invaziv ve ağrılı bir yöntemdir. Bu retrospektif çalışmada, tanı anında evreleme amacıyla çekilen PET/CT'nin Kİ tutulumunu göstermedeki yerini araştırdık.

**Hastalar ve Yöntemler :** Tanı anında PET/CT ve KİB yapılan hastalar çalışmaya alındı.

**Bulgular:** PET/CT'nin lenfoma hastalarının Kİ tutulumunu göstermedeki sensitivitesi %65.8, spesifitesi ise %89.4 idi. Altgrup analizi yapıldığında; 176 Hodgkin lenfoma hastasında sensitivite %81 ve spesifite %84 olarak bulundu. Negatif prediktif değer %98 idi. 201 diffüz büyük B hücreli lenfoma hastasında ise, sensitivite ve spesifite sırasıyla %91.3 ve %94.3 idi. Negatif prediktif değer %98.8 olarak hesaplandı.

**Sonuç:** PET/CT özellikle Hodgkin lenfoma ve difüz büyük B hücreli lenfoma hastalarında yüksek sensitivite ve spesifitesi ile tamamlayıcı ve değerlendirilmesi gereken bir yöntemdir.

**Anahtar kelimeler:** PET/CT, Lenfoma, Kemik iliği tutulumu

## Introduction

Lymphomas are the most common hematologic malignancies in the developed world. Bone marrow (BM) involvement occurs in 30-50% in non-Hodgkin lymphoma (NHL) patients, especially in indolent subtypes [1]. BM involvement is one of the most important prognostic factors in lymphomas. It increases the stage of the disease to stage 4 according to Ann-Arbor staging system and is associated with poor prognosis [2]. Therefore, it is important to determine the presence of BM involvement in lymphoma patients at the time of diagnosis.

Bone marrow biopsy (BMB) is still accepted as the gold standard for evaluating the marrow. BMB is a painful

and invasive procedure. Complications such as bleeding, infection, needle breakage, osteomyelitis and fractures, especially in osteoporotic patients can, though rarely, be seen (0.05-0.07%). Even mortality directly related to the procedure has been reported [3]. Another disadvantage of BMB is that, it gives data pertaining to a limited area that is biopsied. Since the infiltration of lymphoma is usually focal, biopsy can miss the infiltration and the size of the biopsy may be too small to evaluate the infiltration. Although, some studies support the need for bilateral biopsies [4], others concluded that a specimen long enough (approximately 2 cm) may obviate the need for bilateral sampling [5].

New strategies are being searched for evaluating the BM infiltration in lymphoma patients. One of these methods is positron emission tomography combined with computed tomography (PET/CT) using 18F-2-deoxy-2-(18F) fluoro-D-glucose (18F-FDG). It is a whole body imaging technique that gives functional information about the cells using the glucose metabolism. Metabolically active cells such as malignant cells use and take radio-labeled glucose more avidly and become visible. This method can be used for staging and assessing treatment response for various malignant tumors including aggressive NHL and Hodgkin lymphomas (HL) [6-8] but its role in demonstrating BM infiltration is not documented well at present. In this retrospective study, we compare the results of BMB and PET/CT in terms of BM infiltration in lymphoma patients.

## Patients and Methods

### Patients

Four hundred and eighty-six adult patients older than 18 years of age diagnosed with lymphoma histopathologically according to World Health Organization (WHO) criteria [9] between March 2007 and August 2013 were retrospectively reviewed. PET/CT and BMB data obtained at the time of diagnosis of patients were re-assessed. Data of the patients were collected from the archives of Departments of Hematology and Pathology. Age, sex, complete blood count, lactate dehydrogenase and beta-2 microglobulin were recorded. The maximum time between the PET/CT and BMB was 7 days. The patients were excluded if their BMBs were performed more than 7 days after PET/CT.

Using WHO criteria, anemia was defined as hemoglobin lower than 130g/l and 120 g/l in males and females, respectively [10]. This study was approved by local ethics committee.

### Bone Marrow Biopsy

BMBs were performed in the standard way from the iliac spine under local anesthesia. Patients with inadequate sample for interpretation were not enrolled in the study. Bone marrow sections were prepared and stained with haematoxyline-eosin after decalcification procedures of BMB specimens. All bone marrow biopsies were examined for infiltration of lymphoma by specialist hematopathologists. Using paraffin embedded whole tissue sections; immunohistochemical analysis was performed on an automated stainer (Ventana Benchmark XT; Ventana Medical Systems, Tucson, Arizona, USA) according to the standard protocols. Streptavidin-biotin-peroxidase detection system with diaminobenzidine (DAB) as chromogen was used to visualize bound secondary antibodies. In order to determine an infiltration, a panel of antibodies was used according to the initial diagnosis, which included CD3 (Novacastra clone LN10, Novacastra Laboratories Ltd, Newcastle, UK; dilution 1:200), CD20 (Dako clone L26, DakoCytomation Inc, Carpinteria, CA; dilution 1:250), Pax-5 (CONE:34, Thermo Scientific Lab Vision, USA, dilution 1:50), CD30 (Novacastra clone 1G12, Novacastra Laboratories Ltd, Newcastle, UK; dilution 1:100), Bcl-2 (Dako clone 124, DakoCytomation Inc, Carpinteria, CA; dilution 1:50). When necessary, other immunohistochemical analyses were also performed.

### PET/CT

#### FDG PET and Contrast-Enhanced Computed Tomography

All patients underwent FDG-PET on a PET/CT unit (Discovery STE; GE, Milwaukee, USA). Patients fasted for at least 4 hours before imaging, and the glucose level in the peripheral blood was confirmed to be below 150 mg/dL before FDG injection. 5.55 MBq/kg of body weight of FDG was administered intravenously (IV) an hour before the image acquisition. After the initial contrast-enhanced CT scan with 16-multidetector CT (GE), a standard PET protocol was used in the 3D mode to scan the area from the vertex of the skull to the pelvic region with an acquisition time of 3 minutes per bed position.

Scanning was performed using the helical technique after injection of contrast medium to the patients whilst in the supine position. A total dose of 100–130 mL iodinated contrast media (iopromide, Bayer Pharma AG, Berlin, Germany) was administered IV at a rate of 3 mL/s by an

automatic injector. Written informed consents were obtained before PET/CT examination from each patient.

### Image Analysis

Fluoro-D-Glucose/positron emission tomography images were viewed at interactive workstations (Advantage Workstation AW4.6, GE Healthcare) by the same consultant in nuclear medicine and same radiologist both of whom are experienced in oncological imaging. Bone marrow FDG uptake was assessed visually in comparison to the liver uptake. The standardized uptake value (SUV) measurements were also obtained for each of the 3 larger homogeneous vertebrae visible in the field of view (L3, L4, and L5 or S1). A region of interest (ROI) was drawn over the vertebral body, using an automatic isocontour ROI set at 75% of the maximum SUV. The bone marrow SUV was defined as the mean value of the 3 selected vertebrae; vertebrae SUV values higher than the liver were considered as a sign of bone marrow involvement [11]. The absence of tracer uptake or low-grade uptake (less than or equal to liver parenchyma intensity) in the marrow sites was interpreted as absence of disease activity. Tracer uptake of moderate to intense degree (more than liver parenchyma intensity) was interpreted as presence of disease involvement. This was performed as a ratio of SUVmax values obtained from a suitable circular ROI over the spine in patients with bone marrow tracer uptake interpreted as presence of disease metabolic activity on qualitative assessment.

### Statistical analysis

Continuous data were expressed as median (minimum-maximum), and qualitative data were expressed as number of cases and percentages. Patients were categorized according to the status of BM infiltration according to the BMB and 18F-FDG PET/CT results. Correlations between FDG PET/CT and available pathological findings were examined. All positive pathological findings of BMB were considered as true-positive results. A finding of abnormal focal or multifocal increase in FDG uptake by the BM in the initial PET/CT study was considered true positive if the patient had corresponding pathologically confirmed lymphoma with BMB. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FDG PET/CT against BMB were presented for the assessment of BM involvement by lymphoma.

### Results

Four hundred and eighty-six newly diagnosed lymphoma patients (208 females, 278 males) who underwent both PET/CT and BMB were evaluated retrospectively. The median age was 45 years (range: 18-87 years). BM infiltration was documented in 79 patients with BMB, 95 patients with PET/CT and 52 patients with both procedures. There was discordance between the procedures in 70 patients (43 patients with negative BM infiltration and positive PET/CT; 27 patients with negative PET/CT for BM involvement but positive BMB). The characteristics of the patients were summarized in Table I.

**Table I: Characteristics of the patients**

	All patients	Non-Hodgkin lymphoma	Hodgkin lymphoma
Number of patients	486	310	176
Age, years (range)	45 (18-87)	59 (18-87)	38 (18-79)
Sex (male/female)	(278/208)	(173/137)	(105/71)
Involvement in PET/CT (yes/no)	95/391	60/250	35/141
Involvement in BMB (yes/no)	78/408	67/243	11/165
Anemia (yes/no)	178/181*	106/119*	72/62*
Beta 2 level (normal/high)	108/53*	71/38*	37/15*
LDH level (normal /high )	236/139*	145/95*	91/44*

\* Data of other patients are not available, PET/CT: positron emission tomography combined with computed tomography, BMB: bone marrow biopsy, LDH: lactate dehydrogenase

Since the BMB is still regarded as gold standard for evaluating BM infiltration, we compared the PET/CT imaging findings with BMB results in terms of BM infiltration. The overall sensitivity of PET/CT in demonstrating BM involvement in all lymphoma patients was 65.8%, and the specificity was 89.4%. As the lymphoma patients were very heterogeneous, we performed subgroup analysis, separating HL and NHL patients.

### HL Patients

There were 176 (71 females, 105 males) HL patients with the median age of 38 years (range: 18-79 years). BM

infiltration was documented in 11 HL patients with BMB while PET/CT depicted a high SUV value consistent with BM infiltration in 35 patients. The tests were comparable in 148 patients (both documented infiltration in 9 patients and neither documented infiltration in 139 patients). There was discordance between the tests in 28 of HL patients (Table II).

**Table II: The results of PET/CT and BMB in HL patients**

		PET/CT infiltration	
		YES	NO
BMB infiltration	YES	9	2
	NO	26	138

BMB: bone marrow biopsy, PET/CT: positron emission tomography combined with computed tomography, HL: Hodgkin lymphoma patients

Although the BMB was negative for infiltration, PET/CT depicted high uptake (more than liver); in 26 patients with HL which can be interpreted in favor of involvement. In three of these patients, the BM was hypercellular without infiltration. Twenty patients were either anemic or had leukocytosis (>10000/mm<sup>3</sup>). The laboratory tests were consistent with iron deficiency anemia in 6 of the anemic patients and anemia of chronic disease in the remaining anemic patients. The discordance could not be accounted for in 3 patients.

Among the HL patients, the sensitivity and specificity of the test were 81% and 84%, respectively. False positivity and false negativity was calculated as 18% and 16%, respectively. PPV and NPV was 25.7% and 98%, respectively (Table III).

**NHL Patients**

The subgroup of NHL patients comprised of 310 patients with diffuse large B cell lymphoma (DLBCL- 201 patients), follicular lymphoma (22 patients), mantle cell lymphoma (18 patients), marginal zone lymphoma (12 patients), low grade B cell lymphoma- nonspecified ( 3 patients), T- cell lymphoma (11 patients), anaplastic large B cell lymphoma (13 patients), Burkitt lymphoma (9 patients), small lymphocytic lymphoma (21 patients) were analyzed retrospectively. The most common subtype was DLBCL. Since high and low grade lymphomas were heterogeneous groups, the subgroup analysis in NHL patients was performed for the DLBCL group.

There were 201 DLBCL patients (88 females and 113 males). The median age was 59 years (range: 21-87 years). In 178 DLBCL patients, BMB showed no infiltration while in 23 patients it revealed lymphoma infiltration. PET/CT and BMB were consistent in 189 patients (21 patients were reported having BM involvement with both tests and there was no BM infiltration with either test in 168 patients). There was discordance between the tests in 12 patients (Table IV). There were two patients in whom PET/CT missed the infiltration of BM documented by biopsy. In 10 patients, PET/CT indicated infiltration while it could not be confirmed by BMB. Five of them had anemia consistent with chronic disease, three of them had leukocytosis and 2 of them had thrombocytosis which could explain the high activity of the bone marrow and positive PET/CT results.

In subgroup analysis of the DLBCL patients showed that the sensitivity and specificity of the test were 91.3% and 94.3%, respectively. False positivity and false negativity was calculated as 5.6% and 8.6%, respectively. PPV and NPV were 67.7% and 98.8%, respectively (Table III). There was not a specific subgroup in DLBCL patients with a higher specificity or sensitivity.

**Table III: Statistical measures of the performance of PET/CT (%) in HL patients and DLBCL**

	Sensitivity	Specificity	False negative ratio	False positive ratio	Accuracy	Positive predictive value	Negative predictive value
HL	81	84	16	18	84	25.7	98
DLBCL	91.3	94.3	8.6	5.6	94	67.7	98.8

HL: Hodgkin lymphoma, DLBCL: diffuse large B cell lymphoma, PET/CT: positron emission tomography combined with computed tomography

**Table IV: The results of PET/CT and BMB in DLBCL patients**

		PET/CT infiltration	
		YES	NO
BMB infiltration	YES	21	2
	NO	10	168

BMB: bone marrow biopsy, PET/CT: positron emission tomography combined with computed tomography, DLBCL: diffuse large B cell lymphoma

## Discussion

Positron emission tomography combined with computed tomography is being used increasingly for the initial staging and response evaluation in lymphoma patients. Although, its overall usefulness is not well documented in low-grade lymphomas, its role is well established in staging and response evaluation in HL and aggressive NHL patients [12,13]. Its value in showing the BM infiltration in lymphoma patients remains unclear and BMB is still the gold standard for evaluating the infiltration although it has some limitations. In this retrospective study, we compared the demonstration of BM infiltration with BMB and PET/CT which were performed at the time of diagnosis. Because FDG uptake can be affected by various chemotherapies and granulocyte stimulating factors, PET/CT reports obtained before the onset of the therapy were taken into account. The overall sensitivity and specificity of PET/CT against BMB was calculated as 65.8% and 89.4%, respectively. A meta-analysis performed by Pakos et al. found the sensitivity and specificity as 51% and 91%, respectively [14]. In this meta-analysis, no major subgroup differences have been reported in retrospective and prospective studies and the better sensitivity was shown in HL and aggressive NHL patients, a finding which is in agreement with our results [14].

Subgroup analysis of HL patients showed that the sensitivity and specificity of the PET/CT were 81% and 84%, respectively. In various research studies and meta-analyses conducted on HL patients, the sensitivity is in the range of 78.6-100%, which is consistent with our results. The specificity is also high, ranging between 76.5 – 100% [15-18].

In 26 patients, although the BMB was negative for infiltration, PET/CT showed high FDG uptake which may be an indicator of BM involvement. In these patients, leukocytosis, anemia and hypercellular bone marrow were noted. High uptake may be related to active bone marrow

rather than infiltration. But due to the fact that it was a retrospective study, we were unable to perform a rebiopsy from the sites of high FDG uptake to re-assess the infiltration. In a meta-analysis, 6 of 12 patients with negative BMB and positive PET/CT were found to be positive in BMB when the biopsies were repeated according to PET/CT uptake signals [14].

Positive predictive value and NPV of PET/CT in HL patients were 25.7% and 98% in our study. Muzahir et al., reported PPV and NPV to be 29.72% and 76.57% [16]. In a recent meta-analysis, pooled PPV and NPV as high as 97.6% and 98.8%, respectively have been reported [15]. Although, the NPV calculated in our study is consistent with this analysis, PPV is lower in the present study. In the present study, we took BMB as gold standard for evaluating BM infiltration. Therefore, we considered some FDG-avid lesions in PET/CT which could be indicative of true infiltration as false positive based on the negative results in blind BMB. Furthermore, it should be noted that the BMB may not show all the lymphomatous infiltration. BMB may reveal positive infiltration if the biopsy is repeated according to FDG-avid sites. This may explain the low PPV in our study [15,16,19,20].

Non-Hodgkin lymphoma is a heterogeneous group of patients with low and high grade lymphomas with different properties. In the literature, there was a significant difference in the capability of PET/CT to detect BM infiltration according to histological type of NHL. It has been reported in the literature that the performance of PET/CT in evaluating the BM infiltration in indolent lymphomas was poor [18, 21]. Since, indolent lymphomas comprise a number of different lymphoma types, we did not perform a subgroup analysis in this heterogeneous group.

Chen and et al., reported that the performance of PET/CT was better in the aggressive lymphoma group [21]. Among the aggressive lymphoma patients, DLBCL patients constituted the majority of the patients (201 patients, 64% of all NHL). Therefore, in this retrospective analysis, DLBCL were chosen for subgroup analysis among aggressive lymphoma patients. The sensitivity and specificity of the test against BMB were 91.3% and 94.3% respectively. There was discordance in 12 (6%) patients. PPV and NPV were 67.7% and 98.8%, respectively. Cortés-Romera et al., analyzed 147 lymphoma patients (84 DLBCL, 63 HL) [22]. The concordant and discordant results were observed between PET/CT and BMB in 19 (14%) and 128 patients (87%), respectively. The

sensitivity, specificity, accuracy, as well as PPV and NPV of FDG-PET/CT for the detection of BM infiltration were 95%, 86%, 87%, 54%, and 99%, respectively. In a meta-analysis with newly diagnosed DLBCL patients, the sensitivity of FDG PET/CT for detecting BM involvement ranged between 70.8% to 95.8% while the specificity was in the range of 99.0% to 100%, with pooled estimates of 88.7% (95% confidence interval, CI, 82.5 - 93.3%) and 99.8% (95% CI, 98.8 - 100%), respectively [23]. These results are comparable to ours.

In 10 DLBCL patients, PET/CT revealed infiltration while could not be confirmed by BMB. Five of these patients had anemia consistent with chronic disease, three patients had leukocytosis and two patients had thrombocytosis, which all can be held accountable for high activity of the bone marrow and positive PET/CT results. Positive results in PET/CT should be interpreted carefully if they are not confirmed by biopsy because false positive results may be due to chemotherapy, granulocyte colony stimulating factors, infection/inflammation, or hyperplastic bone marrow [24, 25].

False negative results with BMB due to focal infiltration should also be taken into account and repeat biopsy should be considered for the FDG-avid sites. PET/CT guided biopsy will increase the accuracy of BMB [19].

In our study, PET/CT missed the infiltration in 2 patients with DLBCL and 2 patients with HL. False negative results may be due to diffuse low density marrow involvement or low FDG uptake per cell [12, 21].

In the light of these data, PET / CT is an accurate and complementary test with high specificity and sensitivity in detecting BM infiltration, which also gives a prognostic information in DLBCL and HL patients [23, 26, 27]. On the other hand, there are also studies in which the authors argued that PET/CT had limited value in detecting BM involvement [28].

There are limitations of the present study. First, it was a retrospective study on a heterogeneous group of patients at different stages of diseases. Second, the unilateral iliac crest biopsies were carried out blindly and we could not perform a repeat biopsy in patients with negative BMB and positive PET/CT results, which may be the source of the lower PPV of the PET/CT. Lastly, since this retrospective study did not involve the follow up period of the patients, the effect of bone marrow involvement detected by PET/CT on survival and response rates could not be determined.

In conclusion, although BMB is still the gold standard to assess BM infiltration in lymphoma patients, it is a painful and stressful procedure for the patients. It is mostly considered safe but adverse effects such as hemorrhage, infection are also reported. Hence, since PET/CT is a noninvasive, painless and more comfortable procedure than biopsy, it could be an alternative to BMB for initial staging in especially HL and DLBCL patients in the future. However, prospective studies with larger sample size, more homogenous groups and involving follow-up periods are needed to detect the performance of PET/CT in establishing the infiltration and its effects on survival.

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