

The relationship between bone marrow activity detected on PET / CT and prognosis in patients with lymphoma

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Abstract

Aim: In this study, we aimed to evaluate the relationship between survival of patients with lymphoma who were considered to be negative for bone marrow (BM) infiltration and BM FDG uptake on PET / CT.

Material and Methods: This retrospective study included 55 patients diagnosed with lymphoma (33 HL and 22 NHL), with no BM infiltration (by biopsy or clinically negative) and having pre-treatment PET / CT. According to the pattern of BM FDG uptake on PET / CT the patients were divided into three groups as; those with focal FDG uptake (F-FDG), those with diffuse increased FDG uptake (D-FDG) and those with normal FDG uptake (N-FDG). The overall survival (OS) and progression-free survival (PFS) curves of the patients were plotted with Kaplan Meier method. The OS and PS of patients who were grouped according to the pattern of BM FDG uptake on PET / CT, gender, disease stage and lymphoma type were compared with Log Rank test.

Results: The mean follow-up period of our study was 23.7 ± 2.1 months (1-53 months). The mean OS was 41.9 ± 2.8 months, and the mean PFS was 37.8 ± 3 months. Ten patients showed focal or multifocal FDG uptake of BM on PET / CT (F-FDG). 28 patients had diffuse increased FDG uptake in the BM (D-FDG). In 17 patients, BM FDG uptake was within normal limits (N-FDG). There was no significant difference between OS and PFS of patients grouped according to gender, stage of disease, type of lymphoma and BM FDG uptake pattern ($p > 0.05$). Older age was associated with shorter OS and PFS.

Conclusion: In our study, no significant relationship was found between BM FDG uptake on PET / CT and survival of patients with lymphoma with negative BM infiltration. However, although PET / CT does not completely replace BM biopsy, it may be helpful in detecting early infiltration of BM.

Keywords: Lymphoma; bone marrow; FDG; PET/CT

INTRODUCTION

The prognosis in cases of lymphoma depends on the stage at the time of diagnosis (1,2). Bone marrow (BM) infiltration in particular is of critical importance in the staging of lymphoma, in that it indicates the advanced stage of the disease, and therefore may affect both the treatment and the prognosis (3,4). BM infiltration is observed in approximately 25–40% of cases with high-grade non-Hodgkin lymphoma (NHL) and in approximately 5–14% of cases with Hodgkin lymphoma (HL) at the time of diagnosis (5,6).

The commonly accepted method for the detection of BM infiltration is BM biopsy (7,8), however, as an invasive method that assesses only part (iliac crest, sternum) of the BM, the efficacy of the approach is somewhat limited. Although reliable, the BM biopsy approach involves

certain risks, with complications reported in around 0.12% of cases (9).

Fluorine-18 2-fluoro-2-Deoxy-d-glucose (F18-FDG) positron emission tomography/computed tomography (PET/CT) – as a non-invasive and semi-quantitative imaging approach – is the most specific and sensitive molecular imaging technique for the staging of lymphoma and the assessment of treatment response (10, 11). PET/CT is used as a routine for the staging of lymphoma and the assessment of treatment response, however there have been few studies to date assessing the value of PET/CT in the diagnosis of BM infiltration (12,13). Furthermore, the effect of early limited BM infiltration on prognosis and recurrence after standard treatment is not known (14). The present study assesses the relationship of BM activity detected on PET/CT with overall survival (OS) and progression-free survival (PFS) in lymphoma patients

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identified as BM infiltration negative from a biopsy, or those considered negative clinically.

MATERIAL and METHODS

Patients

This retrospective study included 55 cases who had been histopathologically diagnosed with lymphoma (33 HL and 22 NHL) between June 2015 and June 2018, who were negative for BM infiltration, based on the results of a biopsy or who were considered negative clinically, and who underwent a PET/CT scan prior to treatment.

Prior to and immediately after the histopathological diagnosis, a CT or magnetic resonance imaging (MRI) was carried out on the thorax, neck, abdomen and pelvis. For cases suspected of BM infiltration, an MRI of the relevant area or a whole body bone scintigraphy (BS) was additionally requested. All examinations (PET/CT, CT, MRI, BS) were considered together for the establishment of disease stage and treatment method. Chemotherapy and radiotherapy combinations were used for early stage (stages 1–2) cases, while standard treatment combination chemotherapies were used for advanced stage (stages 3–4) cases. The present study was granted ethical approval at a meeting at our hospital dated 01.11.2019, with Decision No: 9.

BM biopsy

Biopsy specimens from the iliac bones of patients were analyzed following standard procedures, including formalin fixation, paraffin-embedding and hemotoxilen-eosine staining.

PET/ CT Imaging and Analysis

The F-18 FDG PET/CT images were captured using a PHILIPS GEMINI TF 16 Slice PET/CT device. An intravenous administration of 8–11 mCi F-18 FDG was made following at least 6 hours of fasting, and one hour after the injection, CT (140 kV, 100 mAs, 5 mm section) and PET (90 seconds per bed position) images were captured. The PET/CT images were assessed using visual and quantitative parameters. Patients with a history of medication use due to anemia or chronic disease were excluded from the study. Based on the BM infiltration patterns on PET/CT, patients were divided into three groups, as focal BM FDG uptake (F-FDG), increased diffuse BM FDG uptake (D-FDG) and normal BM FDG uptake (N-FDG).

The F-FDG group consisted of cases with increased focal or multifocal BM FDG uptake; the D-FDG group consisted of cases with a mean SUV BM higher than the mean SUV liver and with increased diffuse FDG uptake; and the N-FDG group consisted of cases with a mean SUV BM lower than the mean SUV liver.

Survival Analysis

Overall survival (OS) was defined as the time from the date of diagnosis to the date of death or the last follow-up. Progression-free survival (PFS) was defined as the time from the date of diagnosis to the date of progression, death or last follow-up.

The Kaplan-Meier method was used to draw OS and PFS curves for the patients. The OS and PFS of the patients, who were grouped according to BM infiltration patterns on PET/CT, gender, disease stage and lymphoma type, were compared using a Log-Rank test. A comparison of BM FDG uptake from the PET images was made by evaluating D-FDG and N-FDG in the same group and comparing them with the F18-FDG group. The patient's age and the highest maximum standardized uptake value (SUVmax) established on PET were considered as continuous variables, and the OS and PFS relationship was analyzed using the Cox regression method. A $p < 0.05$ value was considered significant in the statistical analyses.

RESULTS

The study included 55 patients (39 male; 16 female) with a mean age of 36.8 ± 0.21 (4–72) years who had been diagnosed with lymphoma (HL, 22; NHL, 33) that was negative for BM infiltration on biopsy or considered negative clinically.

Based on the Ann Arbor staging system, eight patients were at stage I, 12 patients were at stage II, 21 patients were at stage III and 14 patients were at stage IV.

Table 1. Cases grouped according to bone marrow FDG uptake pattern on PET / CT images

	F-FDG	D-FDG	N-FDG
HL	4	24	6
NHL	6	4	11
Total	10	28	17

HL: Hodgkin Lymphoma, NHL: Nonhodgkin Lymphoma, F-FDG: Cases with focal increased FDG uptake in the bone marrow, D-FDG: Cases with diffuse increased FDG uptake in the bone marrow, N-FDG: Cases with normal FDG uptake in the bone marrow

PET/CT images revealed focal or multifocal FDG uptake (F-FDG) in 10 cases; increased diffuse FDG uptake in the bone marrow (D-FDG) was identified in 28 cases; and BM FDG uptake was normal (N-FDG) in 17 patients. Table 1 summarizes cases grouped according to BM infiltration patterns. Figure 1 presents a case with increased diffuse 18FDG uptake in the bone marrow.

The mean follow-up time of the study was 23.7 ± 2.1 months (1–53 months), during which 12 patients died and 17 patients experienced disease progression.

Considering all patients together, the mean OS was 41.9 ± 2.8 months and the mean PFS was 37.8 ± 3 months.

There was no significant difference in the OS and PFS of patients when grouped by gender, disease stage, lymphoma type and bone marrow infiltration pattern ($p > 0.05$). The results are presented in Table 2. Furthermore, no significant difference was noted in OS ($p = 0.518$) and PFS ($p = 0.942$) between the D-FDG and N-FDG groups.

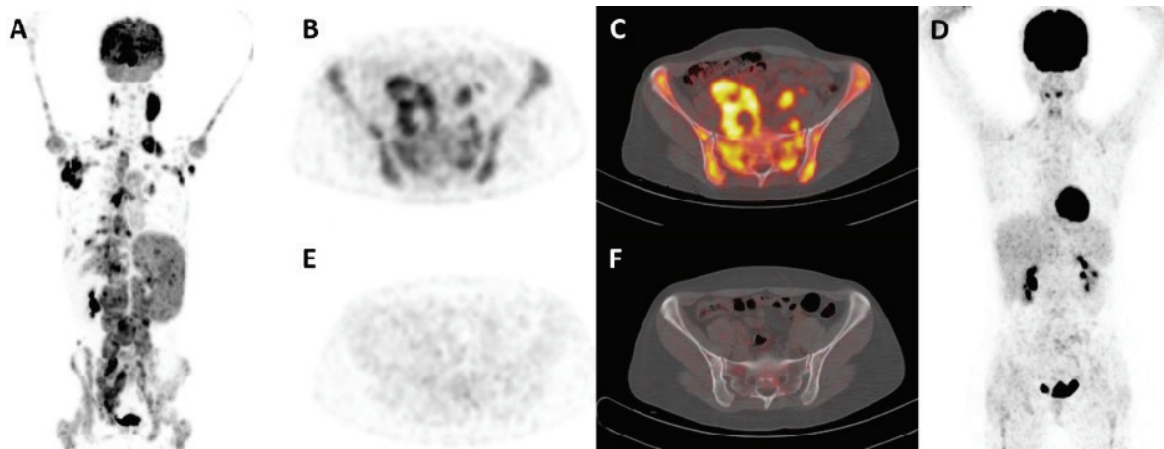


Figure 1. A 36-year old female patient diagnosed with classical Hodgkin lymphoma, nodular sclerosing type, upon a histopathological examination of material from cervical lymphadenopathies. On the PET/CT images taken for pretreatment staging, increased ^{18}F FDG uptake (A-C) was noted in the bone marrow and spleen with increased size, in the conglomerate lymph nodes in the neck, in the mediastinal and abdominopelvic regions. A bone marrow biopsy of the case revealed no infiltration. Complete response on post-treatment PET/CT images is notable (D-F).

Table 2. Survival analysis of patients grouped by sex, disease stage, lymphoma type, and bone marrow uptake pattern

	OS		PFS	
	mean±SE	p	Mean±SE	p
Gender		0.085		0.546
Female	46.6±2.8		37.8±4.8	
Male	38.6±3.6		36.4±3.7	
Stage		0.706		0.199
1-2	43.6±4.2		43.1±4.4	
3-4	41±3.7		35±3.9	
Lymphoma type		0.441		0.849
Hodgkin	43.5±3.4		38.3±3.8	
Nonhodgkin	39.5±4.7		37.1±4.9	
PET		0.530		0.942
F-FDG	38.8±6.9		38.2±7.1	
D-FDG/N-FDG	42.7±3		37.1±3.3	

OS: Overall survival, PFS: Progression-free survival, F-FDG: Cases with focal increased FDG uptake in the bone marrow, D-FDG: Cases with diffuse increased FDG uptake in the bone marrow, N-FDG: Cases with normal FDG uptake in the bone marrow

In addition, the relationship between BM FDG uptake and survival was evaluated in both NHL and HL patients. In patients with NHL no significant difference was noted in OS ($p=0.833$) and PFS ($p=0.945$) between the F-FDG and N/D-FDG groups. Also there was no significant difference in patients with HL in terms of OS ($p=0.662$) and PFS ($p=0.933$) between the F-FDG and N/D-FDG groups.

In addition, no statistically significant relationship was found between the highest SUVmax established on PET, and OS ($p=0.513$) and PFS ($p=0.442$). Increased patient age was found to be associated with a shorter OS ($p=0.003$) and PFS ($p=0.041$) (Table 3).

Table 3. Patient age and relationship between SUVmax and survival

	OS		PFS	
	HR	P	HR	p
Age	1.064	0.003*	1.029	0.041*
SUV_{max}	1.019	0.513	1.020	0.442

OS: Overall Survival, PFS: Progression-free Survival, SUVmax: Maximum Standardized Uptake Value, $p < 0.05$ values are indicated with *.

DISCUSSION

BM infiltration is one of the leading prognostic factors for lymphoma (15). The current standard assessment approach is iliac bone biopsy (16); however, this method does not allow the assessment of focal or multifocal BM infiltrations beyond the iliac bone. A study involving HL and NHL patients made a comparison of unilateral and bilateral iliac bone biopsy results, and found false positivity in 80% of cases undergoing a unilateral iliac bone biopsy (17). The effect of limited BM infiltration on prognosis and recurrence after the standard treatment is not known, and there has not been enough research in this regard (14). The present study examines the extent to which BM activity identified on PET affected prognosis through an assessment of the relationship between FDG uptake on PET and survival in cases diagnosed with lymphoma that was negative for BM biopsy of the iliac bone or considered negative for BM infiltration clinically.

18F-FDG used for PET/CT displays accumulation in the BM physiologically (18). Several factors may increase FDG uptake in BM, such as chemotherapy, infection, inflammation, hyperplastic bone marrow and the administration of a granulocyte colony-stimulating factor, leading to false positive results (19). In HL, Reed-Sternberg cells interact with reactive cells, resulting in inflammatory changes (20). Tumoral inflammation in HL is argued to be responsible for the increased 18FDG uptake (21). The increased benign FDG uptake observed in the bone marrow in relation to the activation of BM against inflammation and infection may lead to incorrect assessments in cases without BM infiltration (22,23). Studies have been conducted into the neutrophil-to-lymphocyte ratio, the platelet-to-lymphocyte ratio and the C-reactive protein aiming to assess the systemic inflammatory response to malignancy (24,25). Neutrophil count has been reported to aid in interpretation while assessing BM infiltration on PET/CT (26). That said, it may not always be possible to determine whether the finding is BM infiltration or a result of systemic response, especially in cases with increased diffuse BM FDG uptake. Previous studies have demonstrated that FDG PET/CT cannot replace the BM biopsy approach due to the low sensitivity of the approach in the detection of BM infiltration, and that fact that a negative FDG PET/CT result cannot rule out BM infiltration (15,28). A meta-analysis study assessing PET/CT and BM biopsy data of 587 lymphoma cases established a positive FDG PET/CT only in half of the patients with BM infiltration detected in a BM biopsy (13). It has been reported that the affinity of 18FDG may be low in some low-grade NHL types (30). Furthermore, it has been stated that FDG PET/CT has low sensitivity in the detection of BM infiltration in NHL cases, and cannot replace BM biopsy for this group of patients (15). The present study also failed to identify any significant difference in the OS and PFS of the patients grouped in terms of BM FDG uptake patterns. Some lymphoma types have low FDG affinity, and the different lymphoma types and age groups in our study population may have affected our findings in this regard. Furthermore, our findings may have resulted from an incorrect assessment of BM infiltration with PET. That said, 18F-FDG PET may sometimes reveal areas of focal BM infiltration that were missed by a BM biopsy (13). There have been studies reporting that the foci indicating 18FDG uptake should be assessed with biopsy or MRI (11). In selected cases, hypermetabolic foci observed focally on PET/CT may act as a guide for a BM biopsy or MRI, although there is insufficient data and studies supporting the clinical effectivity of image-guided biopsy in staging rather than the standard iliac bone biopsy.

In the present study, focally increased FDG uptake beyond the iliac region was identified on PET/CT prior to treatment in two advanced-stage cases, although the iliac bone biopsy and MRI findings of the patients had been negative for BM infiltration.

A study of patients diagnosed with NHL and HL identified no significant relationship between survival and the SUVmax of the lesion displaying the most intense FDG

accumulation on PET/CT (34). In the study, however, survival was found to be associated with metabolic volumetric parameters, including total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG) measured on PET/CT. Similarly, the present study identified no statistically significant relationship between SUVmax of the lesion with the most intense FDG accumulation, and OS and PFS.

The present study also failed to find any significant link between survival, and lymphoma type and stage, which may have resulted from the lack of assessment of additional prognostic factors, different lymphoma types and short follow-up times. There are studies with worse prognosis in female patients in pediatric and young adult lymphoma. There are also studies where there is no statistical significance in terms of gender (35). Studies advocating that hormonal changes in female patients provide the advantage of survival have been published (36). In our study, the heterogeneous and relatively low number of cases and the presence of pediatric patients may have affected our survival results. An earlier study failed to establish any significant relationship between gender and survival, which is in line with the findings of the present study. Additionally, a significant relationship was found between age and survival in the present study, in line with literature.

CONCLUSION

The present study identified no significant relationship between survival and BM FDG uptake in patients with lymphoma negative for BM infiltration on biopsy, or considered negative clinically. That said, PET/CT, although it may not replace BM biopsy completely, may be helpful in detecting and guiding the treatment of early BM infiltration.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

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