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Başlık: Hodgkin lenfomalı hastalarda kemik iliği tutulumunun tespitinde PET/BT

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Hodgkin lenfomalı hastalarda kemik iliği tutulumunun tespitinde PET/BT

The role of PET/CT to detect bone marrow involvement in Hodgkin lymphoma

INTRODUCTION

Hodgkin's lymphoma (HL) comprises 12% of lymphoma cases and 1% of all malignancies (1). It is possible to achieve cure with modern treatment modalities in the first line therapy for about 90 % of patients. However treatment fails in 10% of early stage and 30% of advanced stage disease. Cure rates are around 50% in relapsed disease, extra nodal disease and in patients relapsing early after treatment of advanced stage disease (2-5). Correct staging is necessary for an effective treatment plan (6,7). Bone marrow involvement (BMI) is one of the most important prognostic factors in lymphomas. BMI corresponds to stage IV disease according to Ann Arbor staging system (8). Staging of HL is based on Cotswold's modification of Ann-Arbor system (8,9) and commonly includes computerized tomography (CT) and bone marrow biopsy (9). BMI is detected in 5-14% of HL patients (10,11). Unilateral bone marrow biopsy (BMB) performed from dorsal iliac crest is considered as standard and performed routinely during staging (12,13). However main disadvantages of BMB are its interventional nature and its allowing only a limited region of bone marrow to be investigated. A previous study reported 80% false negativity of a unilateral iliac crest biopsy compared with a bilateral biopsy in lymphoma patients (14). Imaging techniques may be used to detect bone marrow involvement, CT may be able to show bone lesions or late occurring bone changes; however its sensitivity in early stage disease is low (7). Magnetic resonance imaging (MRI) is a sensitive technique although it is not used widely in routine practice. [18F] Fluorodeoxyglucose (FDG) Positron Emission Tomography/Computerized (PET/CT) has been used for staging and evaluating response in lymphoma patients. A number of studies have shown that PET/CT is useful to evaluate bone marrow (6,7,15). It has been shown that PET/CT and BMB are 78-82% compatible, thus PET/CT is recommended as a complimentary technique (14-17).

The aim of this study is to compare BMB and FDG-PET/CT to detect bone marrow involvement and to determine whether FDG-PET/CT can replace BMB in patients with Hodgkin's lymphoma.

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METHODS

Patients over 18 years-old who had been diagnosed with HL between January 2007 and January 2015 in our University Hospital were evaluated retrospectively. Patients who did not have bone marrow biopsy and PET/CT performed simultaneously at diagnosis were excluded from the study. All patients had BMB and PET/CT performed at diagnosis. Age, sex, date of diagnosis, type of PET/CT involvement (focal, diffuse), SUV-max values, BMI, stage of disease, risk score, B symptoms, date of last follow up, treatments, PET/CT results before and after treatment were recorded.

Administration of PET/CT was carried out locally on dedicated machines in accordance with the manufacturer guidelines (……..). During the evaluation of PET/CT, bone marrow activity greater than that of liver was considered positive for bone marrow involvement by HL unless definitively explained by an alternate cause. Involvement was evaluated as diffuse or focal (1,2,3 and>3 areas).

All bone marrow samples were obtained unilaterally from dorsal iliac crest and each was 15-20 mm in length. Samples were evaluated by an expert hematopathologist.

The study was approved by the Instutional Ethical Review Board.

Statistical Analysis

BMB was considered as standard reference to determine BMI. Results that were compatible with BMB and PET/CT were regarded as true positive and true negative initially. Cases that were PET/CT positive and BMB negative initially were evaluated with PET/CT during and at the end of treatment. Sensitivity, specificity, negative and positive predictive values were calculated. PASW 18.0 for Windows software was used for the statistical analysis. Descriptive statistics were provided as average, standard deviation, median, percentile 25 (Q1), percentile 75 (Q3), minimum and maximum. Conformity of the variables towards the normal distribution was analyzed with visual (histogram and probability diagram) and analytical (Kolmogorov–Simirnov/Shapiro-Wilktests) methods. Unable to demonstrate any normal ranges, the paired group comparison was conducted by the Mann Whitney U test for the diagnosis age, SUV Max, tracking duration and phase, the IPS and PET phase escalation. Ki-Square test was used for the paired comparison between the categorical variable, and Fisher Exact Test was used where the Ki-Square condition was unable to be provided. Cases where type-1 error was below 5%

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were regarded as statistically significant.

RESULTS

A total of 159 patients who had been diagnosed with HL between January 2007 and January 2015 in Marmara University Medical Faculty were evaluated retrospectively. Fifty five patients who did not have bone marrow biopsy and PET/CT performed simultaneously at diagnosis were excluded from the study. A total of 104 patients were evaluated.

Both PET/CT and BMB were performed for initial staging in a total of 104 newly diagnosed HL patients (45 female, 59 male). Median age was 32 (18-80), 94.2 % was diagnosed with classical HL (58.3% nodular sclerosis, 28.2 % mixed cellularity, 5.8 %lymphocyte rich, 1.9 % lymphocyte depleted), and the remaining 5.8 % was diagnosed with Nodular lymphocyte predominant type. One patient had stage I, 36 patients had stage II, 37 patients had stage III and 30 patients had stage IV disease. According to IPS risk score; the number of patients were 67, 17 and 18 as for low, intermediate and high risk respectively. Clinical characteristics of patients are summarized in table 1.

Bone marrow involvement was detected in 44 patients (42.3%) with PET/CT and in 17 patients (16.3%) with BMB. Out of 44 patients who had BMI in PET/CT, 27 did not have BMI in BMB, however all 17 patients who had bone marrow involvement in BMB also had involvement in PET/CT (table 2). Two patients with stage II and 17 patients with stage III disease were regarded as stage IV after restaging with PET/CT

Disease stage and higher IPS risk were statistically significant in patients who were PET positive for BMI compared to PET negative patients ($p<0.001$, $p<0.001$ respectively)

Disease stage and higher IPS risk were statistically significant in patients who had BMI in bone marrow biopsy compared to who were bone marrow biopsy negative ($p<0.001$, $p<0.001$ respectively) .

PET/CT was negative for BMI in 60 patients. All of these patients were also negative for bone marrow involvement in BMB. Remaining 44 patients were PET/CT positive. There were not any uncertain cases since FDG values greater than liver was considered as positive. Involvement was evaluated as focal and diffuse. Focal group was examined as 1, 2, 3, and >3 areas. According to this classification 3 patients has focal 1, 4 patients had focal 2, 6 patients had focal 3 and 1 patients had focal >3 areas of

involvement with a total of 28 patients having focal involvement. Sixteen patients had diffuse involvement. PET/CT positive, BMB negative patients had a median SUVmax value of 5.1 while PET/CT positive, BMB positive patients had 6.8 which was not statistically significant.

When evaluating involvement type in PET/CT, it was observed that as the areas of focal involvement increased, the rate of involvement in BMB also increased. BMB was positive in all cases with diffuse involvement. Increase in disease stage of patients who had bone marrow involvement in PET/CT was statistically significant compared to patients who were negative for ($p<0.001$***).*** All patients who had BMI in PET/CT at diagnosis had partial or complete regression after treatment. Twenty-two (81.5%) of PET/CT positive cases had complete regression and 5 (18.5%) had partial regression, a finding that was regarded as a sign of BMI (Table 3).

Analysis revealed a sensitivity of %100 for PET/CT to detect bone marrow involvement, while specificity was found to be %68.97 (Table 4)

DISCUSSION

Anatomical extensiveness and to a lesser degree histological subtype of the disease are factors that define prognosis and guide towards appropriate treatment in HL. Aim of treatment is to achieve cure with minimal complications. Therefore, correct staging is necessary to make an effective treatment plan . Evaluating BMI is an important step in staging. Bone marrow involvement is detected in about 10 % of HL patients (10). In our study BMI was detected in 16.3% of patients, which was higher than previously reported. Standard procedure to evaluate BMI is a unilateral BMB. Bone marrow involvement may be focal or diffuse. Blind biopsy samples may reveal false negative results if performed from uninvolved areas of bone marrow and comparisons with other techniques are necessary. Positivity of bilateral biopsy is 10-50 % which is higher than unilateral biopsy. Therefore standard BMB does not reflect a correct evaluation of bone marrow (18). A negative BMB does not rule out BMI if imaging techniques show abnormalities. BMI is nodular in 65% of HL patients on MRI. This explains a negative BMB when other areas have BMI (19). It has been suggested that PET/CT could replace blind BMB or could be used as a guide to find the correct area for BMB. For patients with a high risk of BMI, FDG may be decisive. Since, PET/CT detects a greater area than BMB and there is no bone marrow involvement if there is not any FDG uptake (15). Therefore it is more sensitive than CT and bone scintigraphy to detect BMI. PET/CT may reveal early bone marrow involvement in patients with a negative CT scan (6,7,10).

For this reason, true positivity should be determined. PET/CT results are evaluated in 3 reference levels in PET/CT positive cases. First of all, if BMB is positive, this is a verification at the highest level. Secondly, skeletal PET/CT findings of multifocal pattern (3 or more skeletal lesions): This pattern is typical for HL and may rarely be seen in other diseases (6). Thirdly, complete or near complete regression in PET/CT after chemotherapy is an intermediate level of verification, since FDG uptake may be observed in inflammatory and traumatic lesions as well. In our study, twenty-seven patients who had BMI in PET/CT but not in BMB were re-evaluated after treatment. Partial or complete regression of BMI was regarded as a clue for true positivity.

PET/CT should not be regarded as positive when FDG uptake is diffuse, homogenous and symmetrical in axial and appendicular skeleton unless the FDG uptake is overt. It is regarded as bone marrow activation when FDG uptake of bone marrow is greater than liver. PET/CT may result false positive when there is a concomitant systemic disease or granulocyte colony stimulating factor use. Such cases and benign increases due to inflammatory reactions may be interpreted as false positive, however bone marrow involvement cannot be ruled out (7,20).

Most studies include a heterogenous population of Non Hodgkin's Lymphoma (NHL) and HL. This results in a variety of FDG uptake due to different subtypes (18). In our research, solely patients with HL were evaluated.

In a study conducted by Guven Cetin et al. 61 patients with HL were analysed. Although, concordant results were revealed between PET/CT and BMB in 52, there were 2 patients with positive BMB while PET/CT was negative. On the other hand, 7 patients had negative BMB, while positive on PET/CT (21). In contrast, our study did not revealed any false negative cases.

Moulin-Romseeet al. repoted 83 patients diagnosed with HL out of which 7 patients had BMI with BMB. Eighteen patients had BMI with PET/CT. Out of 11 patients that were PET/CT positive and BMB negative, 2 had stage IV disease due to lung and liver involvement. Remaining 9 patients were considered having disseminated disease and treated accordingly (22). In our study, 2 patients with stage II and 17 patients with stage III disease initially were regarded as having stage IV disease after detecting BMI with PET/CT and treatment plans were re-evaluated.

We showed that sensitivity and negative predictive value of PET/CT to be 100%. Specificity was 68.9 % and accuracy rate was 74 %. These findings were similar to the data published by Pakos et al. (18). In a

study by Anjum Bashir Khan et al. 130 patients diagnosed with lymphoma was evaluated, when examined together PET/CT and BMB proved BMI in 35 (27%) patients. PET/CT detected BMI in 33 (94%) of these patients, while BMB detected in 14 (40%) patients (23). Sensitivity and specificity of PET/CT to detect BMI was 94% and 100% respectively. Sensitivity of BMB was found to be 40% and specificity was 100%. Accuracy rate was 98.5% for PET/CT and 84% for BMB. We observed similar results for sensitivity and specificity in our current study.

Although, our study confirmed studies previously performed, the most important limitation of our study is the relative small number of study population and its retrospective nature. Therefore prospective studies including larger patient populations are necessary.

CONCLUSION

FDG-PET/CT increased the sensitivity of detecting BMI compared to conventional staging. In patients who have BMI with PET/CT but not with BMB, staging should be reevaluated and treatment should be planned accordingly. Absence of false positive results in PET/CT and the observation about all patients had regression in FDG uptake after treatment may be an indicator to show PET/CT could replace BMB to determine BMI.

Since our study was conducted retrospectively, it was not feasible to get informed consent from the patients, however it was approved by the Instutional Ethical Review Board.

REFERENCES

1. Diehl V. Hodgkin's disease–from pathology specimen to cure. N Engl J Med 2007;357(19):1968–71.
2. Brice P, Bastion Y, Divine M, Nedellec G, Ferrant A, Gabarre J, et al. Analysis of prognostic factors after the first relapse of Hodgkin's disease in 187 patients. Cancer 1996;78(6):1293–9.
3. Moskowitz CH, Nimer SD, Zelenetz AD, Trippett T, Hedrick EE, Filippa DA, et al. A 2-step comprehensive high-dose chemo- radiotherapy second-line program for relapsed and refractory

Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001;97(3):616–23.

4. Josting A, Franklin J, May M, Koch P, Beykirch MK, Heinz J, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. J ClinOncol 2002;20(1):221–30.
5. Brice P. Managing relapsed and refractory Hodgkin lymphoma. Br J Haematol 2008;141(1):3–13.
6. Pelosi E, Penna D, Deandreis D, Chiappella A, Skanieti A, Vitolo U, et al. FDG-PET in the detection of bone marrow disease in Hodgkin's disease and aggressive non-Hodgkin's lymphoma and its impact on clinical management. Q J Nucl Med Mol Imaging. 2008; 52:9-16.
7. Moulin-Romsee G, Hindié E, Cuenca X, Brice P, Decaudin D, Benamor M, et al. ^{18}F-FDG PET/CT bone/bone marrow findings in Hodgkin's lymphoma may circumvent the use of bone marrow trephine biopsy at diagnosis staging. Eur J Nucl Med Mol Imaging. 2010; 37:1095-1105.
8. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classi- fication. Cancer Res 1971;31(11):1860–1.
9. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J ClinOncol 1989;7(11):1630–6. Erratum in: J ClinOncol 1990;8(9):1602.
10. Levis A, Pietrasanta D, Godio L, Vitolo U, Ciravegna G, Di Vito F, et al. A large-scale study of bone marrow in- volvement in patients with Hodgkin's lymphoma. Clin Lymphoma. 2004;5:50-55.
11. Ponzoni M, Ciceri F, Crocchiolo R, Famoso G, Doglioni C. Isolated bone marrow occurrence of classic Hodgkin's lymphoma in an HIV-negative patient. Haematologica. 2006; 91:04.
12. Brusamolino E, Bacigalupo A, Barosi G, Biti G, Gobbi PG, Levis A, et al. Classical Hodgkin's lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplan- tation on initial work-up, management, and follow-up. Haematologica. 2009; 94:550-565.
13. Howell SJ, Grey M, Chang J, Morgenstern GR, Cowan RA, Deakin DP, et al. The value of bone marrow examination in the staging of Hodgkin's lymphoma: a review of 955 cases seen in a regional cancer centre. Br J Haematol. 2002;119:408-411.
14. Wang J, Weiss LM, Chang KL, Slovak ML, Gaal K, Forman SJ, Arber DA () Diagnostic utility of bilateral bone marrow examination: significance of morphologic and ancillary technique study in

malignancy. Cancer. 2002; 94(5):1522–1531

15. Moog F, Bangerter M, Kotzerke J, Guhlmann A, Frickhofen N, Reske SN. 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. J ClinOncol. 1998;16:603-609.
16. Hong J, Lee Y, Park Y, Kim SG, Park SH, Jeong J, et al. Role of FDG-PET/CT in detecting lymphomatous bone marrow involvement in patients with newly diagnosed diffuse large B-cell lymphoma. Ann Hematol. 2012;91:687-695.
17. Fuster D, Chiang S, Andreadis C, Guan L, Zhuang H, Schuster S, et al. Can [18F]Fluorodeoxyglucose positron emission tomography imaging complement biopsy results from the iliac crestfor the detection of bone marrow involvement in patients with malignant lymphoma? Nucl Med Commun. 2006;27:11-15.
18. Pakos EE, Fotopoulos AD, Ioannidis JP. 18F-FDG PET for evaluation of bone marrow infiltration in staging of lymphoma: A meta-analysis. J Nucl Med. 2005;46(6):958-963
19. Inoue K, Goto R, Okada K, Kinomura S, Fukuda H. A bone marrow 18F-FDG uptake exceeding the liver uptake may indicate bone marrow hyperactivity. Ann Nucl Med. 2009; 23:643-649.
20. Agool A, Glaudemans AW, Boersma HH, Dierckx RA, Vellenga E, Slart RH. Radionuclide imaging of bone marrow disorders. Eur J Nucl Med Mol Imaging. 2011;38:166-178.
21. Cetin G, Cıkrıkcıoglu MA, Ozkan T, Karatoprak C, Ar MC, Eskazan AE, et al. Can Positron Emission Tomography and Computed Tomography be a substitude for bone marrow biopsy in detection of bone marrow involvement in patients with Hodgkin's lymphoma and Non-hodgkin's lymphoma. Turk J Hematol. 2015;32:213-219.
22. Moulin-Romsee G, Hindie E, Cuenca X, Brice P, Decaudin D, Benamor M, et al. FDG PET/CT bone/bone marrow findings in Hodgkin's lymphoma may circumvent the use of bone marrow trephine biopsy at diagnosis staging Eur J Nucl Med Mol Imaging 2010-37:1095-1105
23. Khan AB; Barrington SF, Mikhaeel NG, Hunt AA, Cameron L, Morris T, et al. PET-CT Staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood 2013;122(1):61-7

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Table 1: Demographics

Sex, n (%)	Female	45 (43.3)
	Male	59 (56.7)
Age at diagnosis, median (Q1-Q3)		32.00 (24.50-46.00)
Disease subtype, n (%)	Nodular sclerosis	60 (58.3)
	Mixed cellularity	29 (28.2)
	Lymphocyte rich	6 (5.8)
	Lymphocyte depleted	2 (1.9)
	Nodular lymphocyte predominant	6 (5.8)
Stage, n (%)	1A	1 (1.0)
	2A	21 (20.2)
	2B	15 (14.4)
	3A	12 (11.5)
	3B	25 (24.0)
	4A	7 (6.7)
	4B	23 (22.1)
IPS, n (%)	Low risk	69 (66.3)
	Intermediate risk	17 (16.3)
	High risk	18 (17.3)

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Table 2: Bone marrow involvement

		n (%)
Bone marrow involvement in PET/CT		44 (42.3)
Bone marrow involvement in bone marrow biopsy		17 (16.3)
PET/CT –Bone marrow biopsy	PET/CT(+)	
	Bone marrow biopsy (-)	27 (61.4)
	PET/CT (+)	
	Bone marrow biopsy (+)	17 (38.6)

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Table 3: Comparison of Bone Marrow Biopsy positive and negative groups within the PET/CT positive patients

		PET/CT positive n=44		
		BMB (-) n=27	BMB (+) N=17	
SUV Max Value, Median (Q1-Q3)		5.10 (3.60-11.10)	6.80 (4.00-9.80)	0.571
Considering PET/CT, increase in stage, n (%)		19 (70.4)	0 (0.0)	<0.001
Involvement type, n (%)	Focal 1 area	3 (11.1)	0 (0.0)	
	Focal 2 area	3 (11.1)	1 (5.9)	
	Focal 3 area	3 (11.1)	3 (17.6)	-*
	Focal >3 areas	10 (37.0)	5 (29.4)	
	Diffuse	8 (29.6)	8 (47.1)	
Diffuse–Focal Groups, n (%)	Focal	19 (70.4)	9 (52.9)	0.242
	Diffuse	8 (29.6)	8 (47.1)	
Regression of PET after treatment, n (%)	Complete regression	22 (81.5)	16 (94.1)	-*
	Partial regression	5 (18.5)	1 (5.9)	

**Analysis was not performed due to low patient numbers.*

Table 4: PET-BMB Sensitivity, Specificity and Positive-Negative Predictive Values

	Value	Confidence Interval	
		Lower Limit	Upper Limit
Sensitivity	100.00 %	80.49 %	100.00 %
Spesificity	68.97 %	58.14 %	78.45 %
Positive predictive value	38.64 %	24.36 %	54.50 %
Negative predictive value	100.00 %	94.04 %	100.00 %
Accuracy rate	74.04 %	64.52 %	82.14 %

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