Original Article

Can PET-CT replace bone marrow biopsy for lymphoma staging? Retrospective analysis of 198 Hodgkin and non-Hodgkin lymphoma cases

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Abstract

Aim: Lymphoma staging is important from the prognostic and therapeutic point of view and bone marrow biopsy performed for this purpose makes up a large part of current hematopathology practice. PET-CT is the currently preferred method to evaluate bone marrow involvement by lymphoproliferative disorders as it is non-invasive and practical. The aim of this study was to compare trephine biopsy and PET-CT results as regards determining bone marrow involvement in various lymphoma subtypes.

Materials and Methods: A total number of 198 bone marrow biopsies and 185 PET-CT images of cases consisting of various lymphoma subtypes were included in the study. The results of both methods evaluated for bone marrow infiltration were grouped as positive, negative, and suspicious to compare consistency. Statistical agreement was calculated with the kappa coefficient. The sensitivity, specificity, and the positive and negative predictive values were calculated as the diagnostic test measures.

Results: Twenty-six cases (15.8%) had lymphoma involvement in trephine biopsies and 36 cases (21.2%) had positive findings for lymphoma involvement of the bone marrow on PET-CT. The two methods had weak statistical agreement (κ= 0.21). Biopsy and PET-CT results were similar in 132 cases (71.20%). PET-CT showed false negative results in 11 cases in which infiltration was observed with biopsy. Twenty-six cases that were negative for lymphoma involvement on biopsy were accepted as positive on PET-CT and 16 of these cases were classical Hodgkin's lymphoma. One case with suspicious bone marrow biopsy was positive on PET-CT, while four cases with suspicious PET-CT results were positive on biopsy.

Conclusion: The results showed that both of the methods have advantages and disadvantages as regards lymphoma staging. However, histopathology is globally accepted as the gold standard for a definite diagnosis. We believe that the complementary use of the two methods is more beneficial for correct guidance during clinical practice.

Keywords: Bone marrow examination; lymphoma; positron emission tomography computed tomography

INTRODUCTION

Staging is one of the most important steps for determining the prognosis and treatment in all lymphoma subgroups (1-3). Bone marrow biopsy (BMB) is the traditional and gold standard method for this purpose and has been in use for many years. Recently positron emission tomography combined with computed tomography (PET-CT) has also been included in lymphoma staging protocols. A growing number of articles even state that BMB should be replaced by the non-invasive PET-CT method for staging (3-7).

In contrast, there are few articles which state that it is not possible for PET-CT to replace histopathology, and the use of both methods for staging in a complementary manner

is recommended. PET-CT can be used as guidance in selected cases to determine the location for a trephine biopsy. It is emphasized that BMB must be performed, especially when the results could change the treatment protocol (8-12).

Classical Hodgkin's lymphoma (cHL), which is at the focus of the discussion related to staging, is a special lymphoma group that shows proliferation on an inflammatory background and creates a cytokine storm due to its nature. It is therefore usually accompanied by myeloid hyperplasia due to the inflammation. Erythroid hyperplasia due to anemia can develop in the bone marrow (BM) in some patients (13-15). Bone marrow

biopsy is especially needed in cases with diffuse [18F] fluorodeoxyglucose (FDG) uptake for differentiation from reactive myelopoiesis (15,16).

As regards its role in staging, PET-CT is probably most useful in diffuse large B cell lymphoma (DLBCL), which is the most common aggressive lymphoma type in routine practice. PET-CT can provide whole body screening for malignancy as a non-invasive method. However, in BMBs, it is not possible to show any bone marrow infiltration (BMI) outside the iliac crest, which is the preferred area for the routine trephine biopsy, especially in cases with focal random infiltration (2,3,5,7-9,16-18). PET-CT has limited diagnostic value in BMI detection in indolent lymphoma cases with low proliferative activity and there are only a few studies on this subject (7,12,18,19).

The potential false positive/negative results with PET-CT, where the FDG uptake is used as the basis for the evaluation, are also an important handicap of the method. In addition to lymphoproliferative disorders, false positive results with PET-CT are also reported with many neoplastic (lung, esophageal cancer, etc.) (20-22) or non-neoplastic (gelatinous degeneration of the bone marrow, acne vulgaris, round atelectasis, etc.) processes (23-15).

Bone marrow biopsy is also especially important to provide information on the current hematopoiesis status before using many treatment regimens with cytopathic effects. Another advantage of BMB is the possibility of determining potential additional pathologies.

The main aim of this study was to compare the lymphoma infiltration rates detected with BMB with the results of PET-CT, which is becoming increasingly popular in lymphoma staging. We also aimed to discuss the strong and weak aspects of each method and to provide recommendations for appropriate clinical management for maximum benefit for the patients.

MATERIALS and METHODS

A total of 198 pre-treatment bone marrow trephine biopsies from cases diagnosed with non-Hodgkin and Hodgkin lymphoma of various types between January 2014 and December 2018 were enrolled into the study. Lymphoma subtypes of all cases were diagnosed from previously performed lymph node biopsies. The purpose of the trephine biopsy evaluation was to investigate whether there was infiltration. Pathology reports and tissue blocks of trephine biopsies were obtained from the archive of the Pathology Department. All bone marrow biopsy slides were reviewed to confirm the pathology reports. Trephine biopsies contained sufficient intertrabecular space for evaluation. No significant artifact was observed in any of the bone marrow biopsies, which made assessment difficult. As aspiration samples were not present for all cases, bone marrow smears were not evaluated. A PET-CT image of 185 patients obtained at our Nuclear Medicine Department simultaneously with BMB was included in the study. Thirteen cases whose PET-CT images

were evaluated at other centers were excluded from statistical analysis. The hemogram values and recorded demographic data of the patients were obtained from the hospital information system.

Bone marrow biopsy cases where lymphoma infiltration was not detected on the first section routinely underwent six-level serial slide sections. Additional immunohistochemical (CD20, CD3, ALK, CD30) or in situ hybridization (EBER) tests were performed for a few cases that showed infiltration as isolated single cells. The reason is that infiltration that can be observed as scattered cells can be overlooked in hematoxylin and eosin-stained sections of anaplastic large cell lymphoma and NK/T cell lymphoma cases. In cases with discordant results between the methods, the BMBs underwent deep serial sections again and the PET-CT images were also re-evaluated. Cases with involvement areas with PET-CT that were outside the trephine biopsy location and those with diffuse FDG uptake were determined. The BMB and PET-CT imaging results were grouped as positive, negative, and suspicious.

Descriptive statistics are presented as counts and percentages. The agreement between the measurements was calculated with the kappa coefficient. The sensitivity, specificity, and the positive and negative predictive values were calculated as the diagnostic test measures. The IBM SPSS 20.0 software was used for the analyses. The significance level was accepted as 0.05 for all tests.

RESULTS

The age range for the study group was between 1 and 85 years (mean 47.11±20.028). Of these 198 patients, 105 (53.03%), were female and 93 (46.97%) were male. The majority of the cases were diffuse large B cell lymphoma (34.8%), classic Hodgkin lymphoma (26.3%), and follicular lymphoma (FL) (10.6%) in the distribution according to diagnostic groups. The other high grade lymphomas (Burkitt lymphoma (BL), EBV-positive large B cell lymphoma (EBV(+) LBCL), and High-grade B-cell lymphoma (HGBCL)) constituted 8.5% of the study group. The small B-cell lymphoma group consisting of small lymphocytic lymphoma (SLL), MALT lymphoma, mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL) cases made up 5% of the patients. Another 7% of the cases consisted of T-cell lymphomas (ALK (+/-), anaplastic large cell lymphoma (ALCL), T lymphoblastic lymphoma (T-LBL), Peripheral T cell lymphoma (PTCL), Mycosis fungoides (MF), and Extranodal natural killer NK/T-cell lymphoma (NK/T-CL)). Table 1 presents the case distribution and the positive/negative rates by method in the diagnostic groups.

The number of cases that were positive (n=9) or negative (n=123) with both methods was 132 (78.11%). Discordance between the methods was present in 37 (21.89%) cases and the agreement between the methods was weak (Table 2) (Figure 1,2). The FDG involvement was outside the trephine biopsy area in 16 (61.54%) of the 26 cases with positive PET-CT in which infiltration could not be shown with BMB.

Table 1. Bone marrow biopsy and PET-CT positivity rates according to diagnostic groups

Diagnostic Groups	n	%	Bone marrow biopsy			PET-CT		
			Positive	Negative	%	Positive	Negative	%
FL	21	10.6	6	14	30.0	3	18	14.3
SLL	3	1.5	3	0	100.0	0	1	0
MALT	3	1.5	0	3	0	0	3	0
DLBCL	69	34.8	5	61	7.6	11	50	18.1
cHL	52	26.3	0	52	0	16	31	34.1
GZL	1	0.5	0	1	0	0	1	0
Uc-BCL	1	0.5	0	1	0	0	1	0
Uc-TCL	2	1.0	1	1	50.0	0	2	0
BL	8	4.0	0	8	0	1	6	14.3
MCL	4	2.0	4	0	100.0	1	2	33.3
ALK (+/-) ALCL	4	2.0	2	2	50.0	2	1	66.7
EBV(+) LBCL	4	2.0	1	3	25.0	1	2	33.3
MZL	6	3.0	1	5	16.7	0	6	0
T-LBL	4	2.0	0	4	0	0	1	0
NLPHL	3	1.5	0	0	0	0	0	0
PTCL	1	0.5	0	1	0	-	-	-
MF	4	2.0	1	3	25.0	1	3	25.0
NK/T-CL	1	0.5	0	1	0	0	1	0
CNS-LBCL	2	1.0	0	2	0	0	1	0
HGBCL	5	2.5	2	3	40.0	0	4	0
Total	198	100.0	26	165	15.8	36	134	21.2

FL: Follicular Lymphoma, SLL: Small Lymphocytic Lymphoma, MALT: MALT Lymphoma, DLBCL: Diffuse Large B Cell Lymphoma, cHL: Classic Hodgkin Lymphoma, GZL: Grey Zone Lymphoma, Uc-BCL: Unclassified B Cell Non-Hodgkin Lymphoma, Uc-TCL: Unclassified T Cell Lymphoma, BL: Burkitt Lymphoma, MCL: Mantle Cell Lymphoma, ALK (+/-) ALCL: ALK (+/-) Anaplastic Large Cell Lymphoma, EBV(+) LBCL: EBV-Positive Large B Cell Lymphoma, MZL: Marginal Zone Lymphoma, T-LBL: T Lymphoblastic Lymphoma, NLPHL: Nodular Lymphocyte Predominant Hodgkin Lymphoma, PTCL: Peripheral T Cell Lymphoma, NOS, MF: Mycosis Fungoides, NK/T-CL: Extranodal Natural Killer (NK)/T-cell lymphoma, CNS-LBCL: Primary Central Nervous System Lymphoma, HGBCL: High-Grade B-Cell Lymphoma

Table 2. Statistical agreement between methods

	BMB / PET-CT				Kappa (p)	Sp	Sn	PPV	NPV	Ac
	+/+	+/-	-/+	-/-						
DLBCL	3	1	7	47	0.37 (0.002)	75%	87%	30%	98%	86%
cHL	0	0	16	31	0.03 (0.65)	n/a	66%	0%	100%	66%
Small B cell lymphomas	3	8	1	21	0.27 (0.059)	27%	95%	75%	72%	73%
All diagnostic groups	9	11	26	123	0.21 (0.004)	45%	83%	26%	92%	78%

DLBCL: Diffuse Large B Cell Lymphoma, cHL: Classic Hodgkin Lymphoma, Indolent lymphomas: Follicular lymphoma, Small lymphocytic lymphoma, MALT lymphoma, Mantle cell lymphoma, Marginal zone lymphoma.
BMB: Bone Marrow Biopsy, Sp: Specificity, Sn: Sensitivity, PPV: Positive Predictive Value, NPV: Negative Predictive Value, Ac: Accuracy

The diagnostic group with the lowest agreement was cHL with 16/47 cases (Table 2,3). In two of these cases, PET-CT detected a soft tissue mass outside the trephine biopsy area infiltrating the bone tissue and bone marrow. Hemogram data simultaneous with the BMB / PET-CT investigation could be accessed in fourteen cases. Neutrophilic leukocytosis was observed in most of the cases, with a hypercellular bone marrow. The hemoglobin (Hb) level was below 12 gr/dl in some cases. BMI was stated as diffuse FDG uptake in six cases. The FDG uptake areas were outside the trephine biopsy locations in three cases (Table 4).

In the DLBCL diagnostic group, 3 cases were positive, and 47 cases were negative with both methods. Bone marrow biopsy was positive and PET-CT was negative in one case. Infiltration was not detected in the BMB of 7 patients with positive PET-CT and the concordance was less than moderate (Table 2,3). The infiltration was outside the trephine biopsy area in one of these cases. There was a soft tissue mass that infiltrated the bone tissue or bone marrow outside the biopsy area in the PET-CT images of two cases, similar to cases of cHL. The involvement in one of the cases was expressed as heterogeneous FDG involvement in the intramedullary areas.
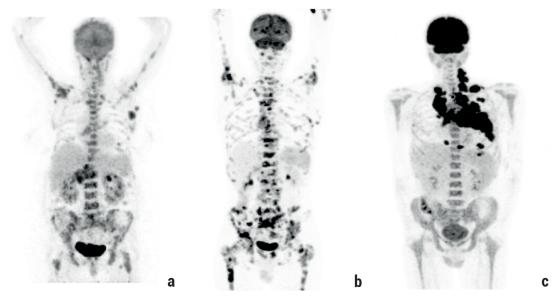
Figure 1. a-c. PET-CT images with various involvement features. Widespread hypermetabolic foci in the bone and bone marrow in the axial and appendicular skeletal system. PET-CT positive / BMB positive, ALK (-) anaplastic large cell lymphoma (a). Extensive intense hypermetabolic foci throughout the skeletal system, PET-CT positive / BMB negative, classic Hodgkin lymphoma (b). Diffuse, moderate hypermetabolism, especially in the humerus and femur diaphysis, pelvic bones and vertebral column, PET-CT suspect / BMB negative, classic Hodgkin lymphoma (c)
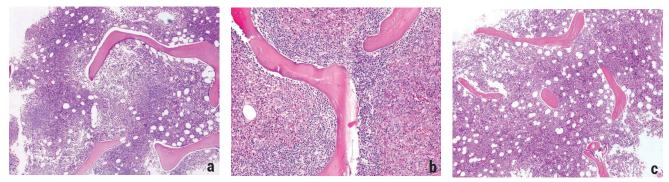

Figure 2. a-c. Bone marrow biopsy samples of various lymphoma subtypes. Diffuse interstitial atypical lymphoid infiltration (x40, Hematoxylin-Eosin), BMB positive / PET-CT suspect (a), Paratrabecular cuff-like atypical lymphoid infiltration (x20, Hematoxylin-Eosin), BMB positive / PET-CT positive (b), Hypercellular bone marrow with myeloid hyperplasia (x40, Hematoxylin-Eosin), BMB negative / PET-CT suspect, classic Hodgkin lymphoma (c)

Infiltration was detected on BMB but could not be shown with PET-CT in one case of high-grade B-cell lymphoma, classified within the aggressive lymphomas group. PET-CT involvement was present with no infiltration on the BMB in one EBV-positive large B cell lymphoma case and one Burkitt lymphoma case (Table 3).

Bone marrow biopsy infiltration was present without PET-CT involvement in 8 small B cell lymphoma cases. In contrast, PET-CT was positive but the BMB negative in 1 follicular lymphoma case. Concordant results were obtained in 15 FL cases (thirteen negative, two positive). There were five marginal zone lymphoma cases that were negative with both methods. Involvement could be demonstrated with both methods in one mantle cell lymphoma case (Table 2,3).

Infiltration was detected with BMB in four cases that were suspicious on PET-CT. The PET-CT was positive in one DLBCL case where the BMB was suspicious (Table 5).

Table 3. Discordant cases				
Diagnostic Groups	**Number of cases**	**BMB**	**PET-CT**	
MZL	1	Positive	Negative	
FL	4	Positive	Negative	Small B
	1	Negative	Positive	cell
SLL	1	Positive	Negative	lymphomas
MCL	2	Positive	Negative	
Uc-TCL	1	Positive	Negative	
HGBCL	1	Positive	Negative	Aggressive
EBV(+) LBCL	1	Negative	Positive	B
BL	1	Negative	Positive	cell
DLBCL	7	Negative	Positive	lymphomas
	1	Positive	Negative	
cHL	16	Negative	Positive	
Total	37			

MZL: Marginal Zone Lymphoma, FL: Follicular Lymphoma, SLL: Small Lymphocytic Lymphoma, MCL: Mantle Cell Lymphoma, Uc-TCL: Unclassified T Cell Lymphoma, HGBCL: High-Grade B-Cell Lymphoma EBV(+) LBCL: EBV-positive Large B Cell Lymphoma, BL: Burkitt Lymphoma, DLBCL: Diffuse Large B Cell Lymphoma, cHL: Classic Hodgkin Lymphoma

Table 4. Bone marrow cellularity, FDG uptake locations and hemogram values in PET-CT positive classic Hodgkin lymphoma cases

BMC	Variant	PET-CT	WBC/uL	N (%-n/uL)	Hb g/dl	Plt/uL
%10	Uk	Diffuse FDG uptake	4666	48.4% - 2260	10.1	301000
%60	NS	FDG uptake at biopsy location	7980	71.2% - 5680	12.9	186000
IB	Uk	FDG uptake at biopsy location	9620	82.9% - 7970	11.7	345000
%60	NS	FDG uptake at biopsy location	8000	62.2% - 4970	10.9	303000
%90	NS	Diffuse FDG uptake	15200	86% - 13100	12	384000
%90	NS	Diffuse FDG uptake	17700	86.7% - 15380	10.4	576000
%90	NS	FDG uptake at biopsy location	15700	81% - 12700	11.4	223000
%95	NS	Diffuse FDG uptake	8040	46.8% - 3760	11.8	475000
%70	NS	Diffuse FDG uptake / Different focus from biopsy location	11700	88.3% - 10300	13.2	321000
%90	NS	Diffuse FDG uptake	9150	64.1% - 5860	11.7	332000
%65	NS	Diffuse FDG uptake / Different focus from biopsy location	18300	80.9% - 14800	13	464000
%85	NS	Diffuse FDG uptake	9340	76.2% - 7120	10	365000
%50	NS	Different focus from biopsy location	10000	80.7% - 8090	13.4	274000
%55	NS	FDG uptake at biopsy location	5140	69.6% - 3580	12.9	239000

* White blood cell; mean 10752.57±4367.42/uL, min/max. 4666-183000/uL; * Neutrophil; mean 8255.00±4328.55/uL, min/max. 2260-15380/uL
* Hemoglobin; mean 11.81±1.16, min/max.10.00-13.40 gr/dl; * Bone marrow cellularity; mean 70±24%, min/max. 10-95%.
BMC: Bone marrow cellularity, IB: Inadequate biopsy, Uk: Unknown, NS: Nodular sclerosis, WBC: White blood cells, N: Neutrophil, Hb: Hemoglobin, Plt: Platelet

Table 5. Results of alternative methods in case of suspicious results

Suspicious BMB	PET-CT positive	Diffuse large B cell lymphoma
	PET-CT negative	Diffuse large B cell lymphoma
		Follicular lymphoma
Suspicious PET-CT	BMB positive	Mantle cell lymphoma
		EBV-positive large B cell lymphoma
		Diffuse large B cell lymphoma
		High-grade B-cell lymphoma
	BMB negative	Classic Hodgkin lymphoma x2
		T lymphoblastic lymphoma
		Diffuse large B cell lymphoma

DISCUSSION

Staging plays a critical role in determining the long-term treatment protocols and the prognosis in lymphoproliferative neoplasia. The present study focuses on determining the method that provides maximum clinical benefit by comparing PET-CT and BMB results applied for this purpose. Can we use only one or must we use both of them? The basic results of this study are outlined as follows: First, focal involvement may cause false negative results in the bone marrow biopsy. However, the accuracy of PET-CT positive results should be questioned, especially in cHL cases. Second, PET-CT can be used alone in lymphoid neoplasms with high proliferative activity. Biopsy will be more useful in determining positive cases in lymphoid neoplasms with low proliferative activity. Finally, bone marrow biopsy is important in determining baseline bone marrow reserve before treatment and detecting concordant/discordant infiltrates.

The trephine biopsy that is taken unilaterally from the iliac crest with the classic approach has disadvantages in lymphoma cases with focal random infiltration. However, only biopsies with adequate and appropriate sampling can make the gold standard of histopathologic evaluation possible. The involvement was outside the biopsy area in more than half of the PET-CT positive cases where BMB showed no infiltration in our study group. Some articles recommend using PET-CT guidance to determine the biopsy area as the solution to this problem (10,11).

PET-CT has entered routine use for malignancy staging and lymphoid neoplasia in recent years. It quantitatively analyzes physiological function using the blood flow, neurotransmitters, metabolism, and radiolabeled drugs. Its common use is for measuring the consumption rate of glucose in the whole body as it is more rapidly metabolized in malignant tumors. The accumulation of the radiolabeled glucose analogue 18-fluorodeoxyglucose (FDG) is evaluated for this purpose (26). It is a secondary method due to its principle of action. Although it is painless and non-invasive, reported false positive and false negative results seem to be the main handicaps of this method (20-25).

The bone marrow involvement (BMI) incidence is approximately 5-15% in classic Hodgkin lymphoma depending on the stage or subtype. However, the rate is reported as <1% for stage IA-IIA cases although it is as high as 27% in a few articles (27,28). There has been an increase in the reported BMI rates with the frequent use of PET-CT for staging purposes (4-6,9,14,15,18). As in our study, significant differences have also been found between BMB and PET-CT results in these reports. Whether all of the increased FDG accumulation actually indicates neoplastic infiltration is an important question

to be asked in this regard. The frequent occurrence of reactive myelopoiesis due to anemia or inflammation in this lymphoma group is well-known. Hemogram findings that could indicate reactive myelopoiesis were present in a significant portion of our classic Hodgkin lymphoma cases. Taking these features into consideration, checking for correlation with the hemoglobin, lymphocyte, leukocyte and albumin values and the erythrocyte sedimentation rate is recommended, especially for cases where diffuse FDG uptake has been detected (15,16).

Diffuse large B cell lymphomas are aggressive lymphomas with high proliferative activity. They therefore show high levels of FDG accumulation. PET-CT can detect BMI with higher sensitivity as it can screen the whole body. In the DLBCL cases, the concordance coefficient was higher than the other subtypes of our study group.

Shorter overall survival (OS) and progression-free survival (PFS) rates have been reported in DLBCL cases where infiltration has been confirmed with BMB in some articles. A possible explanation can be the ability of PET-CT to detect limited lesions, while BMB can show more widespread BM involvement (16,19). Another important point from the prognostic point of view is concordant or discordant BMIs as stated by Shen et al. (30). The risk with concordant involvement is reported to be higher than predicted by the International Prognostic Index (IPI) score. However, discordant involvement has no negative prognostic effect on the OS. In this context, the authors emphasize the importance of biopsy for the correct staging of BMI (30). Our small lymphocytic lymphoma case that was excluded from the study group where Richter transformation of the classic Hodgkin lymphoma type was detected with BMB is an excellent example for this theory. Furthermore, surprising diagnoses were found in three lymphoma cases that were also excluded from the study group where BMB was used for staging. The primary central nervous system lymphoma (CNS-LBCL) case had evidence of small lymphocytic lymphoma/chronic lymphocytic leukemia infiltration (SLL/CLL), the primary colonic DLBCL case had evidence of plasma cell myeloma infiltration, and the FL case had evidence of myeloproliferative/myelodysplastic neoplasia findings that were interpreted as indicating chronic myelomonocytic leukemia together with the clinical picture. These additional findings detected by trephine biopsy caused significant changes in treatment and prognosis evaluation.

The information for other lymphoma subtypes and especially for small B cell lymphomas are more limited (5,7,19). Teagle et al. (7) have reported high specificity of PET-CT in FL cases despite the inconsistent rates reported in previous articles. However, the standard procedure for BMI evaluation in FL is still BMB. Detecting BMI may lead to important changes in treatment planning, especially in local disease. An important benefit of PET-CT in this lymphoma group is the possibility of detecting high FDG involvement areas that could lead to a suspicion of transformation to high-grade lymphoma. These

areas must be considered during biopsy planning (7). Our results with BMB were more successful regarding infiltration detection in our follicular lymphoma cases. The misdiagnosis in a single case can be explained with focal random involvement. Morgan et al. (19) have reported that the use of FDG PET/CT-based voxel analysis is promising for staging in MCL cases. The number of MCL cases was quite low in our sample group. However, PET-CT was positive in only one case while infiltration was detected with BMB in all the cases.

LIMITATIONS

As noted above, FDG uptake is outside the conventional biopsy field in a significant proportion of PET-CT positive and BMB negative cases. Utilizing PET-CT guidance in determining the trephine biopsy location could provide a more accurate comparison. In this way, the accuracy of the cases that were positively predicted with PET-CT could be checked. Lack of clinical evaluation can be counted as another limitation of the study in PET-CT positive classical Hodgkin lymphoma cases where infiltration could not be detected with trephine biopsy.

CONCLUSION

Pretreatment BMB and PET-CT are performed simultaneously during the management of all lymphoma subtypes in our routine practice. We are therefore able to obtain optimum support for the clinical evaluation when a single method is inconclusive. We think that the absence of pathological interpretation in most of the literature on this subject is an important handicap. From this point of view, we would like to emphasize that bone marrow biopsy is not only for staging, but can also provide information about initial hematopoietic reserve and other additional pathological entities. In conclusion, we believe that using the two methods in a complementary manner for the evaluation of lymphoma staging will be more effective, and also that team work is quite important for determining the correct diagnosis that could influence the clinical management of this group of neoplasia.

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