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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

PET/CT-based bone-marrow assessment shows potential in replacing routine bone-marrow biopsy in part of patients newly diagnosed with extranodal natural killer/T-cell lymphoma

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Abstract

Purpose This study aimed to determine the potential of positron emission tomography/computed tomography (PET/CT) in replacing routine bone-marrow biopsies (BMB) in newly diagnosed extranodal natural killer/T-cell lymphoma (ENKTCL).

Methods Newly diagnosed patients underwent PET/CT imaging and routine BMB to assess bone/bone marrow involvement (BMI). Clinical stage and treatment plan were determined, and survival was compared.

Results In a total of 101 patients, 78 were diagnosed as stage I/II and 23 as stage III/IV without using the BMB results. No BMB-positive patients were identified in stages I/II, and therefore, the BMB results did not alter the stage and treatment choice in any patients. The sensitivity and specificity of focal skeletal PET/CT lesion(s) in assessing BMI was 100% and 92.8%, respectively, taking routine BMB as the reference standard. The overall survival (OS) and progression-free survival (PFS) of BMB-positive patients was significantly inferior ($P=0.0011$ and 0.0465, respectively, in advanced-stage patients; both $P<0.0001$ in all patients), and this was corroborated by the PET/CT findings ($P=0.0006$ and 0.0116, respectively, in advanced-stage patients; both $P<0.0001$ in all patients).

Conclusions Based on the results, PET/CT demonstrated satisfactory predictive performance in terms of staging and prognosis in ENKTCL. BMB did not influence staging and treatment in newly diagnosed ENKTCL, and routine non-targeted BMB is not obligatory for early stage patients undergoing PET/CT. Targeted BMB is recommended to confirm BMI in advanced-stage patients.

Keywords Extranodal natural killer/T-cell lymphoma (ENKTCL) · PET/CT · Bone-marrow biopsy · Bone/bone-marrow involvement · Prognosis

Introduction

Extranodal natural killer/T-cell lymphoma (ENKTCL) is a distinct subtype of non-Hodgkin's Lymphoma, which accounts for < 1% of all malignant lymphomas in Western countries and approximately 3–10% of lymphomas in East Asia (Lee et al. 2006; Oshimi 2007). Based on the Ann Arbor staging system, ~70–80% (Au et al. 2009; Lee et al. 2006) of patients are diagnosed with ENKTCL at an early stage, with a 5-year survival rate of 66–80% (Deng et al. 2014; Li et al. 2006, 2012). Others are advanced-stage patients, demonstrating a 2-year survival rate of merely 30–40% (Kim et al. 2015; Yang et al. 2013). Accurate and rapid staging is crucial, since different stages may require different prognosis and treatment strategies.

The diagnostic workup in lymphoma routinely includes bone marrow biopsies (BMB) and fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT). For decades, BMB was considered as a "gold standard" to assess BM infiltration (BMI) in the initial staging of lymphoma (Cheson et al. 2014). However, routine BMB is unilaterally or bilaterally blind at the site of the anterior or posterior iliac crests, which may easily lead

Disclosures Parts of the abstract in this study were invited as an oral presentation in ESMO ASIA Congress 2015, while we did not publish the data and enlarged further research for 3 years. The previous material was presented thoroughly transparent (Yiqin et al. 2015).

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to a false negative result (Cheng et al. 2011; Kwee et al. 2011) and cause bleeding (Bain 2006), pain (Brunetti et al. 2011) and needle tract seeding (Fowler et al. 2008; Hopkins et al. 2014). However, the PET/CT imaging method is rapidly gaining popularity because of its non-invasive potential to identify hypermetabolic lymphoma involvement of lymph nodes and extranodal sites including bone marrow (Adams et al. 2014; Cerci et al. 2014). Consequently, PET/CT is not only widely utilized for diagnosis and staging in lymphoma (Hutchings et al. 2006; Muslimani et al. 2008), but is also applied to predict the prognosis or treatment response of lymphoma (Berthet et al. 2013; Cencini et al. 2014; Heron et al. 2008; Yhim et al. 2014). In certain types of lymphoma, such as Hodgkin's and diffuse large B cell lymphoma, it has been confirmed that PET/CT has the potential to replace BMB in detecting BMI (El-Galaly et al. 2012; Khan et al. 2013).

Considering that ENKTCL is consistently ^{18}F-FDG-avid (Storto et al. 2010; Wu et al. 2010) and PET/CT represents a satisfactory lesion detection and staging (Zhou et al. 2015) method for this lymphoma, we investigated its diagnostic performance in BMI and its prognostic value in ENKTCL, with a view to ascertaining whether this non-invasive technique could obviate the requirement for BMB under some conditions.

Patients and methods

Patients

This retrospective study was based on medical records from our clinical database. Patients aged 15 years or older undergoing pre-treatment staging for newly diagnosed ENKTCL defined based on the World Health Organization classification system (Harris et al. 1999) at the Center of Medical Oncology, West China Hospital, from July 2010 to September 2013, were enrolled. Patients meeting the following conditions were excluded from this experiment: (1) Patients who had undergone previous treatment for ENKTCL or suffered relapsed ENKTCL; (2) patients suffered from other malignant disease or coexisting medical problems which may prevent full compliance with the study protocol; and (3) patients who received hematopoietic growth factor injections before PET/CT or BMB. All patients underwent staging procedures, including clinical and laboratory tests, PET/CT imaging, and unilateral iliac crest BMB. Staging results and BMI were compared with or without BMB. Advanced stage patients underwent LVDP chemotherapy (L-asparaginase, etoposide, dexamethasone, and cisplatin) followed by radiotherapy or no radiotherapy (Jiang et al. 2017; Wang et al. 2015). Early stage patients were treated using two cycles of LVDP chemotherapy followed by concurrent cisplatin chemo-radiotherapy. Chemotherapy was continued for two-to-four cycles thereafter.

Identification of BMI using BMB

Routine untargeted unilateral BMB of the posterior iliac crest was performed (Khan et al. 2013) prior to treatment. BMB material was formalin-fixed, paraffin-embedded and evaluated morphologically under the microscope after hematoxylin–eosin staining by the pathology department of West China Hospital. CD3ε, CD56, and granzyme B were examined in specific morphologic BMI cases. BMB$^{(+)}$ or BMB$^{(-)}$ represent positive or negative BMB results, respectively.

Identification of BMI through PET/CT scanning and image analysis

All patients underwent whole-body ^{18}F-FDG PET/CT (at least vertex or midbrain to upper thigh) using a combined PET/CT scanner (Gemini GXL with a 16-slice CT component, Philips Corp., Netherlands). After fasting for at least 6 h (blood glucose level < 200 mg/dL), an intravenous injection of 185–370 MBq ^{18}F-FDG (5.18 MBq/kg) was administered. Following a ~ 60 min rest period, whole-body CT and PET scans were performed. CT acquisition data were used for attenuation correction and corrected PET images were reconstructed using the line-of-response method. Images acquired from PET and CT scans underwent image registration and fusion using the Syntegra software.

PET/CT data were assessed visually using PET activity in the normal mediastinal blood pool as a reference. All PET images and written PET/CT reports were carefully and separately reviewed by two groups of doctors including nuclear medicine specialists and oncologists. PET/CT-assessed bone or BM lesions were defined as negative [with no skeletal lesions, PET$^{(-)}$], unifocal [a single skeletal lesion, PET$^{(uni)}$], multifocal [two or more skeletal lesions, PET$^{(mul)}$], and both PET$^{(uni)}$ and PET$^{(mul)}$ are defined as a positive PET/CT result [PET$^{(+)}$].

Statistical analyses

During therapy, patients received a PET/CT scan every two courses of chemotherapy to assess disease progression. After completion of treatment, patients were followed up by their oncologist in the outpatient department. The follow-up visit (Wang et al. 2015) routinely consisted of a physical examination, complete blood count, serum biochemistry, adding either magnetic resonance imaging of the involved regions or PET/CT scanning when in progressive disease, this lasted until at least non-progress for 1 year. Follow-up visits were conducted at least every 2 months.

Overall survival (OS) and progression-free survival (PFS) (Dreyling et al. 2005) were calculated from the date of diagnosis to latest follow-up visit or death and date of disease progression, respectively. Survival analysis was estimated through Kaplan–Meier tests and survival curves were compared using a log-rank test. Statistical comparisons of categorical variables were usually calculated with Pearson's χ^2 test. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy (El-Galaly et al. 2012) were calculated using Clopper–Pearson exact confidence limits. A two-sided P value < 0.05 was considered to be statistically significant. All analyses were performed using the SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics and prognostic results

A total of 103 patients subjected to both PET/CT-staging scans and BMB were screened for eligibility. Two patients were excluded because of the presence of other malignant diseases. Consequently, 101 patients were enrolled with a median follow-up of 56.0 (1–93) months, including 78 (77.2%) staged as I/II and 23 (22.8%) as III/IV. The median age was 42 years ranging from 15 to 70 years. The male and female ratio was 1.9:1; 88 patients demonstrated ENKTCL disease primarily at the nose, 10 patients in other organs, and the other three patients were diagnosed with extensive lesions, and therefore, the primary lesion could not be determined. In addition to the nasal cavity and bone/bone marrow, PET/CT also aided identification of lesions in muscle, soft tissue, gastrointestinal tract, skin, liver, and spleen. The patient characteristics are summarized in Table 1. The early and advanced stage patients had a 5-year OS rate of 70.38% and 39.13%, respectively, and early stage patients had significantly better OS and PFS than advanced stage patients (P = 0.0012 and < 0.0001, respectively) (Fig. 1).

Table 1 Patient clinic characteristics

Characteristic	Patients	
	No.	(%)
Age		
Median	42 (years)	
Range	15–70 (years)	
Gender		
Male	66	(65.3)
Female	35	(34.7)
Primary site[a]		
Nasal	88	(87.1)
Nonnasal	10	(9.9)
Disseminated	3	(3.0)
Ann Arbor stage		
I	38	(37.6)
II	40	(39.6)
III	5	(5.0)
IV	18	(17.8)
ECOG PS		
0–1	89	(88.1)
2	12	(11.9)
IPI score		
Low (0 or 1)	81	(80.2)
Intermediate low (2)	9	(8.9)
Intermediate high (3)	8	(7.9)
High (4 or 5)	3	(3.0)
KPI score		
0–2	82	(81.2)
3–4	19	(18.8)
B symptoms present	52	(51.5)
Serum LDH increase	41	(40.6)
Other involved sites[b] by PET/CT		
Skin	3	(3.0)
Lung	3	(3.0)
Muscle, soft tissue	10	(9.9)
Liver	2	(2.0)
Spleen	3	(3.0)
Kidney or adrenal grand	2	(2.0)
Gastric and intestine	2	(2.0)

ECOG PS Eastern Cooperative Oncology Group performance status, *IPI* International Prognostic Index, *KPI* Korean Prognostic Index, *LDH*, lactate dehydrogenase

[a]Primary site, symptomatic site that was initially biopsied

[b]Other involved sites, all sites that found except for the primary sites and nearby lymph nodes. The number on the right side to be the number of patients presented involved site on the left side

Comparison of the staging and diagnostic performance of BMB and PET/CT

First, all 78 early stage patients and 23 advanced-stage patients were diagnosed using PET/CT and other procedures, and the staging result was not changed by the BMB results (Fig. 2). In terms of BMI diagnostic performance, according to the PET/CT results, 90 patients were BMI negative (Fig. 3), two patients were unifocal (Fig. 4a, b) and nine patients were multifocal (Fig. 4c, d). The results of the PET/CT and BMB are shown in Fig. 2. A female advanced-stage patient presented low diffuse homogeneous FDG uptake, she was defined as free of BMI based on PET/CT image and clinical features, and this would be discussed later.

Only four cases of BMI were detected through BMB, which occurred only in PET$^{(mul)}$ patients. None of the 90 PET$^{(-)}$ patients had a positive BMB result. This result

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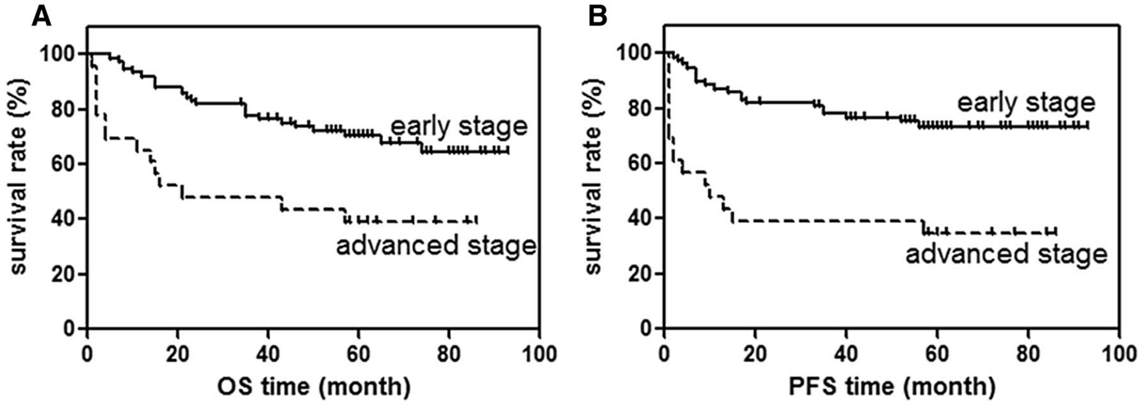
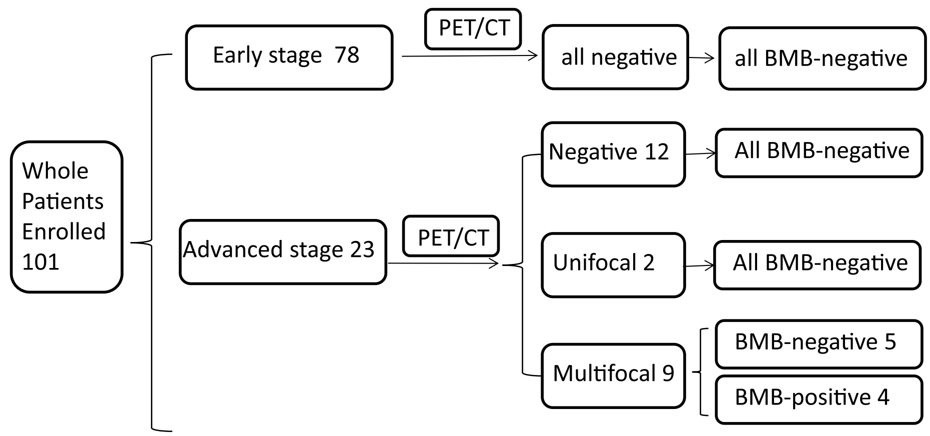


Fig. 1 Basal survival analysis (PFS and OS) of patients with different disease stages

Fig. 2 Case distribution of bone/bone-marrow status as assessed using PET/CT and routing BMB



means that all four cases staged as advanced through BMB were also staged as advance through PET/CT, and BMB adds no useful information compared with PET/CT staging. The diagnostic performance of BMB and PET/CT in BMI detection was compared by evaluating the following parameters: sensitivity, specificity, positive predictive value, negative predictive value, and accuracy based on the reference standard for BMI of positive BMB only or a combination of positive BMB and PET$^{(+)}$, since all BMB positive patients were PET$^{(+)}$, PET/CT presented with sensitivity of 100% and specificity of 92.8% (Table 2).

Prognostic performance of PET/CT and BMB in advanced-stage patients

The basal prognosis of advanced-stage patients was assessed using different BMB and PET/CT results (Fig. 5). The 19 BMB-negative patients presented with a 5-year survival rate of 52.63% and a median PFS of 15 months, which was significantly better than those of the BMB-positive group with a median OS and PFS of 2 and 1.5 months, respectively ($P = 0.0011$ and 0.0465, HR 35.26 and 6.01, respectively) (Fig. 5a, b). The 12 PET$^{(-)}$ patients presented with a 5-year OS and PFS rate of 75.00% and 66.67%, respectively, which was significantly better than those of the PET positive group with a median OS and PFS of 4 and 1 months, respectively ($P = 0.0006$ and 0.0016, HR = 7.40 and 7.45, respectively) (Fig. 5c, d). Although patients in the PET$^{(-)}$, PET$^{(+)}$BMB$^{(-)}$ and PET$^{(+)}$BMB$^{(+)}$ subgroups had a between-group variance of 0.0199 and 0.0231 in terms of OS and PFS, respectively, the PET$^{(+)}$BMB$^{(-)}$ and PET$^{(+)}$BMB$^{(+)}$ groups did not show any significant differences ($P = 0.0762$ and 0.7595, respectively, Fig. 5e, f).

The survival tests showed that assessments of BMI performed using either BMB and PET/CT resulted in better prognostic predictors compared with traditional indexes such as age, gender, Ann Arbor stage, LDH level, and Ki-67 level (Tables 3, 4). On univariate analysis through a log-rank test, advanced stage patient, B symptoms, increased LDH levels, ECOG PS, and KPI score subgroups presented with inferior OS and PFS compared with the control subgroups (HR 0.03–0.47, 95% CI 0.006–1), while BMB-positive and PET$^{(+)}$ patients presented with poorer OS and PFS (HR < 0.0003) (Table 3). On multivariate analysis through

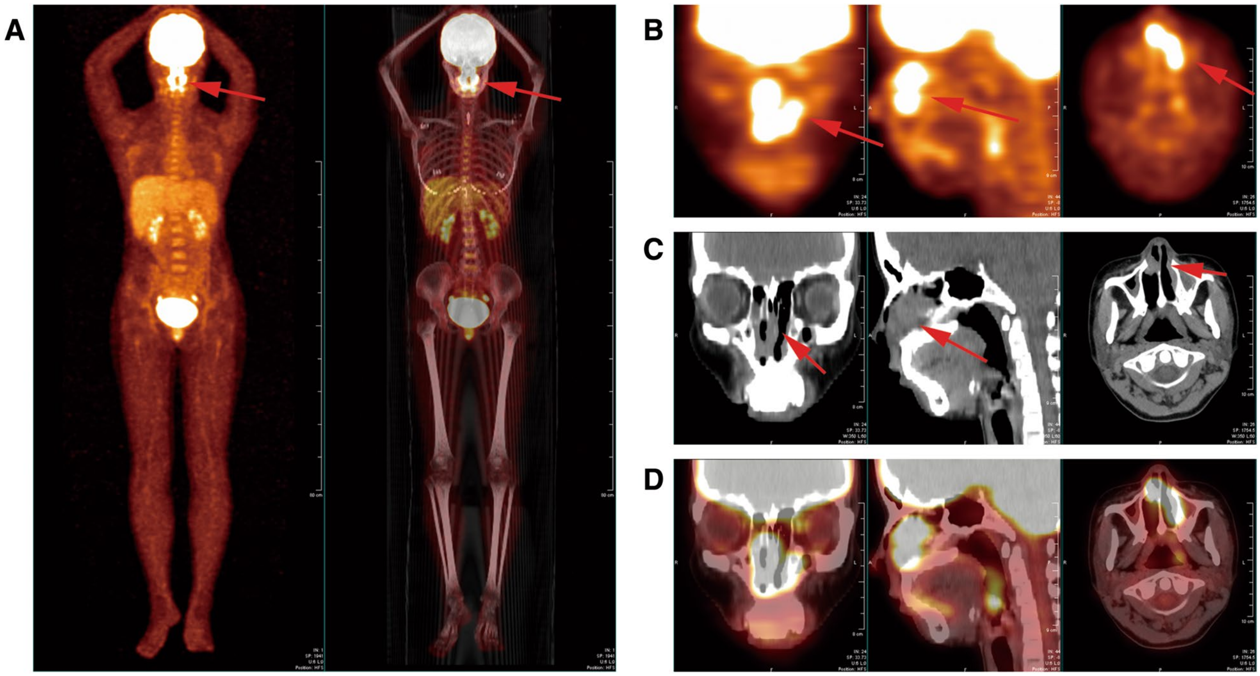


Fig. 3 Case of PET$^{(-)}$. This is a female patient showing a localized lesion in the nasal cavity and left paranasal sinus (indicated by the arrows) without any uptake in the bone/bone marrow, as seen in a whole-body image (**a**). In a detailed image, an elevated ^{18}F-FDG signal can be observed (**b**), tissue destruction can be seen in CT images (**c**), and both can be seen in composite images (**d**)

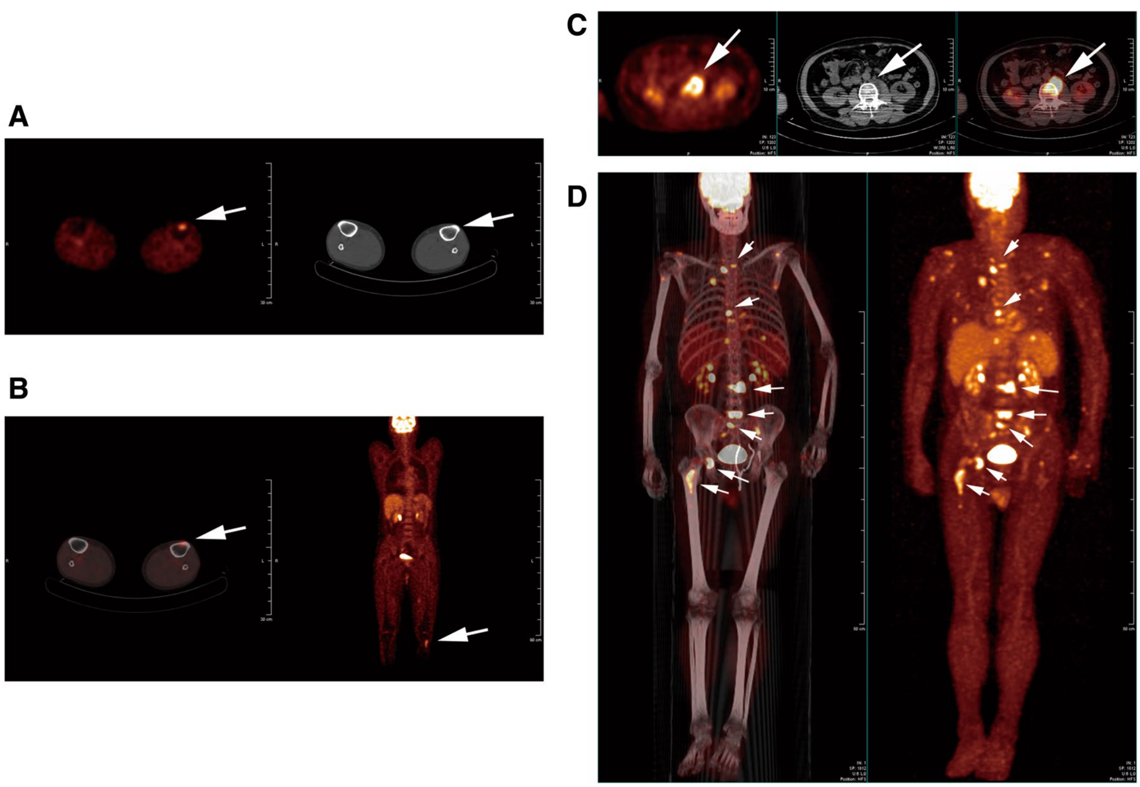


Fig. 4 Mild case of PET$^{(uni)}$ and a severe case of PET$^{(mul)}$. This is a male patient with a single slight bone lesion in the upper left tibia (**a**, **b**). The PET$^{(mul)}$ patient showed several skeletal lesions distributed in the spine, innominate bone, and proximal femur (**c**, **d**). Skeletal lesions are indicated by white arrows

Table 2 Sensitivity, specificity, PPV, NPV, and accuracy of BMB and focal skeletal PET/CT lesions for detection of bone/bone-marrow disease

Diagnostic modality	Bone/bone marrow disease defined only by positive BMB ($N=4$)		Bone/bone marrow disease defined by positive BMB and/or focal skeletal PET/CT lesion(s) ($N=11$)	
	%	95% CI	%	95% CI
BMB				
Sensitivity	N/A[a]		36.4	22.1–58.5
Specificity	N/A[a]		N/A[b]	
PPV	N/A[a]		N/A[b]	
NPV	N/A[a]		92.8	92.6–93.0
Accuracy	N/A[a]		93.1	92.8–93.2
PET/CT				
Sensitivity	100	41.7–100	100	71.5–100
Specificity	92.8	92.6–93.0	N/A[b]	
PPV	36.4	22.1–58.5	N/A[b]	
NPV	100	99.8–100	100[‡]	99.8–100
Accuracy	93.1	92.8–93.2	100[‡]	99.8–100

BMB bone marrow biopsy, *CT* computed tomography, *N/A* not applicable, *NPV* negative predictive value, *PET* positron emission tomography, *PPV* positive predictive value

[‡]$P<0.05$ for difference between BMB and PET/CT for detection of bone/bone-marrow disease

[a]N/A because BMB is considered the gold standard in this analysis

[b]N/A because of missing reference for true positive

Cox regression analysis, OS differed significantly between patients with high and low ECOG PS, KPI scores and different BMB results ($P=0.043$, 0.014 and <0.0001, respectively), and PFS differed significantly between patients with high and low KPI scores, different BMB results, and different BMI results as assessed through PET/CT ($P=0.010$, 0.011, and 0.022, respectively) (Table 4).

Discussion

While considerable research has focused on whether BMB provides useful information in addition to PET/CT staging, BMI detection and prognosis in patients with Hodgkin's lymphoma (El-Galaly et al. 2012), diffuse large B-cell lymphoma (Cerci et al. 2015; Khan et al. 2013), and follicular lymphoma (Smith et al. 2015), the comparative value of PET/CT and BMB in ENKTCL remains unclear. There is a consensus that NK/T-cell lymphoma is intensely FDG hypermetabolic and PET/CT has high sensitivity in detecting the extranodal lesions (Hu 2016; Karantanis et al. 2008; Suh et al. 2008; Wu et al. 2010; Zhou et al. 2014). However, whether PET/CT is indispensable in BMI diagnosis still requires discussion. In an investigation by Zhou et al. (2015), PET/CT demonstrated sensitivity and specificity in BMI of 100% and 86%, respectively, in 55 advanced-stage patients, while in another study by Fujiwara et al. (Fujiwara et al. 2011) comprising 19 patients, PET/CT detected BMI in only four of seven BMB-positive patients, though with no false-positive results. Therefore, further study was needed to determine the relative role of PET and BMB in determining bone-marrow involvement in ENKTCL. To the best of our knowledge, this was the largest retrospective study to investigate the utility of PET/CT in patients newly diagnosed with ENKTCL to determine whether this non-invasive technique has the potential to replace routine BMB.

Compared with untargeted BMB, where lesions are easily missed, targeted BMB performed at a suspected lesion and guided using PET/CT is the most accurate method to test for BMI. However, targeted BMB has risks in terms of seeding, impracticability, and influence on prognosis (Khan et al. 2013). The current study lacked targeted biopsies to define the true incidence of BMI (Khan et al. 2013). Consequently, we investigated two standards of BMI, including $BMB^{(+)}$ alone, and $BMB^{(+)}$ or $PET^{(+)}$ (El-Galaly et al. 2012; Zhou et al. 2015). When using $BMB^{(+)}$ alone as the reference standard, the sensitivity and specificity values of PET/CT in detecting BMI were 100% (CI 47.1–100%) and 92.8% (CI 92.6–93.0%), respectively, which was a satisfactory result. The low positive predictive value of 36.4% (CI 22.1–58.5%) caused by 4 of the 11 patients with $PET^{(+)}$ presenting with positive routine BMB may have contributed to a high false negative rate of routine untargeted BMB compared with a high false positive rate of PET/CT (El-Galaly et al. 2012; Fujiwara et al. 2011).

In the current study, PET/CT demonstrated satisfactory performance in predicting stage and prognosis in ENKTCL. BMB does not influence staging and treatment in every patient. Furthermore, none of the 90 $PET^{(-)}$ patients were BMB positive, leading to a negative predictive value of 100% (Table 2) and certifying a crucial exclusion effect of $PET^{(-)}$, namely all patients with $PET^{(-)}$ were free of BMI. Based on this result, routine non-targeted BMB is not obligatory for early stage patients undergoing PET/CT. In addition, nearly, half of the $PET^{(mul)}$ patients consisted of the four BMB-positive patients (Fig. 1), implying that BMB itself may be predicted by $PET^{(mul)}$. Moreover, given the low BMB-positive rate of 3.96% in all 101 patients, and 0% in PET/CT tested early stage patients, we recommend that non-targeted BMB is not essential in all newly diagnosed ENKTCL patients, especially in early stage patients. Targeted BMB is recommended to confirm BMI in advanced-stage patients.

In terms of prognostic performance, BMB is regarded as an independent indicator related to the prognosis of ENKTCL (Wang et al. 2015; Zhou et al. 2014, 2015), while the

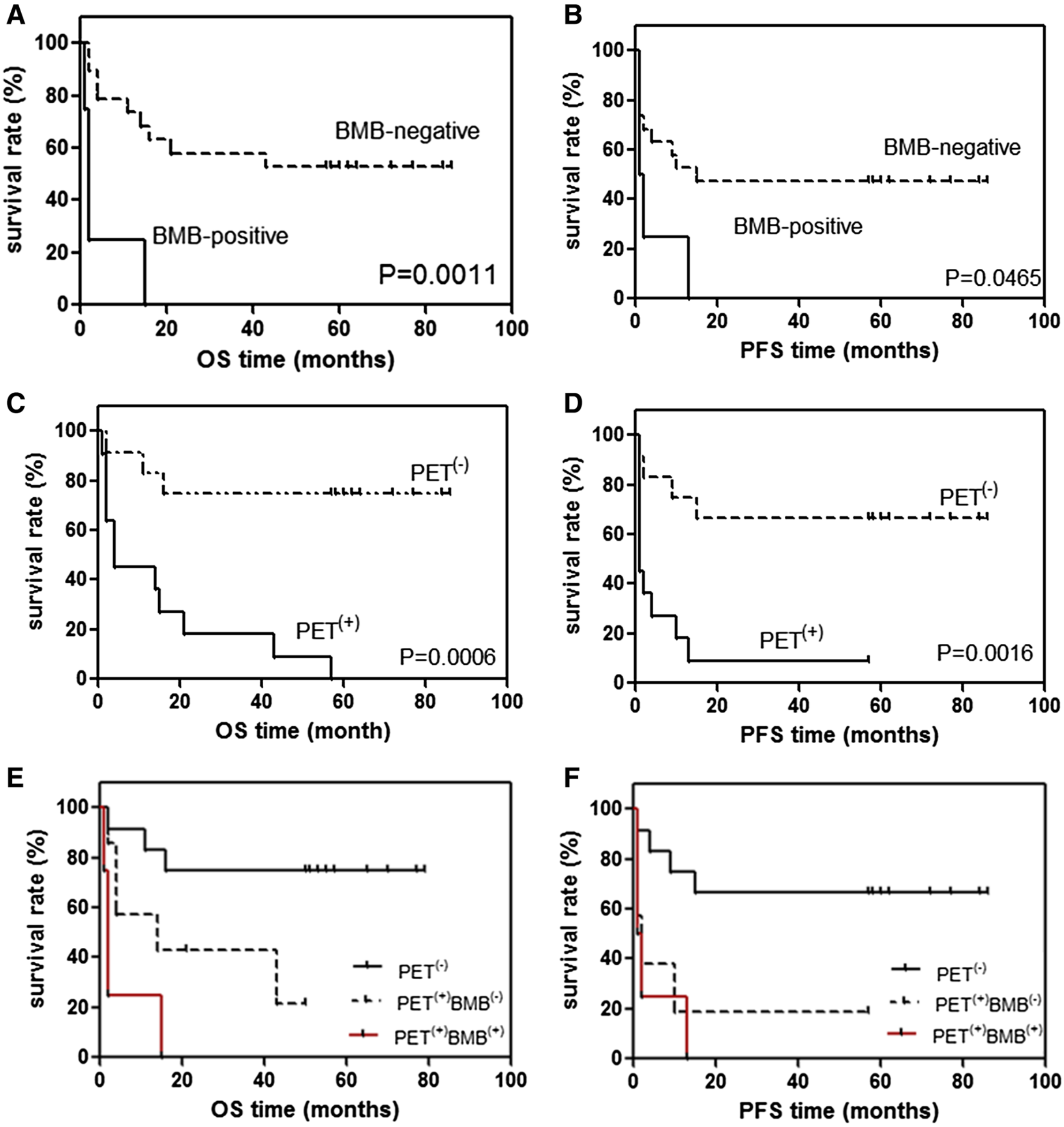


Fig. 5 Basal survival analysis (PFS and OS) of advanced-stage cases identified based on BMB (**a**, **b**) and PET/CT (**c**, **d**). The groups presented significant differences. Further analysis was performed by dividing the patients into subgroups: $PET^{(-)}$, $PET^{(+)}BMB^{(-)}$ and $PET^{(+)}BMB^{(+)}$, $P=0.0199$ and 0.0231, respectively (**e**, **f**)

prognostic value of PET/CT has not been verified (Zhou et al. 2015). In the present study, both BMB and PET/CT presented with satisfactory prognostic value in a log-rank test of survival ($P=0.0011$ and 0.0006, respectively), as did combining them together as an aggregative indicator ($P=0.0199$ for OS) (Fig. 5).

A subgroup survival test showed that KPI score, ECOG PS, advanced stage, B symptoms, and LDH level were reliable prognostic indexes ($P<0.05$), while IPI score was not, on univariate analysis through a log-rank test (Table 3). When all these factors were assessed through a Cox regression analysis, the ECOG PS and KPI score remained valuable, while the IPI score did not ($P=0.043$, 0.014, and 0.068, respectively, Table 4), which is in agreement with other previous studies (Liang et al. 2017; Pak et al. 2017). The poor prognostic value of the IPI score may be caused by the sample size and heterogeneity in different cohorts. The trustworthy prognostic performance of index LDH levels, B symptoms, and advanced stage reported in the previous studies mentioned above provides context for the value of the KPI score, as it includes them all. Furthermore, patients in the $PET^{(+)}$ and BMB-positive subgroups both demonstrated

Table 3 Univariate analysis for overall survival and progress free survival in subgroups by log-rank test (blackbody bold and * for statistically significant difference)

Subgroups	Unfavorable factors	Overall survival		Progression free survival	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	≥ 60 years	1.180 (0.3873–3.593)	0.7712	1.243 (0.4186–3.692)	0.6951
Gender	Male	0.5756 (0.2842–1.166)	0.1252	0.5906 (0.2920–1.195)	0.1428
Stage	III IV	0.1953 (0.08044–0.4740)	0.0003***	0.1338 (0.05376–0.3331)	< 0.0001***
B symptoms	Present	0.4655 (0.2378–0.9111)	0.0256*	0.4587 (0.2363–0.8904)	0.0213*
LDH level	Increase[a]	0.3648 (0.1832–0.7263)	0.0041**	0.3956 (0.1969–0.7949)	0.0092**
KI-67%	> 50%[b]	0.5315 (0.2698–1.047)	0.0676	0.5349 (0.2713–1.055)	0.0708
ECOG PS	Score = 2	0.02555 (0.005643–0.1157)	< 0.0001***	0.02582 (0.005696–0.1171)	< 0.0001***
IPI score	Score > 2	0.6240 (0.2057–1.893)	0.4049	0.6095 (0.1988–1.868)	0.3863
KPI score	Score > 2	0.3647 (0.1450–0.9178)	0.0322*	0.3567 (0.1409–0.9034)	0.0297*
BMI by BMB	Positive	0.000003568 (0.000001409–0.000009035)	< 0.0001***	0.0002713 (0.00001874–0.003928)	< 0.0001***
BMI by PET/CT	Positive	0.0006692 (0.0001112–0.004029)	< 0.0001***	0.00008683 (0.00001167–0.0006458)	< 0.0001***

HR hazard ratio, *CI* confidence interval, *BMI by BMB* bone-marrow infiltration bone-marrow biopsy

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

[a]Increase higher than normal

[b]> 50% of the median level of the whole group

inferior survival ($P < 0.0001$, Table 3). PET$^{(+)}$ did not show satisfactory prognostic value in a Cox regression analysis ($P = 0.159$ for OS and 0.022 for PFS, Table 4), while BMB did ($P < 0.0001$ for OS and $P = 0.011$ for PFS, Table 4), and this result implied a superior prognostic effect for BMB compared with that of PET/CT.

A 48-year-old female patient in this study presented with low diffuse homogeneous FDG uptake (average standardized uptake value of 3.2) was defined as free of BMI. Six days after a lumpectomy of the neck, she got a PET/CT scan and was diagnosed with lesions involving the gastrointestinal tract, left parotid gland, and right inferior nose, which presented FDG uptake as high as 17.9. However, her spleen uptake of FDG got an average SUV of 2.6 and CT showed no increase in spleen volume and no abnormal density in parenchyma. She got an IPI score of 2, a KPI score of 2, and her overall bone-marrow uptake of FDG increased in diffuse uniformity, with an average SUV of 3.2, while no focal significant increase of FDG uptake was observed. She got a complete response after four cycles of chemotherapy (PFS of more than 69 months by now). Based on all these above, we defined her as general inflammation after surgery other than overall BMI by lymphoma. According to our clinical experience, overall BMI is always related to FDG uptake higher than 5, IPI score and KPI score higher than 3, unsatisfactory therapy effect, and an OS no longer than 1 year. This kind of patient can easily get a positive BMB result and be distinct from situations such as general inflammation, glucocorticoid treatment, and post-chemotherapy changes. However, given the lack of a commonly accepted quantitative criterion (Adams and Kwee 2015) to define nonmalignant diffusely homogeneous FDG uptake, cautious judgement (Adams et al. 2015) and a targeted BMB were sensible in this situation to avoid mistake.

In summary, we propose that pretreatment using PET/CT is adequately proficient to replace routine BMB in newly diagnosed early stage patients with ENKTCL, based on its satisfactory performance in the staging and detection of BMI. Based on a superior confirmation of BMI and prediction of prognosis, BMB was of essential value in advanced-stage patients and is optimally conducted under the guidance of PET/CT.

This study has several potential limitations. Owing to the paucity of existing literature and finite study sample sizes, further studies are warranted to confirm the diagnostic and prognostic value of PET/CT in detecting BMI and accurately determining the conditions under which BMB could be omitted in NK/T-cell lymphoma. This is particularly relevant to the only four cases of BMB$^{(+)}$, and whether BMB results could add useful information requires further exploration. In addition, other drawbacks such as a retrospective design and heterogeneity are also present in the current study.

Table 4 Multivariate analysis for overall survival and progress free survival in subgroups by Cox regression analysis (blackbody * for statistically significant difference)

Subgroups	Unfavorable factors	OS			PFS		
		P value	HR	95.0% CI	*P* value	HR	95.0% CI
Age	≥ 60 years	0.857	1.135	0.285–4.518	0.777	1.217	0.312–4.739
Gender	Male	0.137	0.484	0.186–1.260	0.142	0.491	0.190–1.269
Stage	III and IV	0.174	0.349	0.076–1.593	0.241	0.414	0.095–1.805
B symptoms	Present	0.070	0.455	0.194–1.066	0.142	0.548	0.246–1.223
LDH level	Increase	0.354	0.648	0.259–1.623	0.214	0.569	0.234–1.384
ki67	> 50%	0.714	0.867	0.405–1.858	0.922	1.041	0.470–2.305
ECOG	Score = 2	**0.043***	0.335	0.116–0.967	0.435	0.625	0.192–2.033
IPI score	Score > 2	0.068	4.651	0.890–24.292	0.138	3.064	0.697–13.459
KPI score	Score > 2	**0.014***	6.525	1.452–29.323	**0.010***	7.847	1.625–37.896
BMB	Positive	**0.000*****	0.014	0.001–0.143	**0.011***	0.079	0.011–0.562
PETCT	$PET^{(+)}$	0.159	0.319	0.065–1.565	**0.022***	0.106	0.015–0.726

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

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Author contributions YW and MJ performed the research. MJ designed the research study. Other authors analyzed the data; YW and MJ wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declared no conflict of interest to this work.

Ethical approval We abided by ethical standards of the institutional and/or national research committee, the Helsinki Declaration in 1964 and its later amendments or comparable ethical standards in all procedures performed in this study and all human participants involved.

Informed consent Informed consent was obtained from all individual participants included in the study.

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