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Prognostic significance of retention index of bone marrow on dual-phase ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with diffuse large B-cell lymphoma

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Abstract

The purpose of this study was to determine the prognostic significance of F-18 fluorodeoxyglucose (FDG) uptake on a dual-phase positron emission tomography/computed tomography (PET/CT), focusing on the increment in maximal standardized uptake value (SUVinc) of tumor and bone marrow (BM) between initial and delayed phase images and retention index (RI) of tumor and BM, in patients with diffuse large B-cell lymphoma (DLBCL).

From September 2009 to January 2013, 70 patients (37 males and 33 females, aged 60.6 ± 17.5 years) with DLBCL who had undergone dual-phase FDG PET/CT scans for pretreatment staging were enrolled. The patients subsequently received combination chemotherapy with rituximab. The dual-phase SUV, including SUVinc of tumor (SUVinc-t), RI of tumor (RI-t), SUVinc of BM, and RI of BM were measured. The clinical observation period was from September 2009 to December 2014. Both univariate and multivariate analyses were then used to assess the prognostic significance of SUVinc, RI, international prognostic index (IPI), gender, age, clinical stage, and laboratory tests.

The median follow-up time was 35.5 months. The 3-year overall survival (OS) for patients with low/high SUVinc-t (cut-off 2.0) and for patients with low/high RI-t (cut-off 20) were 87.5%/ 62.1% ($P = .08$) and 83.3%/ 62.7% ($P = .14$), respectively. The 3-year OS for patients with SUVinc-i < 0.35 and for those with SUVinc-i ≥ 0.35 were 73.2% and 53.3%, respectively ($P = .10$). The 3-year OS for patients with RI-i < 45 and for those with RI-i ≥ 45 were 72.7% and 37.5%, respectively ($P = .02$). Subsequently, the Cox multivariate forward proportional hazards model revealed that a higher RI-i (hazard ratio: 4.49; 95% confidence interval: 1.64–12.32; $P = .0035$) and IPI were independent prognostic factors affecting OS.

For patients with DLBCL, an elevated RI-i (≥45) was a predictor for shorter OS, independent of IPI score. It added to the value of pretreatment dual-phase FDG PET/CT scans.

Abbreviations: ASCT = autologous stem cell transplantation, BM = bone marrow, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone, CI = confidence interval, CR = complete remission, DLBCL = diffuse large B-cell lymphoma, FDG = F-18 fluorodeoxyglucose, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, Hb = hemoglobin, HR = hazards ratio, IPI = international prognostic index, LDH = lactate dehydrogenase, NCCN = national comprehensive cancer network, NHL = non-Hodgkin lymphoma, OS = overall survival, PET/CT = positron emission tomography/ computed tomography, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, RI = retention index, RI-i = RI of SUVi, RI-t = RI of SUVt, ROC = receiver operating characteristic, SUV = standardized uptake value, SUV-1 = maximal SUV at one hour, SUV-2 = maximal SUV at two hours, SUVi = maximal SUV of the right posterior iliac crest, SUVinc = increment in maximal SUV, SUVinc-i = SUVinc of the right posterior iliac crest, SUVinc-t = SUVinc of the tumor, SUVt = maximal SUV of tumor.

Keywords: bone marrow, diffuse large B-cell lymphoma, dual-phase, FDG PET/CT, prognosis

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1. Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL). It accounts for up to 30% of newly diagnosed cases in the western countries.[1] Positron emission tomography/computed tomography (PET/CT) using the radiopharmaceutics F-18 fluorodeoxyglucose (FDG) has played an important role for the diagnosis, for staging as well as therapeutic monitoring in patients with DLBCL.[2–4] Because the FDG uptake may reflect tumor aggressiveness and is proportional to the metabolic degree of viable tumor cells,[5] the interest in the use of FDG PET/CT to evaluate patient prognosis has been increasing.

DLBCL is characterized by its diversity in clinical course, morphology, immunophenotype, and cytogenicity. Because of the aggressive behavior and a wide range of clinical outcomes, identifying prognostic factors of the disease in order to enable stratification of patients for optimal treatment is very important. Chemotherapy with the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen has been the mainstay of treatment for several decades. In the past 20 years, the international prognostic index (IPI) has been one of the most useful tools to evaluate the prognosis in patients with aggressive NHL. The 5-year overall survival (OS) for low risk (IPI: 0–1), low-intermediate risk (IPI: 2), high-intermediate risk (IPI: 3), and high risk (IPI: 4–5) is 73%, 51%, 43%, and 26%, respectively.[6] In recent years, the addition of rituximab (an IgG1 monoclonal antibody against CD20) to CHOP chemotherapy (R-CHOP) has led to a significant improvement in the clinical outcomes.[7–9] For most patients with newly diagnosed DLBCL, R-CHOP has become the standard treatment. However, the clinical challenge exists. Although the usage of rituximab-containing chemotherapy as the standard therapy has brought patients with this kind of lymphoma to a markedly improved outcome, patients with poor response to the first-line treatment continue to present as a clinical difficulty. Early identification of patients at a high risk may allow for adoption of alternate therapeutic strategies, such as more intensive chemotherapy or upfront autologous stem cell transplantation (ASCT) after the first remission.[10,11]

Dual-phase FDG PET was initially conducted to increase the accuracy in the differentiation between benign and malignant tumors. This was because the FDG PET image at a single time-point lacks the dynamic information regarding the FDG uptake in a lesion, and there is sometimes overlap of the standardized uptake value (SUV), that is, the semiquantitative measurement of FDG uptake, between benign and malignant tumors. The retention index (RI) of the lesion, which is defined as the percentage change in maximal SUV (SUVmax) between initial and delayed phase images, has been found to have clinical potential to predict malignance[12,13] and patient prognosis.[14,15] Another parameter derived from dual-phase FDG PET is the increment in SUVmax (SUVinc) of the tumor between initial and delayed phase image. One study has mentioned SUVinc of the tumor to be an independent prognostic parameter in nonsmall cell lung cancer.[16]

In addition to FDG uptake of primary tumors, the clinical implications of bone marrow (BM) hypermetabolism depicted on FDG PET have been studied. The metabolic activity of the BM can be related to systemic inflammatory response.[17,18] Previous studies regarding nonsmall cell lung cancer[19–21] and head and neck squamous cell carcinoma[22] have also reported that patients with higher BM uptake on FDG PET have poorer survival. Recently, inflammatory response in tumor microenvironments has become an attractive target for cancer therapy[23]; thus, FDG uptake of BM might be used as a clinical biomarker to evaluate and monitor systemic inflammatory response as well as to predict patient prognosis. However, in the literature, there is a paucity of studies mentioning the correlation between clinical outcomes and dual-phase SUV change of tumor and BM in patients with DLBCL.

The purpose of this study was to determine the prognostic significance of FDG uptake on dual-phase PET/CT, focusing on SUVinc and RI of tumor and BM, and to access their independence relative to IPI and some clinical prognostic factors based on OS in patients with DLBCL.

2. Materials and method

2.1. Patient population

The review process and study design was approved by the Institutional Review Board of Kaohsiung Medical University Hospital [KMUHIRB-E(I)-20160009]. Patient consent was waived because all clinical information was collected retrospectively via medical chart reviewing. However, informed consents upon admission for all of the medical procedures including the dual-phase FDG PET/CT scans were required. The data were securely protected, available only to investigators and analyzed anonymously. The medical records were reviewed of patients with DLBCL who were diagnosed between September 2009 and January 2013 and treated in Kaohsiung Medical University Hospital. The inclusion criteria looked for patients who had been pathologically diagnosed as DLBCL, subsequently received rituximab-containing chemotherapy, completed pre-treatment work-up, including history, physical examination, standard laboratory tests, as well as BM aspiration and biopsy, and received a dual-phase FDG PET/CT scan for pretreatment staging. The exclusion criteria included underlying history of other malignancy, younger than 18 years, and absence of a delayed-phase FDG PET/CT image, which covered the pelvic region. Ann Arbor staging criteria were used to stage patients clinically. The observation period was from September 2009 to December 2014.

2.2. FDG PET/CT acquisition

Every patient was asked to be fasting for at least 6 hours. The level of blood glucose was controlled to be under 150 mg/dL. After injection of F-18 FDG intravenously (7 MBq per kilogram), patients were asked to lie on the bed in order to minimize unnecessary muscular uptake. All of the FDG PET/CT images were acquired using the delicate PET/CT scanner (Discovery ST 16; GE Medical System, Waukesha, WI). One hour after FDG administration, spiral low-dose CT (140 kV, 80 mA, 1.0 second per rotation, 3.75 mm of section thickness, and 59.0 mm/s of the table speed) was performed from the vertex to leg. The whole-body emission imaging (4 minutes every bed position) was then acquired in a reverse direction. The whole-body maximum-pixel-intensity projection was used for visual evaluation of the disease extendion and location. For patients who presented lesions with equivocal FDG uptake (SUV ~2.5), especially in the lymph nodes, an additional delayed-phase scan was performed 2 hours after FDG injection. The covering area of the delayed-phase scans was decided by nuclear medicine physician according to the suspicious lesion-presenting sites. PET data were reconstructed iteratively with CT attenuation correction after the decay

correction. The images (PET, CT, and fused PET/CT) were reoriented in the 3-orthogonal slices for diagnosis and SUV measurement. Image evaluation and analysis were performed on the Xeleris workstation (Xeleris Functional Imaging Workstation; GE Medical System). Interpretation of imaging findings and SUV measurements were performed by 2 experienced nuclear medicine physicians who were blinded to the patients' clinical outcomes. Discussion to achieve a consensus interpretation was made if disagreements existed.

2.3. FDG PET/CT analysis

The SUV was defined as the highest activity concentration every injected dose (per body weight) after radioactive decay correction. The sites of lesion with maximal SUV in 2 scans were recorded, respectively. Using CT images from the FDG PET/CT, the maximal SUV was collected by drawing a 1 cm diameter circle of region of interest (ROI) over different foci. In patients with multiple lesions, the SUVmax of tumor (SUVt) was obtained by placing the ROI on the slice with the most intense FDG uptake among primary lesions. The FDG uptake of BM is obtained by measuring the SUVmax of the right posterior iliac crest (SUVi) accordingly to the site of BM biopsy, as demonstrated in Fig. 1. The SUVinc was defined by subtracting the SUVmax at 2 hours (SUV-2) by the SUVmax at 1 hour (SUV-1). The RI (%) was also calculated as follows: RI = 100 x [(SUV-2) – (SUV-1) / (SUV-1).

2.4. Treatment and clinical course

All patients received rituximab-containing combination chemotherapy as an initial treatment. The therapeutic regimens, either R-CHOP or R-COP, were decided with consensus after discussion in the multi-disciplinarily combined conference. Involved field radiation therapy was administered for clinically indicated patients, that is, initial bulky disease (≥10 cm) or residual tumor presentation, after completion of chemotherapy. Complete remission (CR) was defined by follow-up image evaluation either by FDG PET/CT or CT scan according to published criteria.[24] Patients with refractory and relapsed disease were treated with salvage chemotherapy or received ASCT with high-dose chemotherapy if clinically indicated.

2.5. Statistical analysis

OS was defined as the time from diagnosis to death from any cause. Continuous variables are presented as mean (standard deviation) and categorical data are given as frequencies (percentages). The Spearman rank correlation test was used to analyze the correlations between metabolic and clinical parameters. The Mann–Whitney rank-sum and Kruskal–Wallis test were used for comparison of variables between patients in different categories. The Wilcoxon test was used for comparison of SUV between initial and delayed phase images. The survival curves for OS were analyzed using the Kaplan–Meier method on PET/CT parameters as well as on the clinically collected parameters [age, sex, staging, IPI, BM status, B symptom, Eastern Cooperative Oncology Group (ECOG) performance status, glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), creatinine, albumin, lactate dehydrogenase (LDH), β2-microglobulin, hemoglobin (Hb), platelet, and white blood cell counts]. The cut-off values of the variables were dichotomized using normal reference if available in the literature, or determined by the receiver operating characteristic (ROC) curves to get the most discriminative value. Variables with prognostic significance (defined as $P < .05$) in the univariate Cox proportional hazards regression were then chosen into a multivariate Cox proportional hazards models using forward and stepwise selections. All these analyses were conducted using MedCalc Statistical Software (MedCalc Software bvba, version 16.4.3, Ostend, Belgium; https://www.medcalc.org; 2016). All statistical tests were 2-sided, and a 2-tailed $P < .05$ was considered significant.

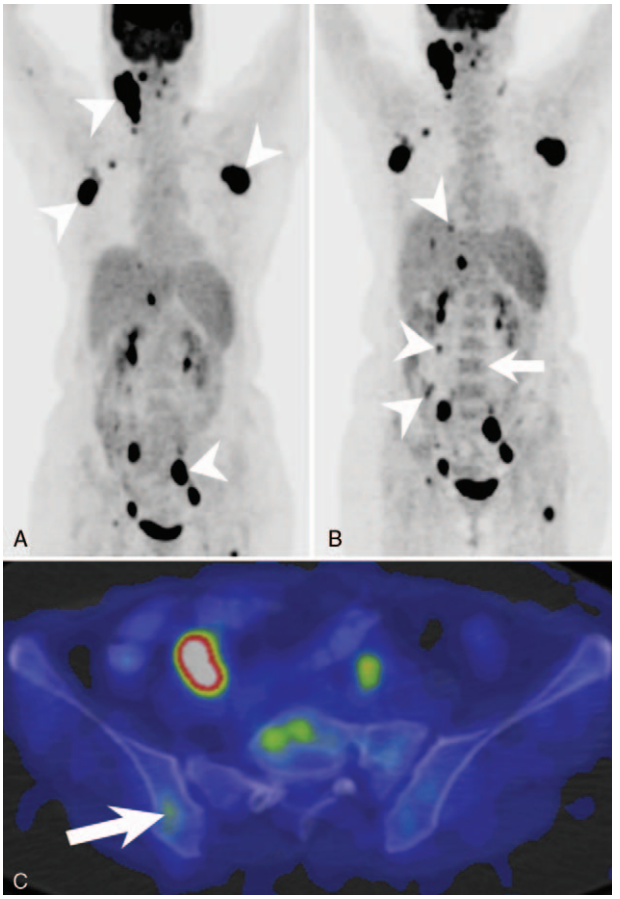

Figure 1. Demonstration of the initial and delayed phase FDG PET, as well as selected ROI for BM FDG uptake. This 53-year-old woman was diagnosed with DLBCL and clinically at stage III. Maximal intensity projection (MIP) of initial phase FDG PET (A) reveals multiple high grade FDG-avid masses in right cervical, bilateral axillary and along bilateral iliac vessels (arrowheads). On the MIP of delayed phase image (B), the lesions with faint FDG uptake on the initial phase image were more obviously delineated because of higher lesion-to-background ratio (arrowheads). The FDG uptake of whole-body BM (arrow) is also depicted more clearly. The dual-phase SUVs of BM (i.e., right posterior iliac crest, arrow in C) were recorded. The SUVi-1, SUVi-2, SUVinc-i, and RI-i were 1.97, 2.59, 0.62, and 31.47, respectively. Thereafter, she received treatment with R-CHOP regimen. The patient is still alive after a follow-up period of 38 months.

3. Result

3.1. Patient characteristics

A total of 70 patients who met the eligible criteria were analyzed, and the clinical characteristics are summarized in Table 1. There were 37 (52.9%) men and 33 (47.1%) women with age range from 20 to 94 years. Thirty-five (50%) patients were at early stages (stage I or II), while the other 35 patients (50%) were

Table 1

Characteristics at diagnosis of all 70 patients with diffuse large B-cell lymphoma.

Variable	Value
Age, y	60.6 ± 17.5
Gender	
Male	37 (52.9)
Female	33 (47.1)
Ann Arbor stage	
I	20 (28.6)
II	15 (21.4)
III	9 (12.9)
IV	26 (37.1)
IPI	
0–1	26 (37.1)
2	26 (37.1)
3	9 (12.9)
4–5	9 (12.9)
Primary lesions	
Lymph nodes	40 (57.1)
Extranodal lesions	30 (42.9)
Bone marrow involvement	
Yes	17 (24.3)
No	53 (75.7)
B symptoms	
Yes	31 (44.3)
No	39 (55.7)
ECOG performance status	
0	26 (37.1)
>0	44 (62.9)
Treatment	
R-CHOP	51 (72.9)
R-COP	19 (27.1)
Hemoglobin, g/dL	11.8 ± 2.0
WBC, $x10^3$ μL	6.72 ± 2.58
Platelet, $x10^3$/μL	233.7 ± 104.9
Albumin, g/dL	3.5 ± 0.6
Creatinine, mg/dL	0.85 ± 0.37
GOT, IU/L	34.3 ± 25.6
GPT, IU/L	29.1 ± 29.7
LDH, IU/L	336.3 ± 496.3
β2-microglobulin, μg/dL	286.7 ± 166.5

ECOG = Eastern Cooperative Oncology Group, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, IPI = international prognostic index, LDH = lactate dehydrogenase, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, R-COP = rituximab, cyclophosphamide, vincristine, and prednisolone, WBC = white blood cell.

at stages III or IV. According to IPI scores, patients with low risk (0–1), low-intermediate risk (2), high-intermediate risk (3), and high risk (4–5) were 26, 26, 9, and 9, respectively. Thirty (42.9%) patients presented extranodal involvement and 17 (24.3%) patients presented with pathologically confirmed BM involvement at diagnosis (Figure S1, http://links.lww.com/MD/C78). Thirty-one patients (44.3%) had B symptom, and 44 patients (62.9%) had an ECOG > 0 at diagnosis. The median follow-up time was 35.5 months. At the end of the study, 48 (68.6%) patients were alive and 22 (31.4%) patients have passed (Table S1, http://links.lww.com/MD/C78).

3.2. Metabolic parameters from dual-phase FDG PET/CT

The site of lesion with maximal SUV in initial phase scan was identical to that in the delayed phase scan in every patient. The mean values of SUVt at 1 hour (SUVt-1) and 2 hours (SUVt-2) were 15.57 ± 8.77 and 21.06 ± 12.23, respectively. There was a significant difference between SUVt-1 and SUVt-2 ($P < .0001$). The mean SUVinc of the tumor (SUVinc-t) was 5.49 ± 4.25, and the mean RI of SUVt (RI-t) was 34.12 ± 18.00. The mean values of SUVi at 1 hour (SUVi-1) and 2 hours (SUVi-2) were 1.41 ± 0.76 and 1.69 ± 0.99, respectively. There was a significant difference between SUVi-1 and SUVi-2 ($P < .0001$). The mean SUVinc of the right posterior iliac crest (SUVinc-i) was 0.27 ± 0.33, and the mean RI of SUVi (RI-i) was 20.50 ± 19.83.

3.3. Correlation between metabolic and clinical parameters

The correlation between hematological parameters and SUVi-1, SUVi-1, SUVinc-I, and RI-i were analyzed by Spearman rank correlation test. There was no significant correlation between the values of Hb and SUVi-1 ($P = .949$), SUVi-2 ($P = .723$), SUVinc-i ($P = .713$), and RI-i ($P = .517$). Similar results were noted in WBC counts ($P = .495$ for SUVi-1, $P = .274$ for SUVi-2, $P = .267$ for SUVinc-i, and $P = .273$ for RI-i) and platelet counts ($P = .657$ for SUVi-1, $P = .937$ for SUVi-2, $P = .532$ for SUVinc-I, and $P = .573$ for RI-i).

The correlations between BM status (regardless the involvement of lymphoma cells) and SUVi-1, SUVi-2, SUVinc-i, and RI-i were also analyzed. Significant correlations between BM involvement and SUVi-1 ($P = .015$), SUVi-2 ($P = .008$), and SUVinc-i ($P = .039$) were shown. However, there was no statistical significance between BM involvement and RI-i ($P = .233$). In the patients with BM involvement (n = 17), only 1 patient (5.9%) had RI-i ≥ 45. In the patients without BM involvement (n = 53), there were 44 (83.0%) patients with lower RI-i and 9 (17.0%) patients with higher RI-i. (Table S2, http://links.lww.com/MD/C78) On the Mann–Whitney rank-sum test, the RI-i did not reveal significant difference ($P = .231$) between patients with and without BM involvement. On the Kruskal–Wallis test, the RI-i did not reveal significant difference ($P = .288$) between patients with different IPI risk scores.

3.4. Overall survival based on dichotomization of metabolic parameters

Using ROC curve analysis, we used minimal P values to define the best discriminative cut-off values for SUVinc-t, SUVinc-i, RI-t, and RI-i as 2.0, 0.35, 20, and 45, respectively. On the Kaplan–Meier survival analysis, patients with higher SUVinc-t, higher SUVinc-i, higher RI-t, and higher RI-i had poorer OS.

The 3-year OS for patients with lower SUVinc-t (<2.0; n = 16)/higher SUVinc-t (≥2.0; n = 54) and lower RI-t (<20; n = 18)/higher RI-t (≥20; n = 52) were 87.5%/62.1% ($P = .08$) and 83.3%/62.7% ($P = .14$), respectively. The 3-year OS for patients with lower SUVinc-i (< 0.35; n = 50) and for those with higher SUVinc-i (≥ 0.35; n = 20) were 73.2% and 53.3%, respectively ($P = .10$; Fig. 2A). The 3-year OS for patients with lower RI-i (< 45; n = 60) and higher RI-i (≥ 45; n = 10) were 72.7% and 37.5%, respectively ($P = .02$; Fig. 2B). The median survival time for the patients with higher RI-i (≥45) was 11.0 months [95% confidence interval (CI): 4.0–31.0]. A similar condition was noted in the patients without BM involvement (n = 53); patients with higher RI-i had significant shorter OS than those with lower RI-i ($P = .004$, Figure S2, http://links.lww.com/MD/C78).

3.5. Comparison of clinical impacts of other prognostic parameters

In the univariate analysis using the Cox proportional hazards model, older age, Hb, WBC count, albumin, LDH level, B

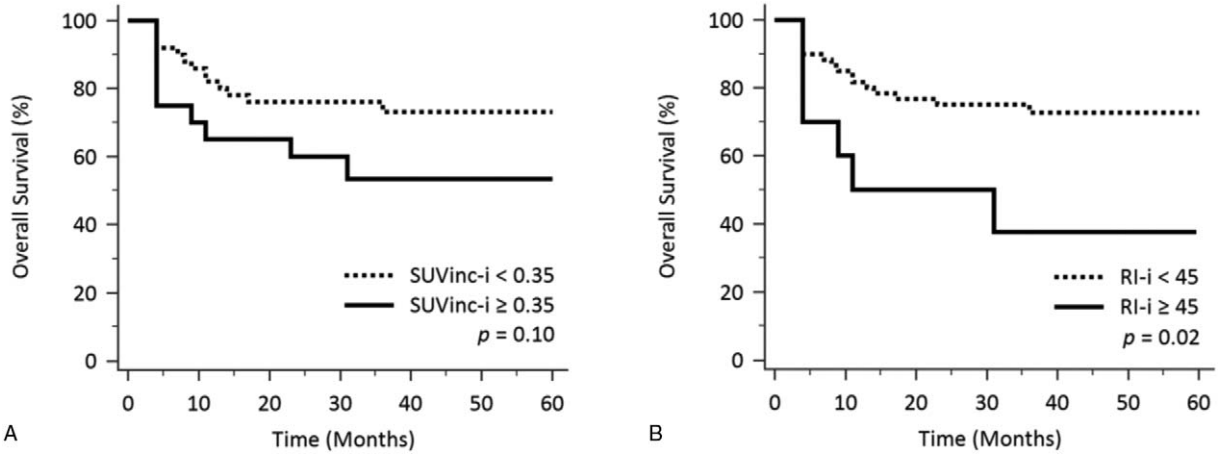

Figure 2. Kaplan–Meier survival curve of the patients according to the SUVinc-i (A) and RI-i (B) on FDG PET/CT for OS. Patients with SUVinc-i ≥0.35 and RI-i ≥45 had a poorer OS. The 3-year OS rates for patients with low RI-i and for those with high RI-i were 72.7% and 37.5%, respectively ($P = .02$).

symptom, clinical stage, IPI risk score, and RI-i were all significant prognostic factors for OS. Patients with thrombocytopenia, elevated GOT, GPT, β2-microglobulin, higher ECOG, SUVinc-t, SUVinc-i, and RI-t had poorer OS, but the results were not statistically significant (Figure S3, http://links.lww.com/MD/C78). Then, the parameters with prognostic significance in univariate analysis were then chosen into the multivariate Cox proportional hazard regression with the forward and stepwise selection schemes. The final model revealed that IPI score 3 [hazards ratio (HR): 4.19; 95% CI: 1.50–11.73; $P = .0063$], IPI score 4–5 [HR: 8.29 (2.71–25.31), $P = .0002$], and higher RI-i [HR: 4.49 (1.64–12.32), $P = .0035$] were poor independent prognostic factors (Table 2).

4. Discussion

The BM produces hematopoietic cells. It is well-known that BM reveals mildly increased FDG uptake in healthy subjects. Some of the patients with different diseases, however, can show relatively higher FDG uptake in the BM.[25] Previous studies have mentioned that FDG uptake in the BM may reflect the BM activation in response to the inflammatory process.[26,27] Bural et al[17] reported that BM can show increased FDG uptake as a result of a systemic inflammatory response secondary to underlying malignancy. Lee et al[21] also showed significant correlation between BM uptake and increased serum inflammatory markers. However, in the present study, we did not find significant correlation between BM SUV and hematological parameters.

To our best knowledge, this is the first study that has used the RI of BM on dual-phase FDG PET/CT to evaluate the prognostic significance in patients with DLBCL receiving rituximab-containing chemotherapy. For some malignant diseases, BM hypermetabolism depicted on FDG PET has been discussed as a survival prognostic factor in the literature.[19–22,28] In DLBCL, however, most studies focused on the capacity of BM FDG uptake on PET/CT scans to detect BM involvement by the tumor cells.[29–33] It is because BM involvement indicates stage IV disease and accounts for 1 point in the IPI scoring. In order to confirm the BM status, BM biopsy remains the gold standard. However, the sensitivity of BM biopsy is relatively poor (~50%) because of the small sample size or focalized pattern of BM involvement.[34,35] Some studies have been conducted to see whether the BM biopsy, which is a relatively invasive procedure with certain risk of complications, is necessary in the FDG PET/CT era. But the results were controversial. Cheson et al [36] recommended that an FDG PET/CT demonstrating bone or BM involvement is sufficient to designate a late disease staging, and the BM biopsy is not required. Adams et al [37] stood on the opposite site, suggesting the FDG PET/CT cannot replace BM biopsy in evaluating patients with DLBCL. Knowledge about the prognostic value of BM FDG uptake is relatively lacking.[38] Berthet et al[39] reported that in patients with newly diagnosed DLBCL, BM status on FDG PET/CT was an independent predictor for progression free survival, but not for OS. In the present study, the RI of the right posterior iliac crest was an independent prognostic factor for predicting OS in patients with DLBCL, in addition to the IPI score. Although pending further validation with a larger patient population, this pilot study may bring about the concept that FDG PET/CT, as a noninvasive measurement, could help to stratify the high-risk patient group at pretreatment staging. More aggressive and intensive therapeutic strategies may be chosen.

For the reason of richer blood supply in the red marrow than in the yellow marrow, the BM involvements by a malignant tumor cells are most often (>90%) confined in the red marrow. However, the frequency of involvement may differ at different sites of the red marrow. Due to the inhomogeneous pattern of BM involvement of the malignant cells, and BM sampling via unilateral iliac biopsy only being able to assess a small portion of the entire BM, there is a difficulty to access the extent of BM involvement precisely at different marrow sites. In the present study, we chose the right posterior iliac crest as the representative site for BM FDG uptake because it corresponds to the site for BM biopsy. On the basis of present study results, SUVi-1, SUVi-2, and SUVinc-i showed significant correlations with BM involvement by the tumor cell, whereas RI-i failed to show any significance. We hypothesize that RI of BM, that is, dividing the SUVinc-i by the SUVi-1, has been "diluted" by the denominator.

It is well-known that dual-phase FDG PET/CT, based on the sustained FDG accumulation in the malignant tumors, improves the diagnostic accuracy in differentiating inflammation from malignancy.[40,41] It also adds diagnostic values especially for evaluation of lymphatic nodal metastases.[42,43] For the reason

Table 2

Cox proportional hazards models analysis of potential prognostic factors affecting OS.

	Univariate analysis		Multivariate analysis†	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥vs<65 y)	2.84 (1.19–6.79)	.019*		
Hemoglobin (< vs ≥10 g/dL)	2.60 (1.11–6.09)	.028*		
WBC (< vs ≥5000 × 10^3 /μL)	2.63 (1.07–6.49)	.036*		
Albumin (< vs ≥3.5 g/dL)	2.51 (1.07–5.88)	.034*		
LDH (≥ vs <192 IU/L)	3.57 (1.39–9.16)	.008*		
Sex (male vs female)	1.03 (0.45–2.39)	.944		
Platelet (< vs ≥160 × 10^3/μL)	1.78 (0.75–4.25)	.194		
Creatinine (≥ vs <1.3 mg/dL)	1.41 (0.33–6.05)	.642		
GOT (≥ vs <42 IU/L)	1.34 (0.53–3.43)	.538		
GPT (≥ vs <40 IU/L)	1.53 (0.56–4.15)	.403		
β2-microglobulin (≥ vs < 340 μg/dL)	1.66 (0.65–4.26)	.289		
B symptom (yes vs no)	3.21 (1.30–7.89)	.011*		
ECOG (> vs = 0)	1.77 (0.69–4.54)	.232		
Stage		.024*		
I	1			
II	0.89 (0.15–5.35)			
III	3.58 (0.80–16.03)			
IV	4.08 (1.16–14.34)			
IPI		.001*		.0001*
Low (0–1)	1			
Low-intermediate (2)	2.43 (0.63–9.42)	.198		
High-intermediate (3)	7.45 (1.85–29.90)	.004*	4.19 (1.50–11.73)	.0063*
High (4–5)	10.3 (2.53–41.87)	.001*	8.29 (2.71–25.31)	.0002*
BM involvement (yes vs no)	1.12 (0.42–3.06)	.813		
SUVinc-t (≥ vs <2.0)	3.30 (0.77–14.15)	.107		
SUVinc-i (≥ vs <0.35)	1.95 (0.83–4.58)	.123		
RI-t (≥ vs <20)	2.39 (0.71–8.10)	.160		
RI-i (≥ vs < 45)	2.77 (1.08–7.10)	.034*	4.49 (1.64–12.32)	.0035*

BM = bone marrow, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group performance status, GOT = glutamate oxaloacetate transaminase, GPT = glutamate pyruvate transaminase, HR = hazard ratio, IPI = international prognostic index, LDH = lactate dehydrogenase, RI-i = retention index of maximal SUV of right posterior iliac crest., RI-t = retention index of maximal SUV of tumor, SUVinc-i = increment in maximal SUV of right posterior iliac crest, SUVinc-t = increment in maximal SUV of the tumor, WBC = white blood cell.

* Statistically significant.

† The final model of the multivariate analysis was conducted using a forward Cox proportional hazards model.

that DLBCL is a kind of malignancy that would influence the lymphatic system (especially lymph nodes) of the whole body, we assume that dual-phase FDG PET/CT may play a potential role in improving the diagnostic and staging accuracy, particularly for the lymph nodes showing doubtful FDG uptake (SUV ~2.5) on the initial phase image. In the present study, the difference between SUVt-1 and SUVt-2 was significant ($P < .0001$). It may help to have precise staging; however, dual-phase SUV of the tumor did not produce significant enough values to predict OS.

BM hypermetabolism in malignancy is possibly associated with factors of both the host and the tumor itself. Micrometastases in the BM may be the cause of increased metabolic status of BM. Secretion of stimulating cytokines such as colony-stimulating factors,[44] interleukin-6,[45] and vascular endothelial growth factor[46] by the primary tumor may also associate with activation of metabolic status of BM. For host factors, coexisting illness such as hypoxemia presented by relatively lower Hb level and decreased PaO_2 can to some degree stimulate hematopoiesis and cause BM hypermetabolism.

The results of the current study underlined the prediction of poor outcomes in the patients with higher RI of BM on pre-treatment FDG PET/CT scan. More positive clinical strategy such as earlier interim restaging may be suggested to these high-risk patients. The second-line therapy, clinical trial, or ASCT may be given if disease remained refractory. Although current study was relatively small with a retrospective design, the results underlined the prediction of poor outcomes in the patients with higher RI of BM on the pre-treatment dual phased FDG PET/CT scan. A delayed phase image covering the pelvic region as well as the simple calculation to get the RI could provide the useful clinical information. According to the national comprehensive cancer network (NCCN) guideline for the treatment of DLBCL, interim restaging after 2 to 4 cycles of induction chemotherapy was suggested, especially for staged III and IV patients. Addition to IPI score, the higher RI of BM helped to identify the high-risk patients. More positive clinical strategy such as earlier interim restaging may be suggested to these patients with higher risk. On the contrary, early identification of high-risk patients allowed clinicians to choose more intensive or high-dose therapy, which is reported to be more beneficial than sequential chemotherapy, followed by stem cell transplantation after the first remission.[11]

There are some limitations in the present study. The most important ones are inherent to a retrospective design as well as the small patient population. The patient number with higher RI-i (≥45) was only 10, which may lead to a statistical bias. Another limitation of studies regarding DLBCL is the data collection that includes patients with different histological subtypes and possibly the use of different first-line regimens for chemotherapy. Further confirmatory results may be warranted with a prospective study design, larger study population, and a more specific histological subtype collection.

5. Conclusion

This study revealed that pretreatment dual-phase FDG PET/CT played an important role in predicting OS in patients with DLBCL receiving rituximab-containing chemotherapy. A pending external validation of an elevated RI-i (≥45) was a predictor for shorter OS, regardless of IPI score.

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