Quantitative Assessment of Interim PET/CT Could Have More Prognostic Relevance than Visual Assessment for Predicting Clinical Outcome of Extranodal Diffuse Large B Cell Lymphoma

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Abstract. *Background/Aim: The present study retrospectively investigated the predictive accuracy of interim positron emission tomography/computed tomography (iPET/CT) based on the Deauville 5-point scale (5-PS) and a quantitative SUV-based assessment in patients with extranodal (EN) diffuse large B cell lymphoma (DLBCL). Patients and Methods: The Deauville 5-PS and the SUVmax reduction (ΔSUVmax) assessment for interpreting the response to iPET/CT were used. Results: A total of 163 patients were enrolled in this study. With a median follow-up of 52.5 months, ΔSUVmax successfully predicted the survival outcomes of patients with one extranodal (EN) involvement in terms of overall survival (OS) (p=0.012) and progression-free survival (PFS) (p<0.001). Visual assessment using the Deauville 5-PS did not predict survival outcomes in patients with one or more EN involvements in terms of OS and PFS. Conclusion: The quantitative SUV-based assessment with iPET/CT was a significant prognosticator for long-term survival outcomes, especially in patients with one EN involvement.*

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Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) worldwide (1). Clinically, most patients present with a rapidly growing tumor mass involving one or more lymph nodes, and approximately 40% of patients have extranodal (EN) disease (2). With the advent of the anti-CD20 monoclonal antibody, R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) combination chemotherapy has improved response rates and overall survival in patients with DLBCL (3, 4).

[18]F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has emerged as a powerful functional imaging tool for staging and response assessment of malignant lymphoma (5-7). New guidelines were presented for incorporating PET/CT into standardized response criteria by the International Working Group (IWG) in 2007 (7). Furthermore, interim PET/CT (iPET/CT) has been used to evaluate the therapeutic efficacy and predict long-term outcomes at early time points. However, the predictive value of iPET/CT has been inconsistent in some studies (8-10). In an attempt to

standardize the reporting criteria for iPET/CT, the First International Workshop on interim-PET scan in lymphoma suggested the visual response criteria using the Deauville five-point scale (5-PS) (11). In addition, the reduction rate of the maximum standardized uptake value (ΔSUVmax) was also introduced by several studies to decrease the frequency of false-positives and inter-observer variability in interpretations (12, 13).

It is widely accepted that DLBCL with EN involvements is less likely to be cured by standard R-CHOP therapy (14, 15). Therefore, early response assessment during the first-line treatment is important to improve clinical outcomes in DLBCL with EN involvements. Although recent studies have demonstrated that PET/CT generally detects EN sites more accurately than conventional CT in lymphomas (16, 17), challenges remain in the assessment of iPET/CT response for EN DLBCL. As FDG is not a tumor-specific substance, it may accumulate in anatomic sites in various benign conditions, which could give rise to false positives, particularly in iPET/CT assessments of patients with multifocal, non-contiguous involvement at EN sites (18). The pitfalls of iPET/CT interpretation in EN DLBCL might be related to the definition of response without the concern of inflammatory physiology or anatomic variations (19-21). Furthermore, several studies have reported that iPET/CT during R-CHOP therapy has poor prognostic significance, possibly due to false determinations by visual assessment methods (22-24).

Accordingly, the purpose of this study is to investigate the predictive accuracy of the iPET/CT response based on visual and quantitative SUV-based assessments in DLBCL patients with EN involvements. In addition, we compared the clinical significance of Deauville 5-PS and quantitative SUV-based assessment for iPET/CT response evaluation to establish an optimal treatment strategy for EN DLBCL.

Patients and Methods

Patients. Patients with newly diagnosed DLBCL and one or more EN involvements between May 2005 and May 2014 from two independent institutions were retrospectively investigated. Patients who had central nervous system involvement or were diagnosed with only nodal involvements were excluded. All patients had an initial PET/CT at diagnosis and a subsequent iPET/CT during R-CHOP chemotherapy. This study was approved by the Institutional Review Board of each participating center.

Treatment and response evaluation. Patients were treated with six to eight cycles of R-CHOP chemotherapy in standard doses (rituximab 375 mg/m^2 *i.v.* on day 1 (D1), cyclophosphamide 750 mg/m^2 *i.v.* on D1, vincristine 1.4 mg/m^2 *i.v.* on D1, doxorubicin 50 mg/m^2 *i.v.* on D1, and prednisolone 60 mg/m^2 *p.o.* on days 1-5) every 3 weeks) (4, 25). Three response evaluations, including PET/CT, were conducted: the first after three cycles (for patients whose plan was treatment with six cycles of primary chemotherapy) or four cycles (for patients whose plan was treatment with eight

Table I. *Patient characteristics.*

Variable	N (%)
Number of patients	163
Age, median years (range)	61 (18-83)
Gender	
Male	93 (57.1%)
Female	70 (42.9%)
ECOG Performance status	
0-1	140 (85.9%)
2-3	23 (14.1%)
Ann Arbor stage	
I-II	75 (46.0%)
III-IV	88 (54.0%)
Increased LDH	82 (50.3%)
Bone marrow involvement	22 (13.5%)
Number of extranodal sites	
1	102 (62.6%)
2	39 (23.9%)
3	18 (11.0%)
4	4 (2.5%)
IPI risk group	
Low	63 (38.7%)
Low-intermediate	32 (19.6%)
High-intermediate	29 (17.8%)
High	39 (23.9%)
NCCN-IPI	
Low	11 (6.4%)
Low-intermediate	73 (42.7%)
High-intermediate	69 (40.4%)
High	18 (10.5%)
Autologous SCT	22 (13.5%)
Relapse	40 (23.4%)
Death	42 (24.6%)

ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: lactate dehydrogenase; NCCN: National Comprehensive Cancer Network; SCT: stem cell transplantation.

cycles of primary chemotherapy) of R-CHOP and the second after primary chemotherapy. The third response evaluation was conducted within a month of completing the first-line chemotherapy. Follow-up restaging was conducted every three or six months during the first year after first-line chemotherapy, and every six months thereafter. The responses were assessed according to the revised International Workshop Criteria (IWC) (7).

^{18}F-FDG PET/CT and image analysis. All patients underwent PET/CT imaging on a Discovery ST PET/CT system (GE Healthcare, Chicago, IL, USA), consisting of a bismuth germanate full scanner and a 16-detector-row computed tomography (CT) scanner. Patients fasted for at least 6 h prior to the intravenous administration of FDG (7.4 megabecquerel (MBq) per kg of body weight) to ensure a serum glucose level below 7.2 mmol/l. One hour after FDG administration, a low-dose CT scan was obtained without contrast enhancement for attenuation correction (120 kV, automated from 10 to 130 mA, a 512×512 matrix, a 50-cm field of view (FOV), 3.75-mm slice thickness), extending from the base of the skull to the proximal thighs. Immediately after CT acquisition, PET
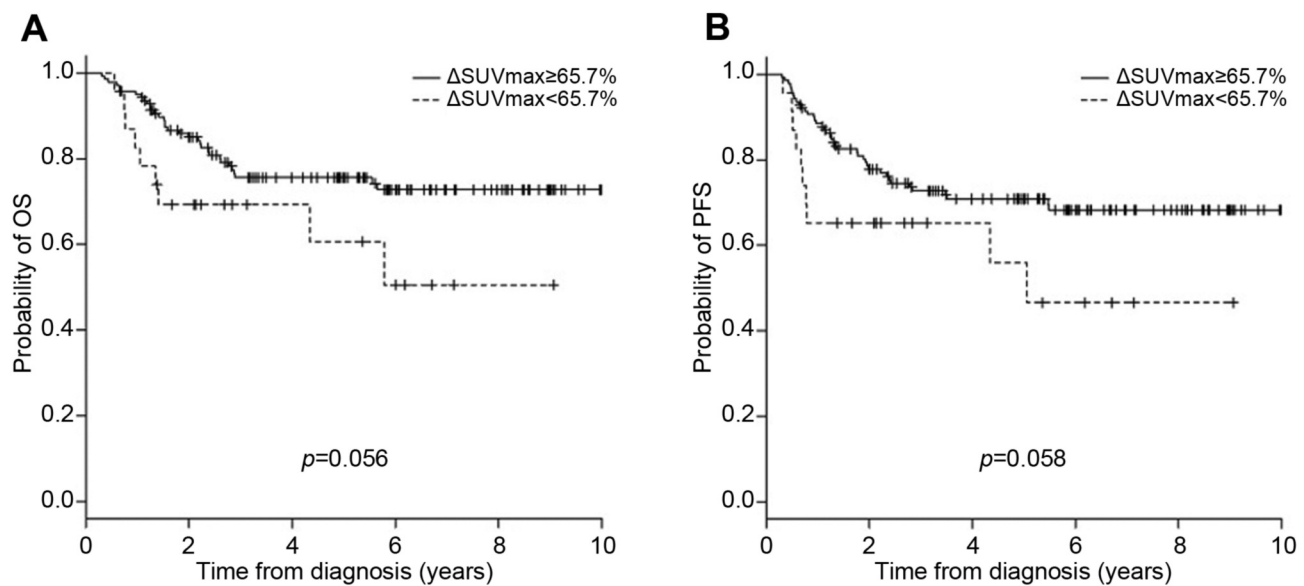
Figure 1. *Kaplan-Meier survival curves for (A) overall survival (OS) and (B) progression- free survival (PFS) of all patients according to SUV-based assessment.*

scans were acquired in the same anatomic locations with a 128×128 matrix and a 15.7-cm axial FOV. The images were reconstructed using a conventional iterative algorithm (OSEM). A workstation (AW Volume Share) providing multiplanar reformatted images was also used for image display and analysis. PET/CT scans were interpreted by two nuclear medicine physicians who had no knowledge of the subject or his or her clinical information.

Visual and SUV-based assessments of iPET/CT response. Visual assessment was classified based on the Deauville 5-PS (11). Deauville scores 1-3 were considered as a good metabolic response, and scores 4-5 were considered as a residual response and progression (26, 27). This grading process was independent of the size of the residual tumor. Patients were assessed simultaneously based on the quantitative analysis of changes in FDG uptake using the percentage of ΔSUVmax between initial and interim PET/CT scans. The ΔSUVmax rate was calculated as follows: ΔSUVmax (%) = 100×[SUVmax (initial) – SUVmax (interim)]/SUVmax (initial). For each PET dataset, the SUVmax was defined as the highest SUV among all hypermetabolic tumor foci. A ΔSUVmax value of 65.7% was used as a cutoff, based on a previous study (26).

Ethical approval. All procedures in this study that involved human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical analyses. Categorical variables were analyzed using the Chi-square test, and continuous variables were analyzed using the Student's *t*-test. Overall survival (OS) was defined as the time from diagnosis to death from any cause, and progression-free survival (PFS) was defined as the time from diagnosis to disease progression or death from any cause. The Kaplan-Meier method was used to estimate OS and PFS. Survival curves were compared using the log-rank test. Prognostic factors for OS and PFS were determined by univariate and multivariate analyses using the Cox-proportional hazard model. Factors with a *p*-value of less than 0.1 in the univariate analyses were entered in the multivariate analyses. *p*-Values<0.05 were considered significant. For statistical analyses, SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) was used.

Results

Patient characteristics. A total of 163 patients were enrolled in this study, and the median age was 61 years (range=18-83 years). According to the International Prognostic Index (IPI) scoring system for risk, 63 patients (38.7%) were classified as low, 32 patients (19.6%) as low-intermediate, 29 patients (17.8%) as high-intermediate, and 39 patients (23.9%) as high risk. The number of EN involvements was as follows: one site involvement in 102 patients (62.6%), two sites in 39 patients (23.9%), three sites in 18 patients (11.0%), and four sites in 4 patients (2.5%). The most common site of EN involvement was the stomach (35 patients, 21.5%), and 17 patients (10.4%) had bulky disease. Twenty-two patients (13.5%) received autologous stem cell transplantation. Among the enrolled patients, 40 patients (23.4%) experienced relapse. Patient characteristics are summarized in Table I.

Response evaluation of iPET/CT according to the SUV-based assessment and the Deauville 5-PS. Based on the quantitative assessment of iPET/CT using a cutoff value of ΔSUVmax, 140 patients (85.9%) were classified as good responders
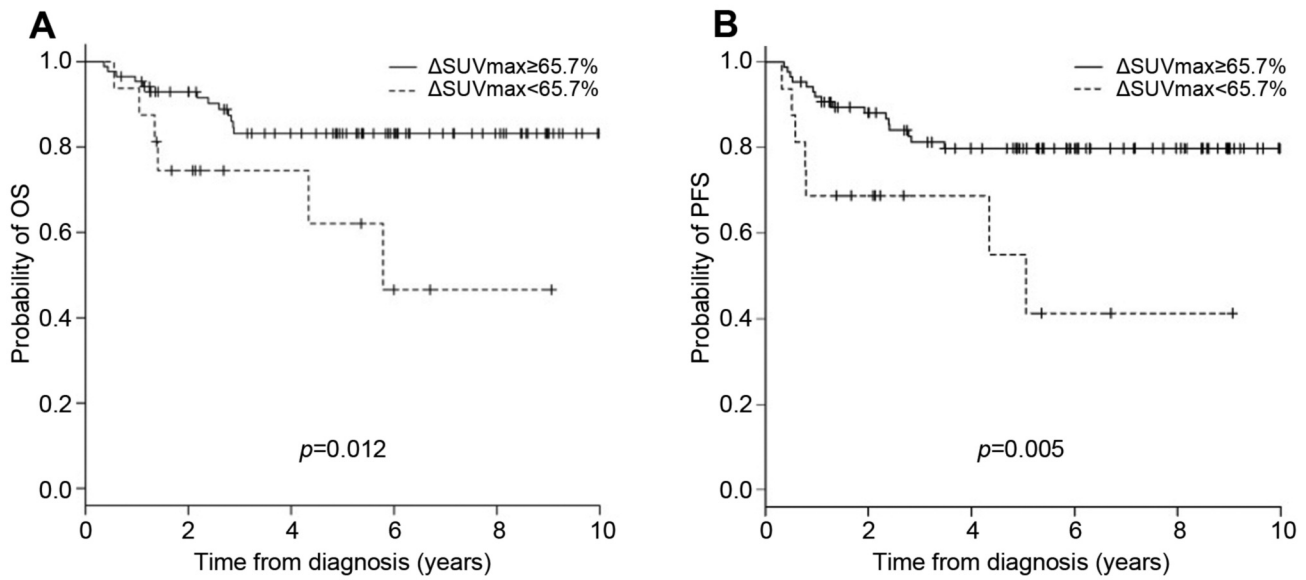
Figure 2. *Kaplan-Meier survival curves for (A) overall survival (OS) and (B) progression free survival (PFS) of patients with one extranodal involvement according to SUV-based assessment.*

(ΔSUVmax$\geq$65.7%) and 23 patients (14.1%) as poor responders (ΔSUVmax<65.7%). According to the Deauville 5-PS, 69 patients (42.3%) were assigned a score of 1 or 2, 30 patients (18.4%) were assigned a score of 3, 57 patients (35.0%) were assigned a score of 4, and 7 patients (4.3%) were assigned a score of 5. Among the patients with one EN involvement, 84 patients (82.4%) were classified as good responders (ΔSUVmax$\geq$65.7%) and 31 patients (15.7%) as poor responders (ΔSUVmax<65.7%) according to the SUV-based assessment, while 60 patients (58.9%) were assigned Deauville 5-PS scores of 1-3, and 42 patients (41.2%) were assigned Deauville scores of 4 or 5, based on visual assessment.

Assessment of the iPET/CT response using the cutoff of ΔSUVmax showed a positive predictive value (PPV) of 89.1% and a negative predictive value (NPV) of 78.2%, while the Deauville 5-PS (scores 1-3 *vs.* 4-5) showed a PPV of 91.9% and an NPV of 68.1%. In patients with one EN involvement, ΔSUVmax showed a PPV of 83.9% and an NPV of 68.7%, while the Deauville 5-PS (score 1-3 *vs.* 4-5) showed a PPV of 89.7% and an NPV of 66.2%.

Survival outcomes. Median follow-up duration was 52.5 months (range=3.7-119.8 months). OS at 5 years was 80% and 63.3% for patients with one and more than one EN involvements, respectively (*p*=0.005). PFS at 5 years was 76.3% and 56.7% in one and more than one EN site involvements, respectively (*p*=0.003). According to the SUV-based assessment, 5-year OS rates were 75.6% and 60.6% in patients who were classified as good (ΔSUVmax65.7%) and

poor (ΔSUVmax<65.7%) responders, respectively (*p*=0.056). Five-year PFS rates were 77.9% and 55.9% in patients who were classified as good and poor responders, respectively (*p*=0.058) (Figure 1). In patients with one EN involvement, ΔSUVmax successfully predicted the survival outcomes in terms of OS (83.2% *vs.* 62.1% at 5 years, *p*=0.012) and PFS (86.9% *vs.* 41.3% at 5 years, *p*=0.005) (Figure 2). However, ΔSUVmax did not predict long-term survival for patients with more than one EN involvements.

According to the Deauville 5-PS, 5-year OS rates were 77.3% in patients assigned scores of 1 or 2, 72.5% in patients assigned a score of 3, 71.4% in patients assigned a score of 4, and 25.0% in patients assigned a score of 5 (*p*=0.061). Five-year PFS rates were 69.7% in patients assigned scores of 1 or 2, 65.8% in patients assigned a score of 3, and 63.4% in patients assigned a score of 4 (*p*=0.001) (Figure 3). There were no statistically significant survival differences between patients classified as good responders (Deauville 5-PS scores 1-3) and poor responders (Deauville 5-PS scores 4-5) in terms of OS and PFS in patients with one EN involvement and those with more than one EN involvements.

Factors affecting long-term survival. In the univariate analyses for OS, old age, Eastern Cooperative Oncology Group performance status (ECOG PS) 2-3, increased lactate dehydrogenase (LDH), EN involvement, bone marrow (BM) involvement, stage III/IV, and international prognostic index (IPI) high/high-intermediate were unfavorable factors in overall patients, while ECOG PS 2-3, BM involvement and ΔSUVmax<65.7% in patients with one EN involvement
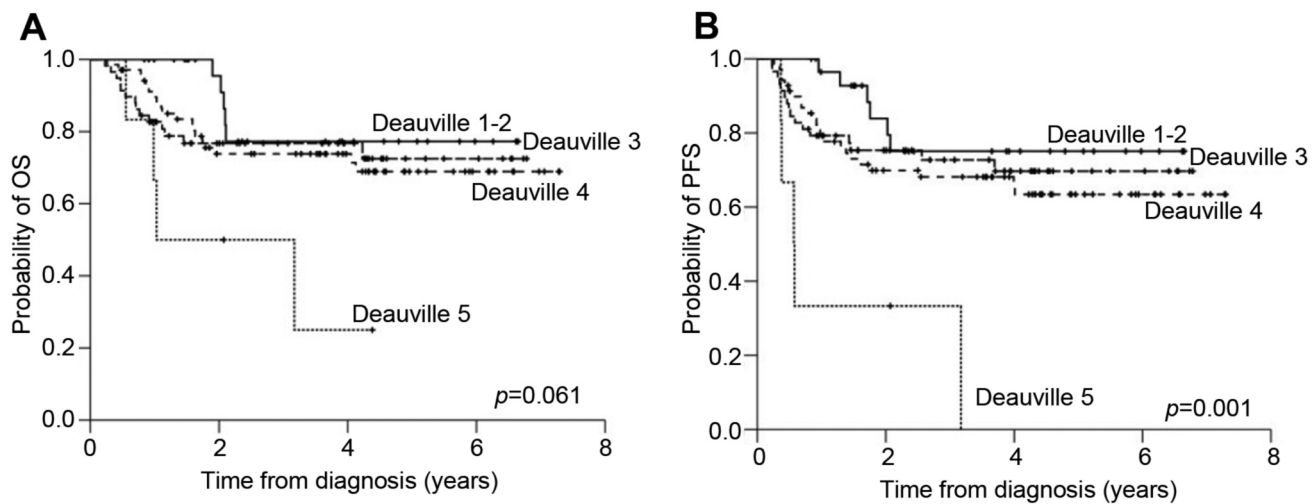
Figure 3. *Kaplan-Meier survival curves for (A) overall survival (OS) and (B) progression-free survival (PFS) of all patients according to visual assessment using Deauville 5-PS.*

were unfavorable factors. In the univariate analyses for PFS, old age, ECOG PS 2-3, increased LDH, EN involvement, BM involvement, stage III/IV, IPI high/high-intermediate, and ΔSUVmax<65.7% were unfavorable factors in overall patients, while ECOG PS 2-3, BM involvement, and ΔSUVmax<65.7% in patients with one EN involvement were unfavorable factors. In multivariate analysis, old age (HR=1.033, *p*=0.022), ECOG PS 2-3 (HR=3.525, *p*<0.001), BM involvement (HR=2.972, *p*=0.002), and ΔSUVmax<65.7% (HR=2.378, *p*=0.034) were significantly associated with inferior OS rates, while ECOG PS 2-3 (HR=2.553, *p*=0.012), EN involvement (HR=2.370, *p*=0.008), and ΔSUVmax<65.7% (HR=2.675, *p*=0.007) were associated with inferior PFS. Among patients with one EN involvement, ECOG PS 2-3 and ΔSUVmax<65.7% were unfavorable factors for OS and PFS (Table II). Visual assessment using the Deauville 5-PS was not an independent prognostic factor in this study, regardless of the number of EN involvements.

Discussion

Although iPET/CT interpretation has become more standardized, the question of which methods are best for iPET/CT assessment in DLBCL with EN involvement remains controversial. The present study investigated the prognostic significance of iPET/CT by comparing SUV-based assessment and the Deauville visual assessment in DLBCL patients with EN involvement. Our results show that the SUV-based assessment is superior to the Deauville score in predicting the long-term survival outcomes for DLBCL patients with EN involvement.

In the current study, iPET/CT responses assessed with ΔSUVmax showed a PPV of 89.1% in EN DLBCL patients. These results suggest that the incidence of false-positive iPET/CT responses may be high in DLBCL patients who are treated with rituximab-containing regimens. Interestingly, some previous studies have observed a lower PPV for iPET/CT after using rituximab-containing therapy compared to the PPV for iPET/CT in the pre-rituximab era (28, 29). This is important since the mechanism of rituximab may involve inflammatory changes associated with recruitment of immune cells to the tumor, which likely accounts for the discrepancy in iPET/CT predictive value (30). Meanwhile, PPV with SUV-based assessment is generally known to be superior to visual assessment (31). However, our results showed the opposite. DLBCL with low baseline SUVmax is one of the pitfalls of the SUV-based method because the baseline SUVmax could be lower than the defined cutoff value, which might lead to false-positives (32). Therefore, when using SUV-based assessments, cautious interpretation is needed in patients with a low baseline SUVmax of DLBCL. In such cases, the Deauville 5-PS might be preferred as an alternative.

Although visual assessment using the Deauville 5-PS is a reliable method for end-of-treatment assessments, it showed limitations for the interpretation of iPET/CT due to the cutoff score (22, 33, 34). Kim *et al*. have demonstrated that a Deauville score of 3 is not an equivalent cutoff value in the visual assessment of iPET/CT. Instead, they suggested a cutoff score of 5 for iPET/CT in patients with DLBCL (24). Similarly, Yang *et al*. have also noted the lack of iPET/CT interpretation with visual assessment in aggressive non-Hodgkin's lymphoma with EN involvement (19). When

Table II. *Factors affecting survival outcomes in the multivariate analysis.*

Overall patients

	OS		PFS	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age ≥65 *vs*. <65	1.033 (1.005-1.096)	0.022	–	–
ECOG PS 2-3 *vs*. 0-1	3.525 (1.813-6.852)	<0.001	2.553 (1.228-5.309)	0.012
EN involvement ≥2 sites *vs*. 1 site			2.370 (1.247-4.504)	0.008
BM involve *vs*. none	2.972 (1.473-5.998)	0.002		
ΔSUVmax <65.7% *vs*. ≥65.7%	2.378 (1.069-5.289)	0.034	2.675 (1.304-5.486)	0.007

Patients with one extranodal involvement

	OS		PFS	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
ECOG PS 2-3 *vs*. 0-1	4.692 (1.655-13.304)	0.004	6.050 (1.815-20.165)	0.003
ΔSUVmax <65.7% *vs*. ≥65.7%	3.849 (1.416-10.465)	0.008	6.979 (2.463-19.777)	<0.001

BM: Bone marrow; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; EN: extranodal; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; HR: hazard ratio; ECOG PS: Eastern Cooperative Oncology Group performance status; EN: extranodal; BM: bone marrow; ΔSUVmax: reduction rate of the maximum standardized uptake value.

iPET/CT responses were assessed using the Deauville score in this study, there was no significant difference between the Deauville scores of 3 and 4 in predicting response, which means that the current Deauville 5-PS is insufficient as a predictive method for iPET/CT in EN DLBCL.

The SUVmax quantitative assessment (ΔSUVmax) has several advantages. Because ΔSUVmax accounts for the reduction in metabolic activity of the tumor during treatment, it is relatively objective with low interobserver variability in interpretations. In addition, ΔSUVmax is easier to apply in clinical practice, and can be used with the different SUVs obtained from different scanners and individual uptake times (35, 36). SUV-based assessments also have drawbacks. In this study, quantitative SUV-based assessment for iPET/CT response predicted survival outcomes accurately in DLBCL patients with one EN involvement. However, it was ineffective for DLBCL patients with more than one EN involvement; one interpretation is that each additional EN site might increase false interpretations. Another possibility is that the predictive value is decreased when the baseline SUVmax is low, as mentioned above. Therefore, well-designed studies are needed to compare visual and SUV-based methods, even though the results of many studies suggest that SUV-based methods are associated with better PPV and long-term survival outcomes (27, 37, 38).

In the multivariate analysis, patients with ΔSUVmax<65.7% showed inferior OS and PFS rates. Moreover, EN involvement was an unfavorable factor for PFS, which agrees with the results of previous studies. Unfortunately, visual assessment using the Deauville 5-PS

was not an independent prognostic factor in patients with EN DLBCL. While the present study indicated significant results, our data should be interpreted cautiously due to certain limitations. First, the current study is a retrospective evaluation. Second, we could not prove each EN site through pathological confirmation. In conclusion, the quantitative SUV-based assessment for iPET/CT was a significant prognostic indicator for long-term survival outcomes, especially in patients with one EN involvement. Whereas, the Deauville 5-PS showed limitations for assessing the iPET/CT response.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

Authors' Contributions

J.H.M and D.H.Y designed the study; D.W.B, H.J.C, J.K, G.S, S.A, S.J and J.S.A collected the data; S.K.S, J.L, H.K, S.J, C.M.H and J.M analyzed and interpreted the data; D.W.B and J.H.M wrote the paper; J.H.M and D.H.Y contributed to the review and revision of the manuscript.

Acknowledgements

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