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Prognostic significance of interim ^{18}F-FDG PET/CT after three or four cycles of R-CHOP chemotherapy in the treatment of diffuse large B-cell lymphoma

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ABSTRACT

Purpose: ^{18}F-fluoro-2-dexoy-D-glucose-positron emission tomography (FDG-PET)/computerised tomography (CT) has been used for staging and monitoring responses to treatment in patients with diffuse large B cell lymphoma (DLBCL). The sequential interim PET/CT was prospectively investigated to determine whether it provided additional prognostic information and could be a positive predictable value within patients with the same international prognostic index (IPI) after the use of rituximab in DLBCL.

Methods: One hundred and sixty-one patients with newly diagnosed DLBCL were enroled; the assessment of the PET/CT was performed at the time of diagnosis and mid-treatment of rituxibmab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP).

Results: Sixty-seven patients (41.6%) presented with advanced stage disease and 27 (16.8%) had bulky lesions. Forty-three patients (26.7%) continued to have positive metabolic uptakes with a significantly high relapse rate (62.8%) compared to the patients with a negative interim PET/CT (12.1%) ($P < 0.01$). After a median follow-up of 30.8 months, the positivity of interim PET/CTwas found to be a prognostic factor for both overall survival (OS) and progression-free survival (PFS), with a hazard ratio of 4.07 (2.62–6.32) and 5.46 (3.49–8.52), respectively. In the low-risk IPI group, the 3-year OS and PFS rates were significantly different in the patients with positive (53.3% and 52.5%) and negative (93.8% and 88.3%) interim PET/CT, respectively ($P < 0.01$). These significant prognostic differences of interim PET/CT responses were consistent with the results of the patients with high-risk IPI group ($P < 0.01$).

Conclusions: Interim PET/CT scanning had a significant predictive value for disease progression and survival of DLBCL in post-rituximab treatment; it might be the single most important determinant of clinical outcome in patients with the same IPI risk.

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1. Introduction

Whole body positron emission tomography/computed tomography (PET/CT) with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) is a functional imaging modality used for staging and monitoring of the response to treatment of the patients with malignant lymphoma; it has been shown to have a higher sensitivity and specificity than conventional imaging.[1–3] Although interim PET scanning has emerged as a powerful prognostic tool for the prediction of the treatment outcome in Hodgkin's lymphoma (HL) and diffuse large B cell lymphoma (DLBCL), the positive predictive value of interim PET or PET/CT scans has been subject to inconsistent results after post-rituximab treatment in DLBCL. The optimal timing of interim PET/CT, the lack of agreed upon response criteria, the different percent risk by the international prognostic index (IPI) and the different treatment modalities including rituximab for the treatment of DLBCL have contributed to the variability of results.[4,5] Despite the prognostic value of interim PET/CT response has important implications for response-adapted therapy in DLBCL, an optimal extension of the use of interim PET/CT is still being investigated.

The IPI is a well-established tool for the prediction of clinical outcomes according to pretreatment characteristics. However, the treatment outcomes of individual patients within the same IPI risk group can be considerably different. If the interim PET/CT can predict which patients have a poor prognosis within the same IPI risk group during chemotherapy, this can add valuable information to tailor the intensity and type of chemotherapy to the individual patient's prognosis. In addition, such a combined approach may improve the detection of positive findings in all risk groups after rituximab treatment.

In a recent study, we showed a correlation between the findings of anatomical imaging using CT and the semiquantitative assessment of the interim PET/CT using the maximal standardised uptake value (SUVmax) for identifying the cut-off value of positivity during first-line chemotherapy; the findings provided important predictive information on disease progression and survival in patients with aggressive non-Hodgkin's lymphoma (NHL).[6] In patients with DLBCL, a fraction of the neoplastic cells are progressively lysed by the chemotherapy and the percentage of the cell destruction is predictive of the treatment response. A quantitative approach using the SUVmax measurement might be more appropriate for the interim PET/CT.[7] In order to reduce the rate of false positive interpretations of the interim PET/CT, the semiquantitative assessment of ^{18}F-FDG uptake using the SUV provided more uniform and potentially more accurate interpretation of the findings during chemotherapy.[8–10]

The goal of this study was to prospectively investigate the interim PET/CT to determine whether it provided additional prognostic information for patients undergoing rituxibmab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) chemotherapy and could be a positive predictable value within patients with the same IPI after the use of rituximab in DLBCL.

2. Methods

2.1. Patients and study design

One hundred and sixty-one patients with newly diagnosed DLBCL were enrolled between August 2004 and December 2009 at a single institution. All patients had interim response analysis by both CT and PET/CT after informed consent was obtained according to the protocol approved by the institutional ethical committee of the Chonnam National University Hwasun Hospital. Patients that had central nervous system involvement or disagreed with the protocol were excluded. All patients had an initial CT and PET/CT at diagnosis and a subsequent interim CT and PET/CT after the third or fourth cycle of R-CHOP chemotherapy. The final response was assessed within a month of completing the primary chemotherapy, with follow-up restaging every 3 months during the second year after primary chemotherapy, and every 6 months thereafter. Patients with localised lymphoma (stage I/II) were treated with six cycles of R-CHOP chemotherapy [rituximab 375 mg/m^2 i.v. on day one (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 D1–5] in standard doses every 3 weeks or three to four cycle of R-CHOP chemotherapy followed by involved field radiation therapy (IFRT, 30–40 Gy). Patients with advanced-stage (stage III/IV) were treated with eight cycle of R-CHOP chemotherapy and patients greater than 65 years and/or those with a frail general condition were treated with only six cycles of R-CHOP chemotherapy if they achieved a complete response (CR) for the interim response. Finally, patients with an initial tumour size larger than 10 cm were categorised as having bulky disease.

3. ^{18}F-FDG PET/CT

All patients underwent ^{18}F-FDG PET/CT imaging on a Discovery ST PET/CT system (GE Healthcare), consisting of a bismuth germanate full scanner and a 16-detector-row CT scanner. The patients fasted for at least 6 h prior to the intravenous administration of ^{18}F-FDG (7.4 MBq per body weight) to ensure a serum glucose level below 130 mg/mL. At 60 min after ^{18}F-FDG administration, transmission data were acquired by means of a low-dose CT scan [120 kV, automated from 10 to 130 mA, a 512×512 matrix, a 50 cm field of view (FOV), 3.75 mm slice thickness, and a rotation time of 0.8 sec], extending from the base of the skull to the proximal thighs. No contrast agent was applied for diagnostic CT. Immediately after CT acquisition, PET emission scans were acquired in the same anatomical locations with a 15.7-cm axial FOV acquired in 2-dimensional mode with a 128×128 matrix. The CT data were used for attenuation correction. The images were reconstructed using a conventional iterative algorithm (OSEM). A workstation (Xeleris) providing multiplanar reformatted images was also used for image display and analysis.

3.1. Response evaluation

The initial and interim staging CT and PET/CT were assessed according to the revised International Workshop Criteria

(IWC).[11] PET/CT scans were read by two nuclear medicine physicians, who were unaware of any subject information or clinical information. On axial, coronal, or sagittal coregistered PET/CT slices, simple circular regions of interest (ROIs) were placed so as to cover the lesion or background. SUV measurements were corrected for body weight according to the following standard formula: mean ROI activity (MBq/mL)/[Injected dose (MBq)/Body weight (kg)].[12] Patients that had mild or diffuse FDG uptake at any site were considered negative for intensities lower than or equal to that of the mediastinal blood pool structures with SUVmax cut-off value of 3.0. However, patients with diffuse or focal uptake exceeding that of the mediastinal blood pool structures at sites other than those with residual disease should be performed a tissue biopsy to exclude false positive uptake.

3.2. Statistics

All statistical analyses were performed using SPSS statistical software version 13.0 (SPSS Inc., Chicago, IL, United States of America). The progression-free survival (PFS) was calculated from the treatment start time to the first recording of disease progression or death from any cause. Patients with disease that did not progress would be censored using the date when they were last known to show no progression. The overall survival (OS) was defined as the period from the start of treatment to the date of the last follow-up or death from any cause. Patients who received high dose chemotherapy followed by autologous stem cell transplantation (ASCT) were censored at the time of transplantation. The distribution of patient for OS and EFS was estimated using the Kaplan–Meier method, and the log-rank test was used to compare the clinical prognostic factors and the probability of treatment failure. Multivariate Cox's proportional-hazard model was used to analyse all of the factors significant on the univariate analysis. P-values < 0.05 were considered statistically significant and the results were expressed as the mean ± SEM.

4. Results

The clinical characteristics of the 161 patients enroled are summarised in Table 1. Their median age was 61 years (range 17–85) with 50.9% of patients over the age of 60. The mean number of R-CHOP chemotherapy before the interim response was assessed was 3.5. Sixty-seven patients (41.6%) presented in advanced stage disease (III/IV) and 27 (16.8%) had a bulky disease. At diagnosis, 53 patients (32.9%) were classified as high/high-intermediate risk according to IPI and the median number of R-CHOP was six. Fifty-three patients (32.9%) received a short course of chemotherapy followed by IFRT and 10 (6.2%) patients underwent high dose chemotherapy followed by ASCT for consolidation. One hundred and forty three (88.8%) patients achieved a complete response (CR), four (2.5%) patients achieved a partial response (PR) and 12 (7.4%) patients showed a stable disease (SD) or progression by the response to R-CHOP. Seventy-eight patients (48.4%) were evaluated the interim PET/CT response after three cycles of R-CHOP chemotherapy and 81 patients (50.3%) were evaluated after four cycles of R-CHOP. Two patients could not have the interim response assessed due to treatment-related mortality (TRM).

Table 1 – Patient characteristics.

Parameters	No. of patients (%)
Age, median, years	61 (range: 17–85)
Age > 60	82 (50.9)
Male/female	94/67
Stage	
I–II	94 (58.4)
III–IV	67 (41.6)
Bulky	27 (16.8)
Bone marrow involvement	
Involved	15 (9.3)
Not involved	146 (90.7)
International prognostic index	
Low	75 (46.6)
Low-intermediate	33 (20.5)
High-intermediate	27 (16.8)
High	26 (16.1)
Number of R-CHOP, median	6 (range: 1–8)
Involved field radiation therapy	53 (32.9)
Interim positron emission tomography/computed tomography (PET/CT)	
Positive	43 (26.7)
Negative	116 (72.0)
Response to R-CHOP	
CR	143 (88.8)
PR	4 (2.5)
SD	10 (6.2)
PD	2 (1.2)
Non-measurable	2 (1.2)

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Forty-three patients (26.7%) had positive metabolic uptake on the interim PET/CT. Among the IPI risk groups, 20.4% of patients with low/low-intermediate risk were positive, whereas, 39.6% of patients with high/high-intermediate risk were positive interim PET/CT ($P = 0.02$). In addition, a high LDH, poor performance status, bulky disease and BM involvement were significantly associated with a positive interim PET/CT ($P < 0.05$). Twenty six out of 43 patients with positive interim PET/CT response improved and responded to primary chemotherapy, whereas 14 patients with positive interim PET/CT had SD or progression after completion of R-CHOP.

The patients with positive interim PET/CT showed a higher relapse rate (62.8%) than the patients with negative interim PET/CT (12.1%) ($P < 0.01$). After a median follow-up of 30.0 months (range 0.4–70.5), 42 (26.1%) patients had a relapse and 37 (23.0%) were censored death. The 3-year OS and PFS rates were 73.8 ± 3.9% and 71.3 ± 3.9%, respectively (Fig. 1A). The univariate analysis showed that age (>60), performance status, stage, bone marrow involvement, IPI and the interim response were significant prognostic variables for the OS and the PFS. There were significant differences in the 3-year OS and PFS between the patients with a positive interim PET/CT (31.1% and 29.2%, respectively) and the patients with

a negative interim PET/CT (86.4% and 86.0%, respectively) (Fig. 1B). The response of interim conventional CT scans also showed a significant potential as a prognostic variable in OS and PFS, respectively (Fig. 1C). We also found a significant prognostic value of interim PET/CT in both the 47 patients who destined to undergo eight cycles of R-CHOP with interim PET/CT-4 and the 56 patients who destined to undergo six cycles of R-CHOP with interim PET/CT-3 for OS and PFS, respectively (Fig. 2A and B). We retrospectively re-classified the patients with the response of interim PET/CT based on the five-point scale of the Deauville criteria and evaluated the prognostic significance in OS and PFS (Fig. 3A).[7] In addition, the response of interim PET/CT could predict the prognosis after R-CHOP chemotherapy regardless of the IPI risk group. In the low/low-intermediate risk group, the 3-year OS and PFS rates of patients with positive interim PET/CT were 53.3% and 52.5%, respectively, compared to those of patients with negative interim PET/CT were 91.4% and 88.3%, respectively. These significant prognostic differences by positivity of interim PET/CT were consistent with the results of the high/high-intermediate risk group (Fig. 3B and C). In high/high-intermediate risk group, the 3-year OS and PFS rates in patients with positive interim PET/CT were only 30.4% and 20.6%, respectively. The multivariate analysis showed that the performance status, bulky disease, BM involvement and positive interim PET/CT response were independent prognostic variables associated with the OS. Bulky disease, high IPI ($\geqslant 3$), the performance status and a positive interim PET/CT emerged as significant independent predictors of prognosis for the PFS (Table 2). Positivity of interim PET/CT was the significant prognostic factor for both the OS and PFS, with a hazard ratio of 4.07 (2.62–6.32) and 5.46 (3.49–8.52), respectively.

Four patients with a positive uptake on the interim PET/CT were determined to be false positives uptakes after primary chemotherapy. Two patients continued to have significant metabolic uptake in the mediastinal lymph nodes and lungs which was confirmed to be tuberculous lymphadenitis and pneumonia by a bronchoscope. In addition, two patients with hot uptake in the nasal cavity and colon were confirmed as inflammatory changes by locoregional biopsies. On the other hand, one patient with a thoracic cord mass and cerebrospinal seeding of lymphoma cells had a false negative on the interim PET/CT, nevertheless the original lesion partially regressed.

5. Discussion

Patients with DLBCL are stratified into prognostic groups according to the IPI or molecular profiling.[13,14] These therapeutic measures make it possible to predict survival after chemotherapy as well as alter the therapeutic strategies in poor-risk groups, which called “risk-adapted therapy”. After addition of the anti-CD20 monoclonal antibody, rituximab, to CHOP, the therapeutic outcomes of these patients have improved. The use of rituximab for the treatment of DLBCL has required change of the prognostic risk groups based on the IPI, which is referred to as the revised IPI.[15] However, there are still 20–40% of patients that will not be cured with R-CHOP and the failure of R-CHOP chemotherapy might be associated with a less effective response to salvage chemotherapy.[5]

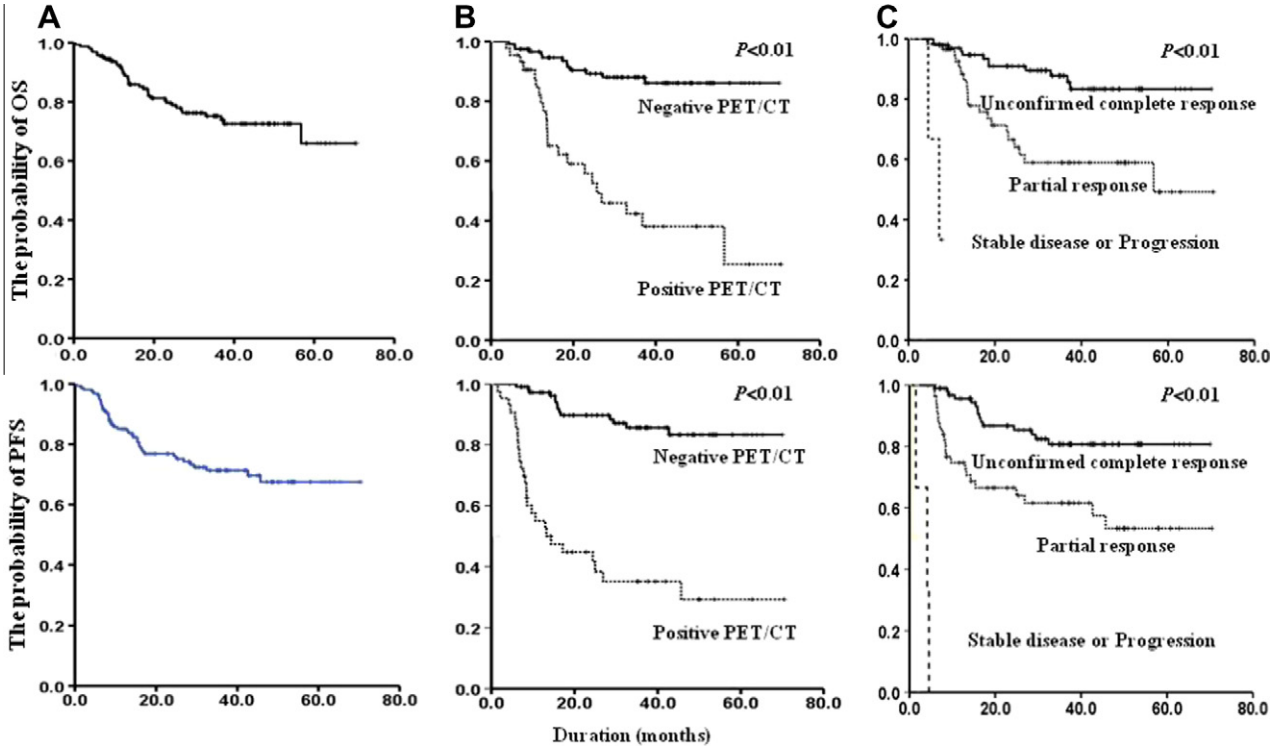

Fig. 1 – Kaplan–Meier estimates of the overall survival (OS) and progression-free survival (PFS) of all patients with diffuse large B cell lymphoma (DLBCL) (A), according to the response of interim PET/CT (B) and according to the response of interim conventional CT (C) after R-CHOP chemotherapy.

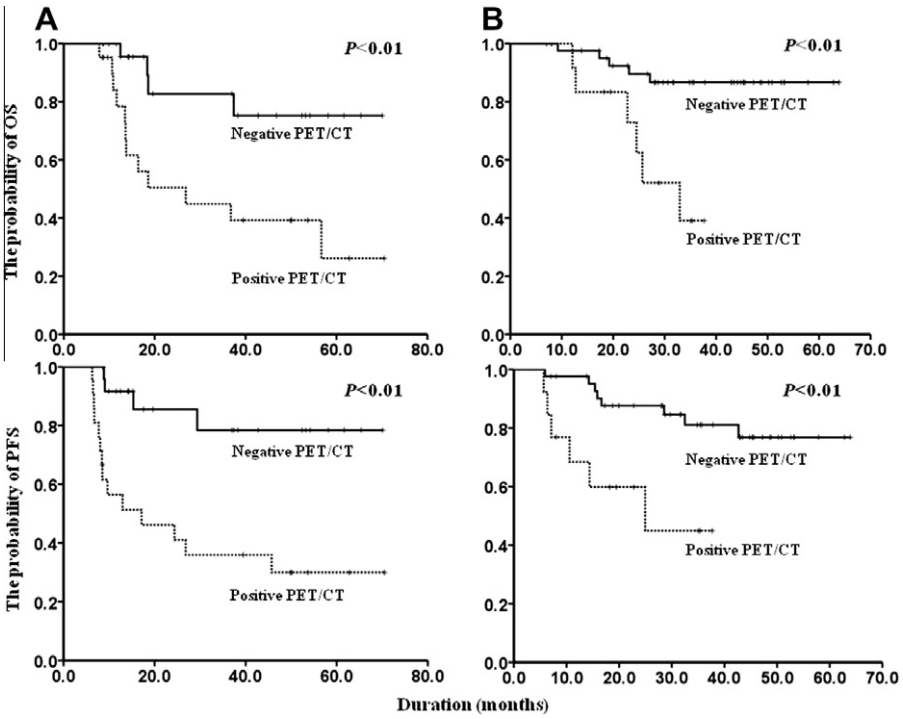

Fig. 2 – Prognostic significance of interim PET/CT in both the patients who destined to undergo eight cycles of R-CHOP with interim PET/CT-4 (A) and the patients who destined to undergo six cycles of R-CHOP with interim PET/CT-3 for OS and PFS, respectively (B).

Therefore, there is a continuous effort to improve immune-chemotherapy and to determine which patients have a poor prognosis based on their response to treatment.

The interim FDG-PET has emerged as a powerful predictive method of assessing HL and DLBCL. The predictive value of the interim PET scans appears to be positively correlated with the IPI or international prognostic score in HL. Recent studies have demonstrated that the prognostic value of the FDG-PET, shortly after the initiation of induction chemotherapy or at mid-treatment, could predict the long-term clinical outcome in patients with HD or NHL.[16–20] These studies categorised patients by the PET-positive or PET-negative based on visual analysis, and subsequently compared the relapse rate and the progression/failure-free survival between the two groups. However, a major drawback of the interim PET analysis appeared to be the absence of uniform criteria and the false positive rate in the modern therapeutic era, especially post-rituximab treatment of DLBCL.

In the present study, the interim PET/CT assessment was performed after the third or fourth cycle of R-CHOP-21 to reduce the rate of false positive findings after rituximab, which has a dose-dense cumulative pharmacokinetics and a unique mechanism of cytotoxicity, and is usually used with granulocyte colony-stimulating factor. We also applied the semiquantitative interpretation with SUVmax cut-off for defining the minimal residual or non-specific benign uptake at any of the sites during serial PET scans.[8,21] Using a SUVmax cut-off value of 3.0, we were able to reduce the false positive interpretations (only 2.6%) and a high positive predictive value (PPV) for the OS and PFS. When compared to the prognostic significance of interim PET/CT interpretation using the five-point scale of Deauville criteria, our positivity criteria using mediastinal blood pool with cut-off value of SUVmax (equal to 1 or 3 by the five-point scale) showed equivalent differentiation potency in predicting the prognosis. The high PPV of 0.90 in this study could be associated with several factors; decrease of inter-interpreter variability at a single institution, avoiding physiological pitfalls using semiquantitative assessment with a SUVmax cut-off and sequential PET/CT with the assessment of SUV changes compared to the initial FDG-uptake.

Although the IPI remains the standard for predicting treatment outcome in patients with DLBCL, the prognostic accuracy of the IPI could be altered by the addition of the results of new treatment modalities such as monoclonal antibody. Thus, the additional prognostic value of the interim PET/CT in the post-rituximab era is becoming an important addition to determination of patient prognosis. However, previous studies have shown dichotomous results for the positive predictive value of the interim PET/CT, this might have been due to use of the PET/CT too early during the course of treatment, high false positive rates and heterogeneous treatment modalities.[15,16,22–24] The interim PET/CT had an excellent prognostic ability to predict treatment failures in patients with both low and high risk IPI scores. After analysing the relapse rate in patients that showed positive metabolic uptake based on the IPI, the relapse rates between the low/low-intermediate risk group (45.5%) and the high/high-intermediate risk (81.0%) were found to be significantly different. Moreover, among the patients with interim PET/CT positive response, the patients with high-risk IPI had an extremely poor prognosis compared to those with low risk IPI for the 3-year OS and PFS (Fig. 2). The results are consistent with those of previous

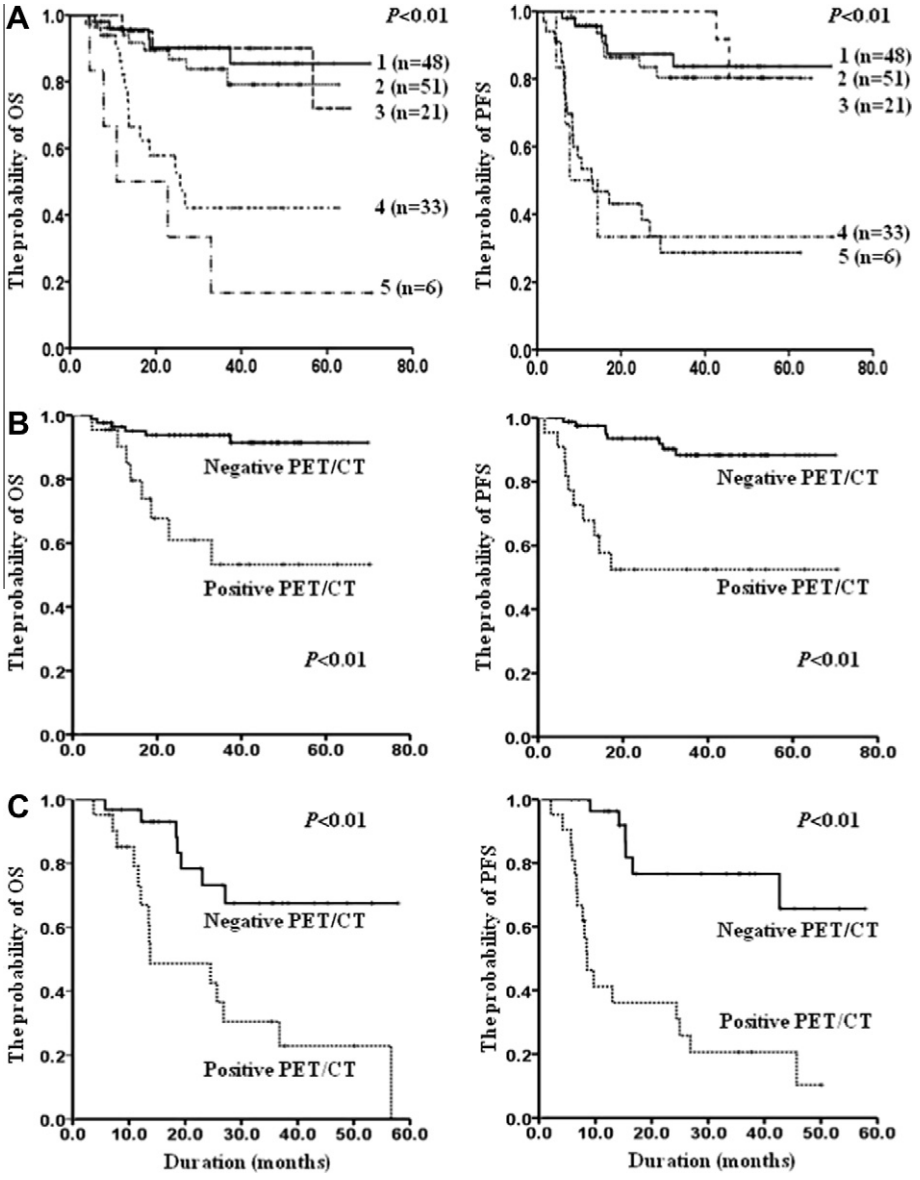

Fig. 3 – Kaplan–Meier estimates of the OS and PFS by five-point scale of Deauville criteria (A), according to the interim PET/CT in the low/low-intermediate IPI risk group (B) and in the high/high-intermediate IPI risk group (C).

Table 2 – The multivariate analysis of prognostic factors associated with overall survival (OS) and progression-free survival (PFS).

Parameter	OS			PFS		
	P	RR	(95% CI)	P	RR	(95% CI)
High IPI (⩾3)	0.176	1.70	(0.78–3.70)	0.004	2.50	(1.32–4.70)
Bulky (>10 cm)	0.025	0.42	(0.20–0.89)	0.003	0.30	(0.17–0.69)
BM involvement	0.008	0.31	(0.13–0.74)	0.073	0.38	(0.19–1.04)
Performance status	0.000	2.26	(1.49–3.44)	0.017	2.30	(1.08–2.36)
Positivity of interim PET/CT	0.000	4.07	(2.62–6.32)	0.000	5.46	(3.49–8.52)

IPI, international prognostic index; BM, bone marrow; RR, relative ratio.

studies that reported that the patients with interim PET/CT positive had a poor OS and PFS.[10,25,26] The multivariate analysis showed that the combined evaluation with the positivity and the size of the tumour mass, as a function of the interim PET/CT, were independent prognostic factors and had a stronger predictive value than all other factors.

In conclusion, sequential interim PET/CT analysis had a significant predictive value for disease progression and

survival in modern DLBCL treatment with rituximab and was probably the single most important determinant of outcome in patients with the same IPI risk. The patients with interim PET/CT positive and high-risk IPI should be considered an intensive therapeutic plan for overcoming their poor clinical outcome.

Conflict of interest statement

None declared.

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D.H.Y and J.J.L designed the study and protocol, performed the data analysis and interpretation and prepared the manuscript; J.J.M, H.C.S, Y.Y.J, W.K.C and H.S.B performed the image analysis; S.Y.B, J.S.A, Y.K.K, I.J.C and H.J.K critically reviewed the manuscript.

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