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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 $512 \times 512$ 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 $128 \times 128$ 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