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# Metabolic tumor volume changes assessed by interval $^{18}$fluorodeoxyglucose positron emission tomography-computed tomography for the prediction of complete response and survival in patients with diffuse large B-cell lymphoma

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**Abstract.** An early discrimination of survival probability is required for patients with diffuse large B cell lymphoma (DLBCL), which may identify patients that require other treatment options, for example clinical trials. To the best of our knowledge, the impact of interim evaluation with $^{18}$fluorodeoxyglucose positron emission tomography-computed tomography ($^{18}$F-FDG PET/CT) has not yet been determined in this type of neoplasia. The aim of the present study was to determine the role of changes in metabolic tumor volume (MTV) between baseline and interim $^{18}$F-FDG PET/CT scans, following three courses of chemotherapy in order to predict complete response (CR) and overall survival (OS) in patients with DLBCL. Patients with previously untreated DLBCL who had received the standard 6-8 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone were included in the present study. A predictive model was constructed using changes in MTV and other clinical factors including age, gender, East Cooperative Oncology Group (ECOG) status, clinical stage, B symptoms, the presence of bulky disease and elevated lactate dehydrogenase levels, and data were analyzed using logistic regression analysis. In total, 50 patients with DLBCL were included in the present study. The majority of patients presented with stage III/IV disease (64%), B symptoms (72%) and bulky disease (58%). According to the International Prognostic Index score, 44% of patients were in the intermediate-high or high-risk categories for risk of relapse, and therefore considered to have poor prognosis. In total, ≥94% of patients achieving a decrease in total MTV had a 2-year OS rate of 95%, compared with the 58% OS rate of those with a suboptimal response. A multivariate model, including a change in MTV (a decrease of ≥94%), the ECOG performance status ≥2, a change in leukocyte counts and age, was used to predict CR. This model was used to define two groups according to the predicted probability of recurrence (cutoff, 0.69). The 2-year survival rates of the two groups were 95 and 59%, respectively. Analysis of changes in MTV in the interim $^{18}$F-FDG PET/CT revealed significant prognostic value for the prediction of CR and OS in patients with DLBCL.

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*Key words:* diffuse large B-cell lymphoma, positron emission tomography, multivariate analysis, prognostic model in lymphoma, survival in lymphoma

## Introduction

Non-Hodgkin's lymphoma (NHL) is a malignancy with an incidence rate that varies according to geographical region. Overall, the global incidence is 4.3/100,000 individuals; however, the incidence is higher (≤12.8-fold) in developed countries compared with a 2.8-fold reduced incidence in less developed countries, and NHL is the 12th leading cause of mortality among different types of cancer (1). Lymphomas comprise a heterogeneous group of hematological malignancies classified according to their clinical and anatomicopathological features and, more recently, their cytogenetic markers. Diffuse large B cell lymphoma (DLBCL) is the most common of all aggressive types of lymphoma (2).

At present, the standard therapy for DLBCL includes administration of the anti-cluster of differentiation 20 monoclonal antibody, rituximab, which is typically added to chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), or other drugs in infusion with etoposide, prednisone, vincristine and cyclophosphamide (R-EPOCH) (2). However, first-line treatment fails in 20-40% of patients (3). At present, clinical scores, including the International Prognostic Index (IPI) (4) and the revised-IPI (5) are used in order to assist

in the prediction of patient outcome, to provide information for patients who are at risk of early relapse or progression and to aid in developing risk stratification tools. However, these scores were developed prior to the introduction of rituximab and therefore may not be applicable for the current therapies that incorporate rituximab. $^{18}$Fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET/CT) is now widely used in the staging of the majority of lymphomas and is accepted as a tool for the assessment of therapeutic response (6). Among the numerous $^{18}$F-FDG PET/CT parameters, the most frequently studied is the standardized uptake value (SUV). Recently, Park *et al* (7) reported that interim $^{18}$F-FDG PET/CT scans may be able to predict the outcome of patients with DLBCL using interpretation based on $SUV_{max\text{-}liver}$. Although this comparison (changes in $SUV_{max\text{-}liver}$) increased the utility of this tool, this value is a semi-quantitative index as it cannot reflect tumor dimensions or volume. However, the metabolic tumor volume (MTV) is a parameter that integrates tumor activity and volume (7).

The present study aimed to evaluate the clinical implications of interim $^{18}$F-FDG PET/CT scans in combination with clinical parameters as an early prognostic indicator of complete response (CR) and overall survival (OS) in patients with DLBCL.

## Materials and methods

*Patients*. The present study was a prospective, non-randomized, non-comparative and observational trial. Patients with a diagnosis of DLBCL who had attended the National Cancer Institute (Mexico City, Mexico) between January 2013 and June 2014 were invited to participate. The inclusion criteria were as follows: Untreated patients, >18 years of age, with a histopathological diagnosis of DLBCL. The exclusion criteria were as follows: Patients presenting with any active infection, including hepatitis B, hepatitis C and human immunodeficiency virus, uncontrolled diabetes mellitus, pregnancy or lactation. In total, 60 patients with a histological diagnosis of DLBCL who fulfilled the inclusion criteria were invited to participate in the present study; 52 patients accepted and provided written informed consent. In total, 2 patients presented with severe disease progression prior to the initiation of treatment and were therefore excluded from the study. The study protocol was approved by the Institutional Review Board of National Cancer Institute in Mexico City (register no. 013/006/ICI; Mexico City, Mexico), and all patients provided written informed consent prior to participation in the study.

Patient clinical parameters that were analyzed included sex, age, clinical stage, Eastern Cooperative Oncology Group (ECOG) performance status (8), clinical stage [Lugano classification (9)], baseline levels of lactic dehydrogenase (LDH), β2 microglobulin, blood hemoglobin and serum albumin, absolute leukocyte and lymphocyte counts, International Prognostic Index (IPI) score, date of diagnosis, date of relapse, date of mortality and last hospital visit (8,9).

All patients were treated with the rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) regimen [intravenous (IV) rituximab, 375 mg/m$^2$ on day 1; IV cyclophosphamide, 750 mg/m$^2$ on day 1; IV doxorubicin, 50 mg/m$^2$ on day 1; IV vincristine, 1.4 mg/m$^2$, with capping at 2 mg, on day 1; and oral prednisone, 100 mg daily on days 1-5]. Patients with localized disease (stages I-II) and advanced-stage disease (stages III-IV) were treated with 6 and 8 cycles of the R-CHOP regimen, respectively.

*$^{18}$F-FDG PET/CT*. An $^{18}$F-FDG PET/CT scan was performed at the time of diagnosis. The interim $^{18}$F-FDG PET/CT scan was performed 15 days after the third cycle of treatment and the final response was assessed by a third $^{18}$F-FDG PET/CT performed six weeks after the end of treatment. All $^{18}$F-FDG PET/CT scans were performed using the Biograph 16 PET-CT scanner (Siemens AG, Munich, Germany). Patients fasted for at least 6 h prior to the intravenous (IV) administration of $^{18}$F-FDG (5.5 MBq/kg body weight) to ensure a serum glucose level of <10 mmol/l.

A whole-body CT scan was performed 50-70 min following IV administration of a dose of 5.5 MBq/kg (150 $\mu$Ci/kg) $^{18}$F-FDG, and transmission data were acquired using low-dose CT [120 kV, automated from 100-130 MA, 512x512 matrix, 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. Immediately following CT acquisition, a whole-body $^{18}$F-FDG PET scan was acquired in 3D (matrix 168x168). For each bed position (16.2 cm with an overlapping scale of 4.2 cm), a 3 min acquisition time was used with a 15.5 cm FOV. The emission data were corrected for randomness, scatter and decay. Reconstruction was performed with an ordered subset expectation maximization (OSEM) algorithm with 3 iterations/12 subsets. The images were processed with a Gauss-filter, in order to normalize the data, with a full width at half-maximum of the Gauss curve, at 6 mm. Attenuation correction was performed using the low-dose non-enhanced CT.

A workstation (Multimodality Workplace, Siemens AG), providing multi-planar reformatted images, was also used for image display and analysis. The MTV and $SUV_{max}$ of whole-body tumors were measured using the isocontour tool provided by TrueD Syngo software, version VE36A (Siemens AG), with manual adjustment; all adjustments were made to the isocontour threshold in order to delimitate the metabolic activity site. MTV was measured from FDG-PET/CT images using a SUV-based automated contouring program (TrueD Syngo software, version VE36A (Siemens AG). The margins of the tumor were drawn to incorporate each target lesion in the axial, coronal and sagittal $^{18}$F-FDG PET/CT images. The contour around the target lesions inside the limits was automatically produced using manual adjustment. A fixed threshold value of 40% $SUV_{max}$ was used (Fig. 1).

*Response evaluation*. The response was evaluated according to the Deauville criteria (10). The MTV was measured for each lesion and was defined as the volume of tumor tissue with increased $^{18}$F-FDG uptake. This represented the quantity of highly metabolic tumor cells, thereby aiding in the volumetric estimation of the active tumor burden.

For interim $^{18}$F-FDG PET/CT analysis of the MTV, each lesion was evaluated, and the change in total MTV was calculated. The total MTV was measured by summing the MTV of each metabolic lesion. Patients were classified using quantitative analysis of MTV changes based on the percentage change in the MTV (ΔMTV) between baseline and interim $^{18}$F-FDG PET/CT scans. This comparison was also performed for the final therapeutic response assessment.

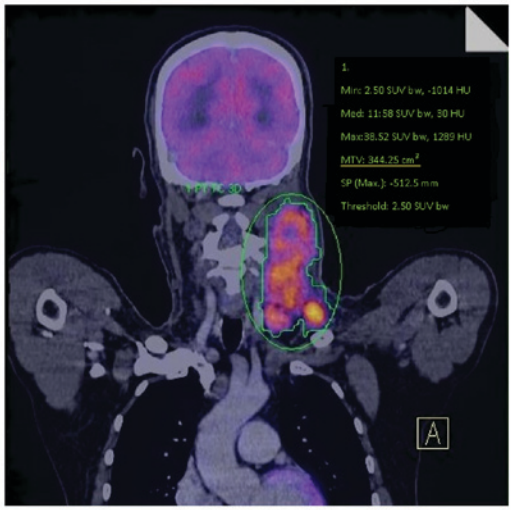


Figure 1. MTV assessment. MTV was measured using a SUV-based automated countering program. The margins of the tumor were drawn in order to incorporate each target lesion in the axial, coronal and sagittal $^{18}$F-FDG PET/CT images. MTV, metabolic tumor volume; SUV, standardized uptake value.

*Statistical analysis*. Following descriptive analysis, the diagnostic accuracy was calculated using the ΔMTV as the proposed diagnostic test. The complete response (CR) was determined using the final $^{18}$F-FDG PET/CT evaluation. The receiver operating characteristic (ROC) curve analysis used different cut-off values for the ΔMTV. The cut-off obtained to separate two groups; an MTV decrease <94 vs. ≥94%.

A sample size of 50 patients was calculated, and the model was assumed to have a sensitivity of 90% with regards to correctly predicting CR, with a lower limit of 80% sensitivity [with a confidence interval (CI) of 95%].

Bi- and multivariate analyses performed with an analysis of variance and a logistic regression model, respectively, were performed to evaluate factors associated with CR on the assessment at final PET-CT. Factors analyzed included: Gender, B symptoms, bulky disease, clinical stage, ECOG score, bone marrow infiltration, biochemical parameters (increased LDH, increased β2-microglobulin, basal creatinine, hemoglobin, albumin, leukocytes and lymphocytes values), IPI score, and decrease in MTV. The associations between various factors (including all clinical factors, $SUV_{max}$, and the MTV observed in the baseline and interim $^{18}$F-FDG PET/CT scans) and CR were evaluated using the logistic regression model. The odds ratios (OR) and their respective 95% CIs were calculated as a measure of association. A final model was defined and interaction analysis was performed; no significant interaction were identified. Subsequent to constructing the final model, the predicted probability of achieving CR was calculated for each case. Thereafter, along with ROC curve analysis, two groups were defined according to this predicted probability, with a cut-off of 0.69.

Overall survival (OS) was calculated using the Kaplan-Meier method, followed by the log-rank test. Two-tailed distributions were considered in all analyses, and P<0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using SPSS (version 20; IBM Corp., Armonk, NY, USA).

## Results

*Patients*. A total of 50 patients were included [19 women (38%) and 31 men (62%)]. The mean age was 55 years (standard deviation, 11.38; range, 21-73 years). In total, 32 patients presented with advanced disease (stages III/IV) 18 patients had early disease (stages I/II), 72% exhibited B symptoms and 58% exhibited bulky disease. Based on the IPI scores, 44% of the patients were within the intermediate-high or high risk of relapse. The clinical characteristics of the patients are summarized in Table I.

*$^{18}$F-FDG PET/CT*. Baseline, interim and final $^{18}$F-FDG PET/CT scans were performed in all cases. $^{18}$F-FDG PET/CT scans performed at the time of diagnosis revealed that 16 patients exhibited DLBCL at one site, 13 patients exhibited DLBCL at two sites, 5 patients exhibited DLBCL at three sites, 7 patients exhibited DLBCL at four sites and 9 patients exhibited DLBCL at five or more sites. In total, 33 cases (66%) were located in the neck and 17 cases (34%) were located in the abdomen. As demonstrated in Table II, the median total MTV was 1,205.34 $cm^3$ (range, 1.74-9,597.45) at the baseline $^{18}$F-FDG PET/CT. The median $SUV_{max}$ for lesions 1-5 and changes during and following treatment are presented in Table II.

*Clinical response*. The baseline median MTV was 1,205.34 and 61.74 at baseline and interim $^{18}$F-FDG PET/CT, respectively, demonstrating a 93.64% decrease in total MTV. The baseline median $SUV_{max}$ sum was 707.54 and 8.52 for interim PET/CT (range, 0-89). The interim $^{18}$F-FDG PET/CT scans also identified CR in 30 (60%), partial response (PR) in 19 cases (38%) and progressive disease (PD) in 1 case (2%).

At interim $^{18}$F-FDG PET/CT 30 patients exhibited CR and 10 exhibited PR. However, at the end of treatment, CR was identified in 38 patients, PR was identified in 5 patients (all of whom had also achieved PR at interim $^{18}$F-FDG PET/CT), and PD was identified in 7 cases (4 with PR, 2 with CR and 1 with PD at interim $^{18}$F-FDG PET/CT). Additionally, a decrease of ≥94% in total MTV in the interim $^{18}$F-FDG PET/CT achieved 86% sensitivity and 50% specificity for the accurate prediction of CR.

Following bivariate analysis, only 4 factors were statistically (P<0.05) associated with CR: An ECOG performance status >2, elevated leukocyte and β2 microglobulin levels, and a decreased in ΔMTV. Furthermore, all these were included in the multivariate analysis, which demonstrated that an ECOG performance status <2, decrease of $SUV_{max}$ by >94%, the absence of leukopenia and age <65 were independent prognostic indicators of CR.

ROC curve analysis examined the ΔMTV between the baseline and interim $^{18}$F-FDG PET/CT scans and observed its role in predicting CR [Fig. 2A; area under the ROC curve (AUC), 0.677; P=0.084]. Additionally, Fig. 2B demonstrates the ROC curve analysis performed on the prognostic indicators in the prediction of CR identified by the multivariate analysis (Table III; AUC, 0.814; P=0.001).

*Patient survival*. A total of 6 patients (12%) did not survive the entire study period; 4 succumbed to lymphoma and two succumbed to febrile neutropenia (following chemotherapy

Table I. Clinical and demographical characteristics of patients at the time of diagnosis (n=50).

| Characteristic | Number of patients, n (%)[a] |
|---|---|
| Age, years | 55±11.38 (21-73) |
| Male/female | 31 (62)/19 (38) |
| Lugano stage classification, n (%) | |
| I-II | 18 (36) |
| III-IV | 32 (64) |
| B symptoms present, n (%) | 36 (72) |
| Bulky disease, n (%) | 29 (58) |
| LDH level, n (%) | |
| High | 28 (56) |
| Normal | 22 (44) |
| B2M, n (%) | |
| High | 24 (48) |
| Normal | 26 (52) |
| IPI, n (%) | |
| Low | 15 (30) |
| Low-intermediate | 13 (26) |
| High-intermediate | 15 (30) |
| High | 7 (14) |
| Hematological parameters | |
| Mean hemoglobin level, g/dl (range) [normal range] | 13.87±2.59 (8.5-19.50) [13-15] |
| Leukocyte count, 1,000/mm$^3$ | 8.02±2.39 (3.2-13) [4.8-10-8] |
| Lymphocyte count, 1,000/mm$^3$ | 1.69±0.8 (0.6-4.1) [1.4-3.4] |
| Platelet count, 100/mm$^3$ | 340.28±148.39 (94-788) [130-400] |
| Creatinine, mg/dl | 0.86±0.19 (0.5-1.34) [0.5-1.2] |
| LDH, UI/l | 421.7±843.9 (123-6136) [114-198] |
| B2M, mg/l | 2.74±0.99 (1.27-5.68) [1.4-2.5] |

[a]Percetage for categorical variables. LDH, lactic dehydrogenase; B2M, β2 microglobulin; IPI, international prognostic index.

cycles 4 and 6, respectively). The mean OS and disease-free survival rates were 28.33 months (95% CI, 26.91-29.75) and 25.9 months (95% CI, 23.5-27.2), respectively. Fig. 3 demonstrates the OS curves of patients based on ΔMTV following interim $^{18}$F-FDG PET/CT, using 94% as the cut-off value. The mean survival times of these groups ≥94 vs. <94% reduction of MTV) were 29.4 months (95% CI, 27.6-31.1) and 19.6 months (95% CI, 13.8-25.3), respectively (P=0.014).

Two groups were defined based on the predicted probability of recurrence obtained following the final multivariate model, presented in Table III. A cut-off value of 0.69 for the estimated probability. The OS curves for patients depended on this probability value and are presented in Fig. 4. The median survival times for these groups were 29.9 months (95% CI, 28.4-31.3) and 20 months (95% CI, 15.2-24.8), respectively (P=0.004).

## Discussion

Current treatment approaches based on disease staging are not satisfactory for DLBCL, as these systems rely on data obtained prior to the current staging procedures, including PET-CT (3). Prognostic factors, including IPI score, have been evaluated in patients with high-grade lymphomas since the 1990s (4,5). Despite the revised IPI identifying three prognostic groups with different outcomes: Very good [4-year progression-free survival (PFS) 94%, and OS 94%], good (4-year PFS 80%, OS 79%), and poor (4-year PFS 53%, OS 55%) outcome, respectively (5), this system demonstrates inconsistency for patients stratified with an intermediate score (10). Therefore, markers that identify an early treatment failure are required for patients with DLBCL, in order to allow them to access novel treatment modalities. The role of $^{18}$F-FDG PET/CT in the diagnosis and the determination of treatment efficacy in patients with DLBCL as a highly sensitive method to diagnostic lymphoproliferative activity has been clearly defined (2,11). However, the extent of $^{18}$F-FDG PET/CT and whether a standardized definition of interim $^{18}$F-FDG PET/CT ($SUV_{max}$, $SUV_{max\text{-}liver}$, MTV or other parameters that may improve the utility of this tool) require further investigation (12). A qualitative three-point scoring (PS) system and qualitative 5-PS methods, which designated lesions as positive or negative, without a measure, were initially proposed for assessment of CR (12). Since then, other studies have proposed semi-quantitative methods, either alone or in combination with clinical parameters, as prognostic factors for the prediction of patient survival (13-20). Among

Table II. $^{18}$FDG PET/CT parameters at baseline, interim and final assessments (n=50).

A, Baseline $^{18}$FDG PET/CT

| Parameter | Value |
|---|---|
| $SUV_{sum}$ | 707.54 (10-2,374)[a] |
| $SUV_{max}1$ | 22.59 (1.12-141)[a] |
| $SUV_{max}2$ | 10.26 (0-83)[a] |
| $SUV_{max}3$ | 4.49 (0-38.7)[a] |
| $SUV_{max}4$ | 2.44 (0-19.1)[a] |
| $SUV_{max}\geq5$ | 1.04 (0-23.40)[a] |
| Total MTV | 1,205.34 (1.74-9,597.45)[a] |

B, Interim $^{18}$FDG PET/CT

| Parameter | Value |
|---|---|
| $SUV_{sum}$, median (range) | 8.52 (0-89)[a] |
| Total MTV | 61.74 (0-1,178)[a] |
| ΔMTV | -1,143.60 (0-9,552.26)[a] |
| Decrease in MTV (%) | 93.64 (0-100)[a] |
| CR, n (%) | 30 (60)[b] |
| PR, n (%) | 19 (38)[b] |
| SD, n (%) | 0 (0)[b] |
| PD, n (%) | 1 (2)[b] |

C, Final $^{18}$FDG PET/CT

| Parameter | Value |
|---|---|
| $SUV_{sum}$ | 4.51 (0-42.94)[a] |
| Total MTV | 8.47 (0-146.72)[a] |
| CR | 38 (78)[b] |
| PR | 5 (10)[b] |
| SD | 0 (0)[b] |
| PD | 7 (14)[b] |

[a]Mean (range). [b]n (%). $^{18}$FDG PET/CT, $^{18}$fluorodeoxyglucose positron emission tomography-computed tomography; SUV, standardized uptake value; MTV, metabolic tumor volume; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

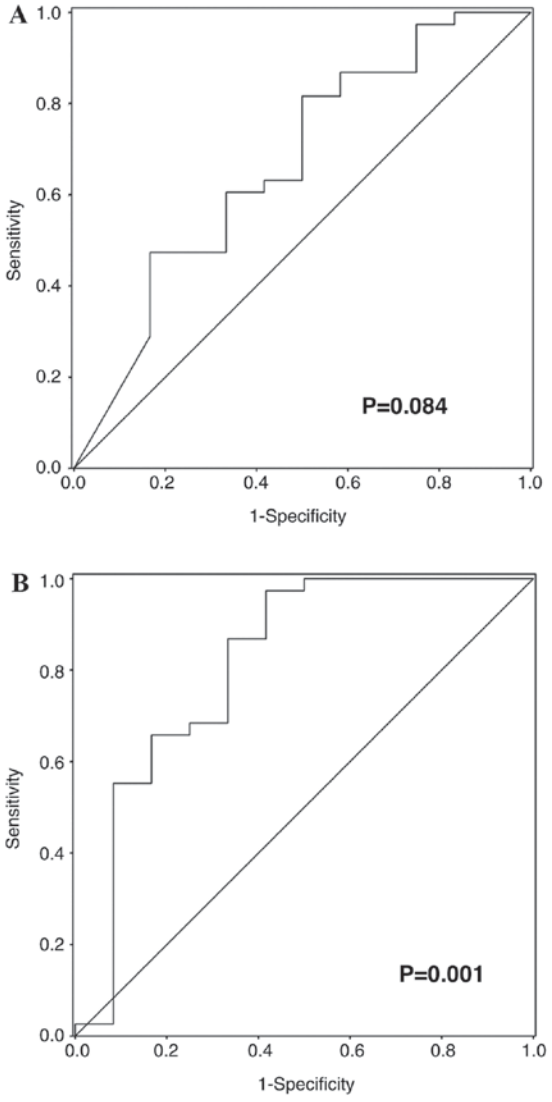


Figure 2. ROC curve analysis. (A) Change in tumor metabolic activity following 3 courses of chemotherapy for the prediction of CR following 6 courses of chemotherapy (AUC, 0.677; P=0.084). (B) The use of a multivariate model for the prediction of CR following 6 courses of chemotherapy (AUC, 0.814; P=0.001). ROC, receiver operating characteristic; CR, complete response; AUC, area under the ROC curve.

the $^{18}$F-FDG PET/CT parameters, $\Delta SUV_{max}$ between baseline and interim $^{18}$F-FDG PET/CT scans is the most commonly used semi-quantitative index for $^{18}$FDG uptake. This validated measurement is confined to the detection of the most hyper-metabolic tumor activity at a single site. In contrast, the MTV and total lesion glycolysis reflect tumor energetic turnover (13,15,20). The present study evaluated the association between $SUV_{max}$ and total MTV for the assessment of CR in patients with DLBCL.

In the present study, a multivariate model was used to identify patients who may not achieve CR at the end of treatment. This model comprised various factors, including the IPI, and the ΔMTV between the baseline and interim $^{18}$F-FDG PET/CT scans.

In a prospective trial, Fuertes *et al* (13) concluded that an optimal $\Delta SUV_{max}$ cut-off value that was able to predict PFS and OS in patients with DLBCL was 76% (95% CI, 62.7-89.2) and 75% (95% CI, 54.6-95.4), respectively. The study also estimated that the 5-year PFS and OS rates were 78 and 92%, respectively, in patients with an interim $^{18}$F-FDG PET/CT scan, demonstrating uptake that was not greater compared with that of the liver. These rates were significantly higher compared with the 50% (for OS and PFS) in patients with uptake greater compared with that of the liver (20). In the present study, two groups were defined with 95 and 60% OS rates at 30 months, with the cut-off point of a decrease in MTV of ≥94%. Safer *et al* (18) observed similar OS rates of

Table III. Analysis of factors associated with complete response using logistic regression analysis (n=50).

| | Bivariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Factor | OR | 95% CI | P-value | OR | 95% CI | P-value |
| Age | 1.032 | 0.977-1.091 | 0.257 | 1.082 | 1.001-1.17 | 0.048 |
| Sex | 1.304 | 0.333-5.108 | 0.703 | | | |
| ECOG performance status ≤2 | 5.83 | 1.084-31.377 | 0.04 | 7.996 | 0.918-69.61 | 0.06 |
| B symptoms | 0.722 | 0.165-3.156 | 0.665 | | | |
| Bulky | 0.37 | 0.087-1.585 | 0.18 | | | |
| Stage | 0.761 | 0.546-1.061 | 0.108 | | | |
| LDH | 0.333 | 0.078-1.426 | 0.138 | | | |
| B2M | 0.217 | 0.051-0.936 | 0.040 | | | |
| Creatinine | 1.526 | 0.052-44.347 | 0.806 | | | |
| Hemoglobin | 1.143 | 0.881-1.482 | 0.314 | | | |
| Leucocyte count | 1 | 1-1.0001 | 0.022 | 1 | 1.000-1.000 | 0.029 |
| Lymphocyte count | 1.001 | 1-1.002 | 0.065 | | | |
| Platelet count | 1 | 1-1.0001 | 0.423 | | | |
| IPI | 0.765 | 0.408-1.434 | 0.404 | | | |
| Decrease in total MTV of ≥94% | 1.055 | 0.986-1.128 | 0.0121 | 1.097 | 1.011-1.192 | 0.027 |

OR, odds ratio; CI, confidence intervals; ECOG, East Cooperative Oncology Group; LDH, lactic dehydrogenase; B2M, β2 microglobulin; IPI, international prognostic index; MTV, metabolic tumor volume.

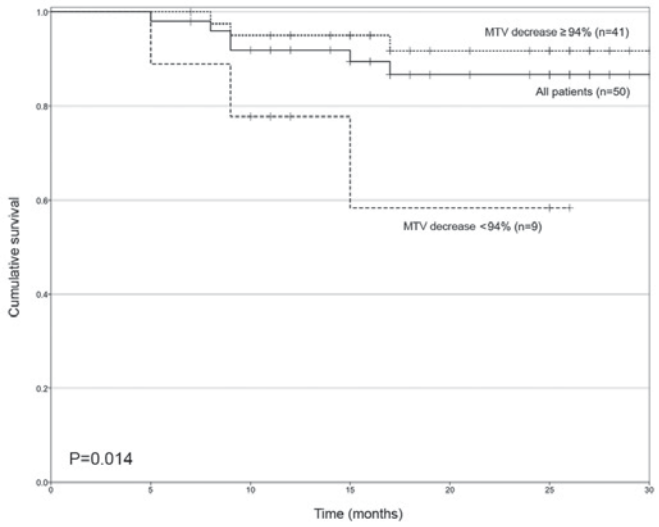


Figure 3. Overall survival curves of two subgroups according to the cut-off value of a 94% decrease in total MTV: 41 patients had a decrease of MTV >94% and the survival was 92% at 30 months, in contrast to only 58% at 30 months in those cases achieving <94% decrease of MTV. P-value was obtained by comparison between subgroups. MTV, metabolic total volume.

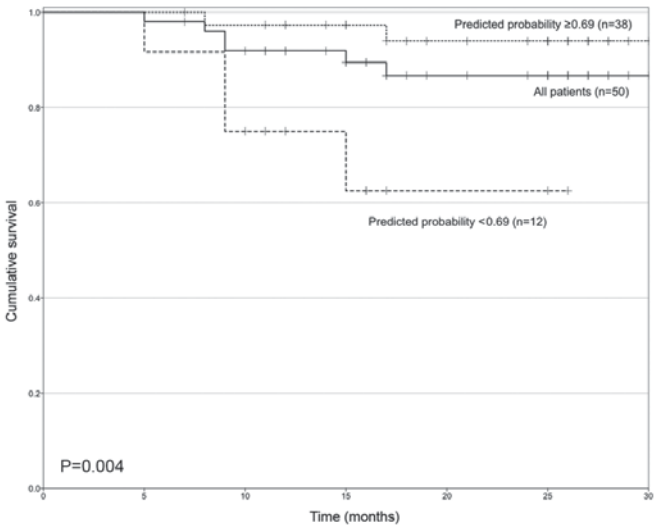


Figure 4. Overall survival curves of two subgroups according to the predicted probability of recurrence using the model obtained from multivariate analysis (cut-off value, 0.69). P-value was obtained by comparison between subgroups.

88 and 62% at 3 years in patients with interim $^{18}$F-FDG PET/CT scans negative and positive for cancer, respectively. Recently, Kwon *et al* (21) revealed that calculating $SUV_{max}$-$SUV_{in\ liver}$ and using a cut-off value of 1.6 created two groups; those considered as non-responders exhibited a 3-year OS rate of 33% compared with 86% in patients who responded to therapy, at the same follow-up (21). In this aforementioned study, interim $^{18}$F-FDG PET/CT scans were performed following two cycles of treatment, in contrast with the present study in which scans were performed following three cycles. Therefore, it is not possible to draw a reliable comparison between the two trials.

Regarding the combination of clinical parameters with $^{18}$F-FDG PET/CT results, Kwon *et al* (21) concluded that the IPI score was able to predict the PFS of patients with an interim $^{18}$F-FDG PET scan negative for cancer. Among

these patients, those in the high IPI group (4-5 points) were predicted to achieve a 20% PFS rate at 100 months. In the present study, only two cases with a CR at interim $^{18}$F-FDG PET/CT experienced a relapse, one with a high IPI score (4-5 points) and the other with a low-intermediate IPI score (2 points).

In contrast with the results of a study undertaken by Gallicchio *et al* (15), which reported that $SUV_{max}$ and LDH levels were parameters capable of predicting response in patients with DLBCL, $SUV_{max}$ and LDH levels were not prognostic factors in the present study, but a decrease in total MTV constituted a prognostic factor influencing OS, as demonstrated in Fig. 3 and Table III.

To the best of our knowledge, previous studies have not reported a prognostic role of metabolic parameters evaluated by interim $^{18}$F-FDG PET/CT scans in patients with DLBCL (21-24). However, patients with higher $SUV_{max}$ and $SUV_{sum}$ values at interim $^{18}$F-FDG PET/CT exhibited a poorer PFS and OS, as demonstrated by Park *et al* (7). A meta-analysis identified a sensitivity of 0.78 and a specificity of 0.87 for interim $^{18}$F-FDG PET/CT scans in patients with DLBCL (25). However, there were limitations to this meta-analysis given that it included patients from 6 studies who were treated with a variety of regimens with and without rituximab, radiation and stem cell transplantation. In addition, $^{18}$F-FDG PET/CT scans were performed following 2, 3 or 4 cycles of therapy. The heterogeneity of these populations prevented a reliable conclusion from being drawn. Although $^{18}$F-FDG PET/CT is currently an essential part of the management of patients with lymphoma, including Hodgkin's lymphoma, and has improved patient outcome by reducing the requirement for chemotherapy and selective radiotherapy (25), in aggressive NHL, particularly DLBCL, the role of interim $^{18}$F-FDG PET/CT remains inconclusive. The low positive prognostic value of this approach may the result of false-positive $^{18}$F-FDG PET/CT results associated with residual activity due to inflammatory changes within the tumor bed secondary to immunochemotherapy (26).

The present study included patients from a single center, which explains the relatively small sample size. However, the present study comprised a homogeneous population who received standard immunochemotherapy over the same time period, and baseline, interim and final $^{18}$F-FDG PET/CT interpretations.

To conclude, the assessment of quantitative parameters from interim $^{18}$F-FDG PET/CT scans combined with clinical variables led to the generation of a model with four variables (an ECOG performance status of <2, a decrease in total MTV of >94%, the absence of leukopenia and age <65 years), which predicted CR at the end of treatment. The presence of these parameters also impacted the OS time of patients with DLBCL.

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## Competing interests

The authors declare that they have no competing interests.

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