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Prognostic significance of metabolic tumor burden by positron emission tomography/computed tomography in patients with relapsed/refractory diffuse large B-cell lymphoma

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Key words

[F-18] fluorodeoxyglucose, diffuse large B-cell lymphoma, lymphoma, metabolic tumor burden, positron emission tomography/computed tomography

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The aim of the present study was to investigate the feasibility of measuring metabolic tumor burden using [F-18] fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) treated with bendamustine–rituximab. Because the standardized uptake value is a critical parameter of tumor characterization, we carried out a phantom study of ^{18}F-FDG PET/CT to ensure quality control for 28 machines in the 24 institutions (Japan, 17 institutions; Korea, 7 institutions) participating in our clinical study. Fifty-five patients with relapsed or refractory DLBCL were enrolled. The ^{18}F-FDG PET/CT was acquired before treatment, after two cycles, and after the last treatment cycle. Treatment response was assessed after two cycles and after the last cycle using the Lugano classification. Using this classification, remission was complete in 15 patients (27%) and incomplete in 40 patients (73%) after two cycles of therapy, and remission was complete in 32 patients (58%) and incomplete in 23 patients (42%) after the last treatment cycle. The percentage change in all PET/CT parameters except for the area under the curve of the cumulative standardized uptake value–volume histogram was significantly greater in complete response patients than in non-complete response patients after two cycles and the last cycle. The Cox proportional hazard model and best subset selection method revealed that the percentage change of the sum of total lesion glycolysis after the last cycle (relative risk, 5.24; $P = 0.003$) was an independent predictor of progression-free survival. The percent change of sum of total lesion glycolysis, calculated from PET/CT, can be used to quantify the response to treatment and can predict progression-free survival after the last treatment cycle in patients with relapsed or refractory DLBCL treated with bendamustine–rituximab.

Diffuse large B-cell lymphoma, a major aggressive mature B-cell lymphoma, is often refractory and the cause of high mortality. Recent studies have indicated a favorable response and the safety of bendamustine in combination with rituximab (a cytotoxic agent with alkylator) in relapsed or refractory patients with DLBCL.[1,2]

Sequential PET/CT using ^{18}F-FDG is a sensitive method for evaluating response to therapy in patients with lymphoma.[3] The finding that interim PET/CT is more accurate than CT alone highlights the potential use of interim PET/CT in "response-adapted" treatment strategies, where the treatment can be tailored (escalated or de-escalated) according to the individual's response to chemotherapy. As the treatment course is not complete in the setting of interim PET/CT, the emphasis is on characterizing the response as either positive or negative,[4] which is not ideal because therapeutic changes in tumors occur on a continuum. Thus, it is becoming increasingly desirable to use continuous criteria to grade the tumor response.

Several methods of quantitative assessment can predict treatment response or outcome. The SUV is most commonly used to give a semiquantitative measure of response, and ΔSUVmax is considered to be a significant prognostic indicator in DLBCL.[5–7] The ΔSUVmax at baseline and after two or four cycles are predictive indicators of PFS in patients receiving rituximab, whereas visual assessment of PET is not a significant

predictive indicator.[8] Metabolic tumor burden can express not only intensity of FDG accumulation but extent in volumetry. Some investigators have reported the greater usefulness of metabolic tumor volume or total lesion glycolysis for response assessment, because these volumetric parameters reflect metabolic tumor burdens.[9–15] In contrast, genetic analyses of malignant tumors indicate intratumoral heterogeneity between individual tumors.[16] Recent studies showed that the quantitative assessment of intratumoral heterogeneity could be used to evaluate malignant tumors.[17–19]

The purpose of the present study was to clarify the feasibility of a PET/CT volumetric approach reflecting metabolic tumor burden for assessment of therapeutic response in patients with relapsed or refractory DLBCL.

Materials and Methods

Patient eligibility. The study group was based on the multicenter, open-label, single-arm, phase II clinical study. All patients have been previously described.[2] This prior article dealt with the efficacy of bendamustine–rituximab therapy, whereas this report focuses on the prognostic significance of metabolic tumor burden assessed by ^{18}F-FDG PET/CT. The criteria for eligibility were histologically confirmed DLBCL unresponsive to, or relapsed after, prior therapy in patients aged 20–75 years. The number of prior therapies ranged from one to three. Patients were required to have a measurable lesion >1.5 cm in one dimension. Adequate hematologic, renal, hepatic, respiratory, and cardiovascular functions were required. No carry-over effects of prior therapy were allowed, and a 3-week wash-out period was required. Patients who failed to obtain CR, CR unconfirmed, or PR in any prior treatment, or who had a prior history of allogeneic hematopoietic stem cell transplantation or radioimmunotherapy, uncontrolled diabetes, pregnancy, apparent infection, spread of the lymphoma to the central nervous system, or concomitant malignancy were not eligible according to the protocol. This study was carried out in accordance with the amended Helsinki Declaration and approved by the local ethics committees of all participating institutions in Japan and Korea after all the patients had provided their informed consent to participate.

Treatment. Bendamustine 120 mg/m^2 was given on days 2 and 3 in combination with rituximab 375 mg/m^2 on day 1 of every 21-day treatment cycle for up to six treatment cycles. Dose reductions were carried out and described previously.[2] No dose escalation was allowed after a dose reduction, and no dose reduction of rituximab was required. The use of G-CSF was permitted during cycles 2–6, as well as during cycle 1 when grade ≥3 neutropenia was confirmed. When G-CSF was given, PET study was carried out at least 3 weeks after the last dosing of G-CSF.[20]

Positron emission tomography/computed tomography. A phantom study was carried out in accord with previously published recommendations and guidelines[21–23] to establish the necessary and sufficient conditions of PET data acquisition for quality assurance prior to clinical study in all institutions. In all, 28 PET/CT machines (nine types of machine) were used for this study in 24 institutions (Japan, 17 institutions; Korea, 7 institutions). The European Association of Nuclear Medicine /National Electrical Manufactures Association's image quality phantom (NU 2-2001) was used for cross-calibration. Patients received an i.v. injection of 3.5–5.0 MBq/kg of ^{18}F-FDG after at least 6 h of fasting, and the injection was followed by an uptake phase of 63 ± 8 min. The patients were then placed in a supine, arm-up position, immediately after urination. Data acquisition was carried out for each patient from the top of the skull to the mid-thigh. Although the published recommendations and guidelines give no recommendation regarding the SUV,[21–23] we obtained values for 12 ROIs defined in the phantom background area to evaluate the accuracy with an allowance of 1.0 ± 0.1.[24]

Image interpretation. The PET and CT images in all standard planes were reviewed on a dedicated workstation (PET-STAT; AdIn Research, Tokyo, Japan). Images were analyzed by two board certified nuclear medicine physicians as the central review committee. When their interpretations were discrepant, the judgment of a third board certified nuclear medicine physician was sought. Largest diameter of the lesion with the greatest amount of ^{18}F-FDG uptake was measured. The SPD within the lesion was assessed in up to six target lesions. The percentage reduction rates of SPD (ΔSPD) were also calculated. For the visual analysis, abnormal ^{18}F-FDG uptake was defined as substantially greater activity than in the mediastinal blood pool on attenuation-corrected images. An ROI was outlined within areas of increased ^{18}F-FDG uptake and measured on each slice. The SUVmax was calculated after correction based on body weight. The SUL was calculated for a maximal 1.2-cm diameter ROI located within the tumor.[25] As an index of metabolic tumor burden, MTV was calculated by tumor uptake above a cut-off SUVmax >2.5 as a reference.[13] Total lesion glycolysis (the response score)[26] was also calculated as the product of the volume obtained by PET and the average SUV as a reference of metabolic tumor burden. Intratumoral heterogeneity of ^{18}F-FDG uptake was assessed by estimating the AUC-CSH.[18] The SUVmax, SUL, MTV, TLG, and AUC-CSH of the lesion with the greatest amount of ^{18}F-FDG uptake were measured for each patient. The ΣMTV and ΣTLG for a maximum of six target lesions per patient were also calculated. Evaluation of the metabolic response was accomplished by comparing the changes from baseline in ΔSUV, ΔSUL, ΔTLG, ΔMTV, ΔΣMTV, ΔΣTLG, and ΔAUC-CSH.

Tumor responses were assessed by PET/CT after two treatment cycles and after the last treatment cycle. Patients were classified based on the best tumor response according to the Lugano classification,[4] which is visual five-point scale designed to reduce interobserver variability as: 1, no uptake; 2, uptake ≤mediastinum blood pool; 3, uptake ≤liver; 4, moderately increased uptake >liver; or 5, markedly increased uptake >liver and/or new lesions. A score of 1–3 was regarded as negative and 4 or 5 as positive. The PFS was calculated as the time from day 1 of the first cycle to either disease progression (including relapse and exacerbation), onset of another treatment, or death from any cause.

Statistical analysis. The sample size was calculated based on the expected and threshold ORRs of 45% and 25%, respectively, described previously.[2] The ORR was calculated as the proportion of treated patients who achieved PR or better. Comparison of the means between groups was carried out using a three-way ANOVA with Bonferroni's adjustment for multiple comparisons. The thresholds of PET/CT measurements to predict CR were determined by receiver operating characteristic analysis. The median PFS was estimated according to the Kaplan–Meier method, and 95% CIs were calculated using Greenwood's formula. The log–rank test was used to compare PFS between subgroups. Cox's proportional hazard model and the best subset selection method were used for multivariate

analysis of factors related to PFS. A P-value < 0.05 was considered statistically significant. Statistical analysis was carried out using the PASW Statistics 19 software program (IBM SPSS, Chicago, IL, USA).

Results

After review of imaging data from 63 patients with relapsed or refractory DLBCL described previously,[2] the quality of imaging data from 55 patients (41 Japanese and 14 Korean) were sufficient to be evaluated (Table 1). Fifty-three patients (96%) received at least one cycle of rituximab-containing chemotherapy. The number of prior treatment cycles ranged from one to three. Eight patients (15%) had undergone autologous stem cell transplantation. In 51 patients (93%), targeted nodal lesions were identified in less than four nodal sites. Eight patients (15%) had bone marrow involvement at baseline. A high proportion of patients had low (36%) or low-intermediate (38%) IPI risk. The median number of cycles administered was four (range, 1–6).

Table 1. Characteristics of patients with relapsed/refractory diffuse large B-cell lymphoma (n = 55) treated with bendamustine–rituximab

Variables	n (%)
Gender	
Male	22 (40)
Female	33 (60)
Age, years	
<65	22 (40)
≥65	33 (60)
Clinical stage (Ann Arbor staging)	
I	3 (5)
I-E	2 (4)
II	16 (29)
II-E	2 (4)
III	14 (25)
III-E	4 (7)
III-S	2 (4)
IV	13 (24)
B symptoms	
Yes	6 (11)
No	49 (89)
Prior medication	
Yes	50 (91)
No	5 (9)
Prior ASCT	
Yes	8 (15)
No	47 (55)
No. of regimens	
1	37 (67)
2	12 (22)
3	6 (11)
Performance status	
0	37 (67)
1	18 (33)
LDH, U/L	
<240	26 (47)
≥240	29 (53)
Nodal sites	
<4 nodular sites	51 (93)
≥4 nodular sites	4 (7)
Extranodal sites	
<2 extranodular sites	26 (47)
≥2 extranodular sites	29 (53)
Bone marrow involvement	
Positive	8 (15)
Negative	47 (85)
IPI risk category	
Low	20 (36)
Low–intermediate	21 (38)
High–intermediate	10 (18)
High	4 (7)

ASCT, autologous stem cell transplantation; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

The mean PET/CT parameters of all target lesions at baseline, two treatment cycles, and the last treatment cycle are listed in Table 2. The mean LD (P = 0.002), SPD (P = 0.036), SUVmax (P = 0.004), SUL (P = 0.005), MTV (P = 0.001), ΣMTV (P < 0.0001), TLG (P = 0.001), and ΣTLG (P < 0.0001) were significantly lower in CR patients than in non-CR patients after two cycles of treatment by three-way ANOVA with Bonferroni's adjustment. However, the mean AUC-CSH (P = 0.975) of both groups was similar after two cycles. Similarly, all PET/CT parameters (P < 0.0001–0.035) except for AUC-CSH (P = 0.413) were significantly lower in CR patients than in non-CR patients after the last cycle of treatment by three-way ANOVA with Bonferroni's adjustment.

The response after two cycles of therapy was complete in 15 patients (27%) and incomplete in 40 patients (73%) using the Lugano classification. The percent changes in the PET/CT parameters ΔSUV_{02} (P = 0.023), ΔSUL_{02} (P = 0.024), ΔMTV_{02} (P = 0.005), $\Delta\Sigma MTV_{02}$ (P = 0.002), ΔTLG_{02} (P = 0.004), and $\Delta\Sigma TLG_{02}$ (P = 0.001), but not ΔAUC-CSH_{02} (P = 0.674), were significantly greater in the CR group than non-CR group after two treatment cycles by three-way ANOVA with Bonferroni's adjustment (Fig. 1).

After the last cycle of therapy, evaluation by the Lugano classification revealed complete response in 32 patients (58%) and incomplete response in 23 patients (42%). The percent changes in the PET/CT parameters ΔSUV_{0L} (P = 0.0015), ΔSUL_{0L} (P = 0.003), ΔMTV_{0L} (P = 0.001), $\Delta\Sigma MTV_{0L}$ (P < 0.0001), ΔTLG_{0L} (P < 0.0001), and $\Delta\Sigma TLG_{0L}$ (P < 0.0001), but not ΔAUC-CSH_{0L} (P = 0.267), were significantly greater in the CR group than the non-CR group RC by three-way ANOVA with Bonferroni's adjustment (Fig. 2).

Table 2. Absolute values of PET/CT parameters during treatment of patients with relapsed/refractory diffuse large B-cell lymphoma (n = 55) using bendamustine–rituximab

	Baseline	Two cycles	Last cycle
LD, mm	38.8 ± 3.5	31.8 ± 4.3	29.9 ± 5.5
SPD, mm^2 ($\times 10^2$)	15.2 ± 3.1	14.9 ± 4.0	15.5 ± 6.2
SUVmax, g/mL	15.0 ± 1.1	6.3 ± 1.0	6.8 ± 1.2
SUL, g/mL	12.4 ± 1.1	5.3 ± 0.9	5.6 ± 1.0
MTV, mm^3 ($\times 10^1$)	66.1 ± 14.5	34.7 ± 13.4	41.7 ± 10.9
ΣMTV, mm^3 ($\times 10^1$)	105.8 ± 23.2	59.1 ± 22.7	75.1 ± 19.6
TLG, g ($\times 10^1$)	105.5 ± 23.2	61.4 ± 21.7	52.3 ± 16.3
ΣTLG, g ($\times 10^1$)	173.1 ± 38.1	108.7 ± 38.4	97.7 ± 30.4
AUC-CSH ($\times 10^{-1}$)	5.2 ± 0.7	5.3 ± 0.8	5.3 ± 0.2

AUC-CSH, area under the curve of cumulative standardized uptake value (SUV)–volume histogram; LD, largest diameter; MTV, metabolic tumor volume; ΣMTV, sum of MTV for a maximum of six target lesions per patient; SPD, sum of products of the maximum perpendicular diameters; SUL, peak value of SUVmax corrected for the lean body mass; SUVmax, maximum SUV; TLG, total lesion glycolysis; ΣTLG, sum of TLG for a maximum of six target lesions per patient.

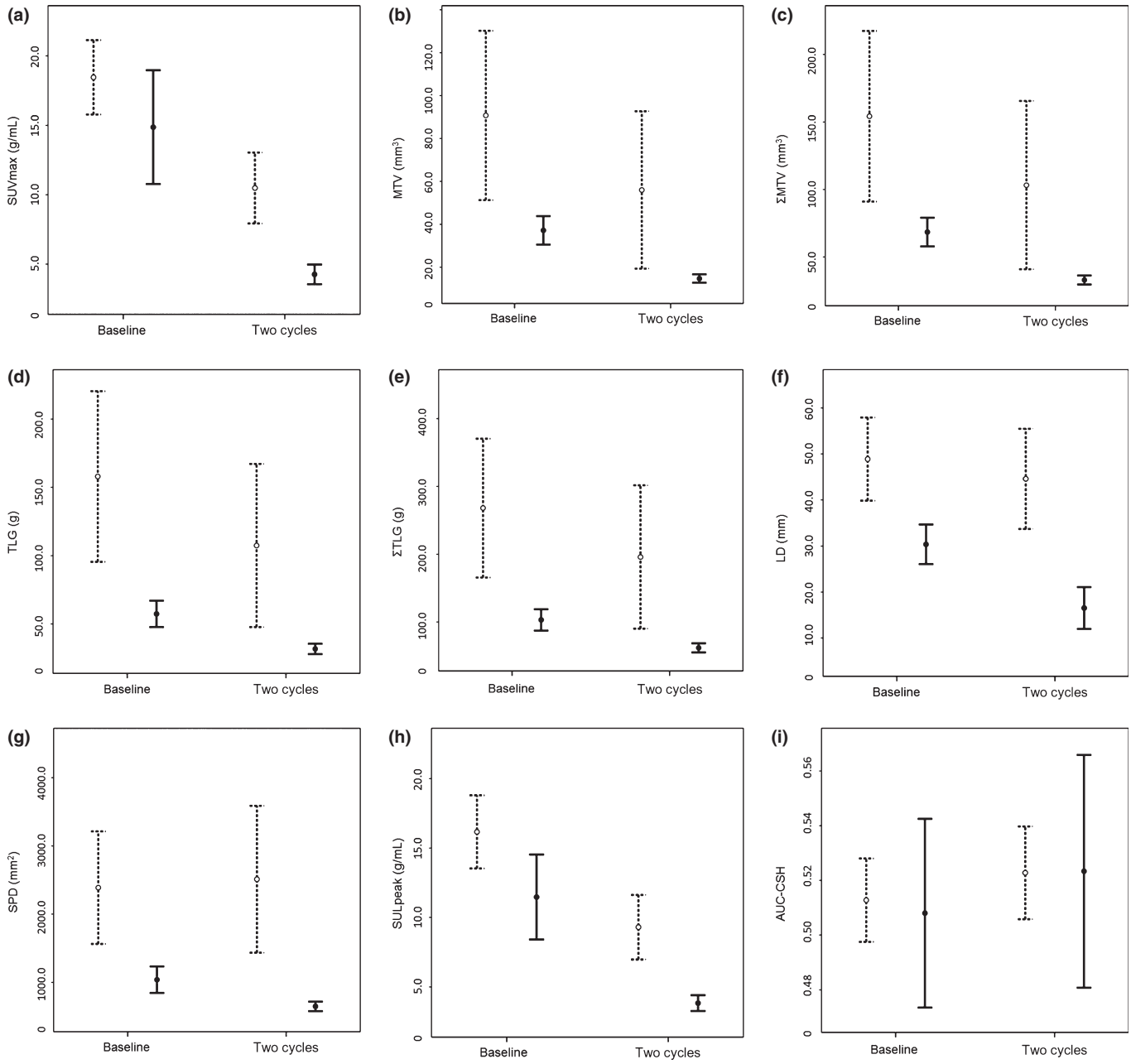

Fig. 1. Absolute values of PET/CT parameters in complete response (CR, solid bar) and non-CR (dashed bar) groups after two cycles of treatment assessed according to the Lugano classification. Maximum standardized uptake value (SUV_{max}, g/mL) (a), metabolic tumor volume (MTV, mm^3) (b), sum of MTV for a maximum of six target lesions per patient (ΣMTV, mm^3) (c), total lesion glycolysis (TLG, g) (d), and sum of TLG for a maximum of six target lesions per patient (ΣTLG, g) (e) are shown. Large diameter (LD, mm) (f), sum of the products of the maximum perpendicular diameters (SPD mm^2) (g), peak value of SUV corrected for lean body mass (SUL_{peak}, g/mL) (h), and the area under the curve of cumulative SUV–volume histogram (AUC-CSH) (i) are shown. The absolute values of all PET/CT parameters except for AUC-CSH did not overlap between baseline and after two cycles in the CR group.

The performance of percent change in PET/CT measurements for predicting CR after two cycles and the last cycle of therapy is summarized in Table 3. The $\Delta\Sigma TLG_{02}$ and $\Delta\Sigma TLG_{0L}$ showed the highest sensitivity and specificity for predicting CR, respectively. However, the *P*-values of $\Delta\Sigma MTV_{02}$ and $\Delta\Sigma TLG_{02}$ showed marginal significance because of the small patient population.

The ORR, CR rate, PR rate, stable disease rate, and progressive disease rate were 58.2% (95% CI, 45.2–71.2%), 41.8% (95% CI, 28.8–54.8%), 16.4% (95% CI, 6.6–26.2%), 12.7% (95% CI, 3.9–21.5%), and 29.1% (95% CI, 17.1–41.1%), respectively. The median PFS was 155 days (range, 20–576 days). After a median follow-up of 185 days (range, 19–575 days), disease progression was observed in 31 patients (56.4%; 95% CI, 43.3–69.5%). The median PFS was achieved. The estimated PFS rate at 1 year was 39.2% (95% CI, 26.3–52.1%) in all patients.

Univariate analyses of potential prognostic factors showed an association of PFS with B symptoms, prior medication, ECOG performance status, nodal sites, IPI risk category, the Lugano classification, and all percent changes in PET/CT parameters except for ΔAUC-CSH_{0L} (Table S1). Gender, age,

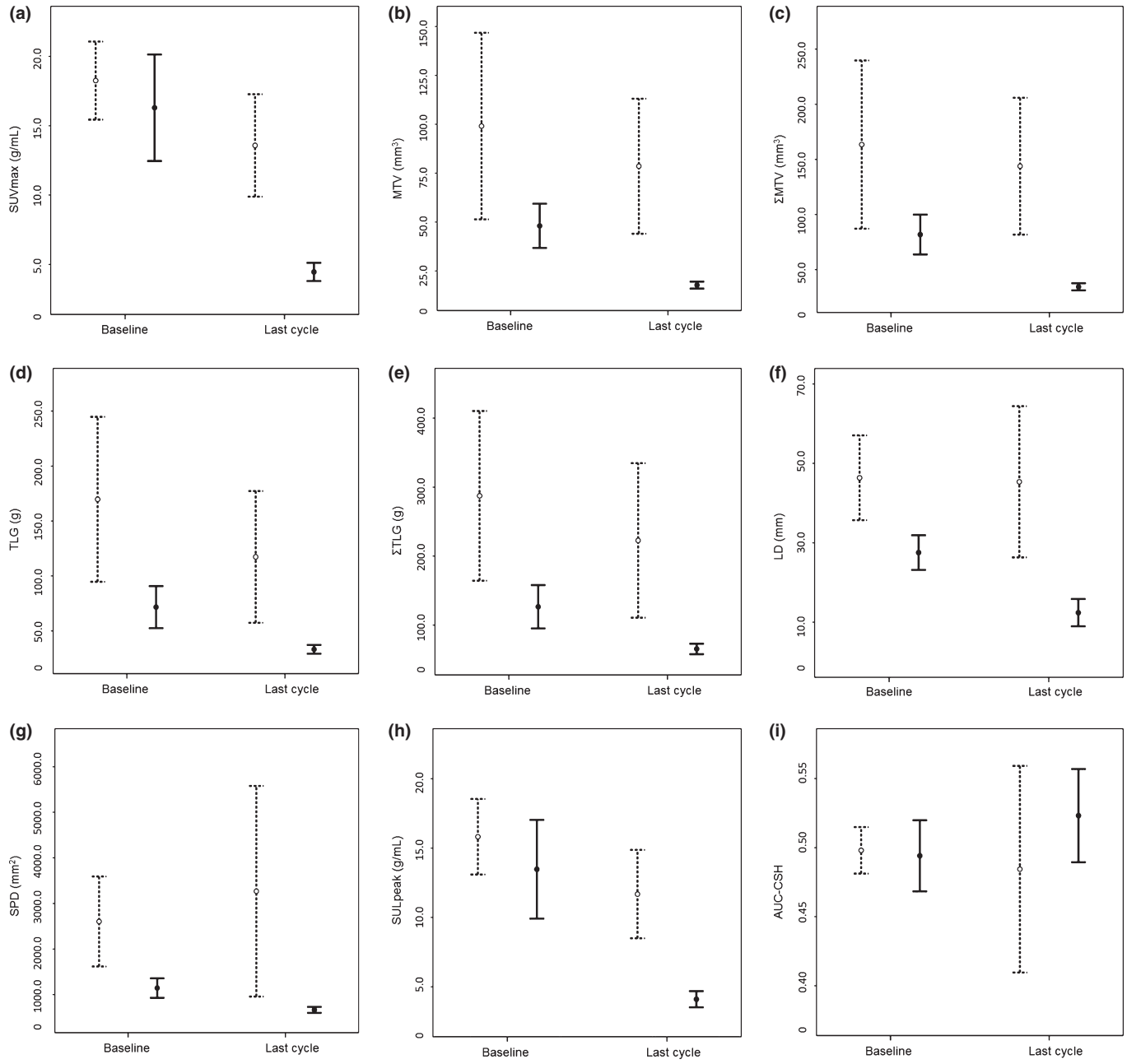

Fig. 2. Absolute values of PET/CT parameters in the complete response (CR, solid bar) and non-CR (dash bar) groups after the last cycle of treatment assessed according to the Lugano classification. Maximum standardized uptake value (SUV_{max}, g/mL) (a), metabolic tumor volume (MTV, mm^3) (b), sum of MTV for a maximum of six target lesions per patient (ΣMTV, mm^3) (c), total lesion glycolysis (TLG, g) (d), and sum of TLG for a maximum of six target lesions per patient (ΣTLG, g) (e) are shown. Large diameter (LD, mm) (f), sum of the products of the maximum perpendicular diameters (SPD, mm^2) (g), peak value of SUV corrected for lean body mass (SUL_{peak}, g/mL) (h), and the area under the curve of cumulative SUV–volume histogram (AUC-CSH) (i) are shown. The absolute values of all PET/CT parameters except for AUC-CSH did not overlap between baseline and after the last cycles in the CR group.

clinical stage, prior autologous stem cell transplantation, number of regimens, serum lactate dehydrogenase, extranodal sites, and bone marrow involvement lacked predictive value. An analysis of factors related to disease progression was carried out using a Cox proportional hazard model and the best subset selection method. In order of relative risk, $\Delta\Sigma TLG_{0L}$ was identified as an independent predictor of PFS (threshold 66.0%; relative risk, 5.24; 95% CI, 1.76–15.60; $P = 0.003$) (Fig. 3). Other percent changes in PET/CT measurements were not identified as independent predictors.

Discussion

In this study, we documented the feasibility of quantitating metabolic tumor burden with PET/CT to assess therapeutic response in patients with relapsed or refractory DLBCL. Although several studies have described the results of response evaluation based on visual score,[3,4] ΔSUV,[5–8] and volumetric measurements,[9–15] direct comparisons between these indices have not been carried out in a single study. Univariate and multivariate analyses identified ΔΣTLG among the various

Table 3. Diagnostic accuracy of PET/CT parameters to discriminate between complete response and non-complete response groups of patients with relapsed/refractory diffuse large B-cell lymphoma ($n = 55$) after two cycles and the last cycle of treatment with bendamustine–rituximab

	Threshold, %	AUC	*P*-value	Sensitivity, %	Specificity, %
Baseline – two cycles					
ΔSUV_{02}	66.0	0.770	0.0230	80.0	60.0
ΔSUL_{02}	65.0	0.700	0.0300	80.0	60.0
ΔMTV_{02}	68.0	0.776	0.0400	73.3	62.0
$\Delta\Sigma MTV_{02}$	66.0	0.867	0.0490	73.3	60.0
ΔTLG_{02}	68.0	0.784	0.0300	74.6	63.8
$\Delta\Sigma TLG_{02}$	67.0	0.875	0.0470	80.0	65.0
$\Delta AUC\text{-}CSH_{02}$	−3.7	0.419	0.3590	53.3	55.0
Baseline – last cycle					
ΔSUV_{0L}	75.0	0.728	0.0010	73.8	67.8
ΔSUL_{0L}	70.0	0.697	0.0140	72.7	66.7
ΔMTV_{0L}	65.0	0.758	0.0010	80.1	69.7
$\Delta\Sigma MTV_{0L}$	61.0	0.865	0.0010	77.3	75.8
ΔTLG_{0L}	67.0	0.765	0.0010	77.3	75.8
$\Delta\Sigma TLG_{0L}$	66.0	0.878	<0.0001	81.8	75.8
$\Delta AUC\text{-}CSH_{0L}$	−6.0	0.591	0.2570	63.6	54.5

AUC, area under the curve; Δ, percentage change; 02, from baseline to after 2 cycle; 0L, from baseline to after last cycle; SUV, maximum standardized uptake value; SUL, standardized uptake value corrected by lean body mass; MTV, metabolic tumor volume; ΣMTV, sum of MTV for a maximum of 6 target lesions per patient; TLG, total lesion glycolysis; ΣTLG, sum of TLG for a maximum of 6 target lesions per patient; AUC-CSH, area under the curve of cumulative SUV-volume histogram.

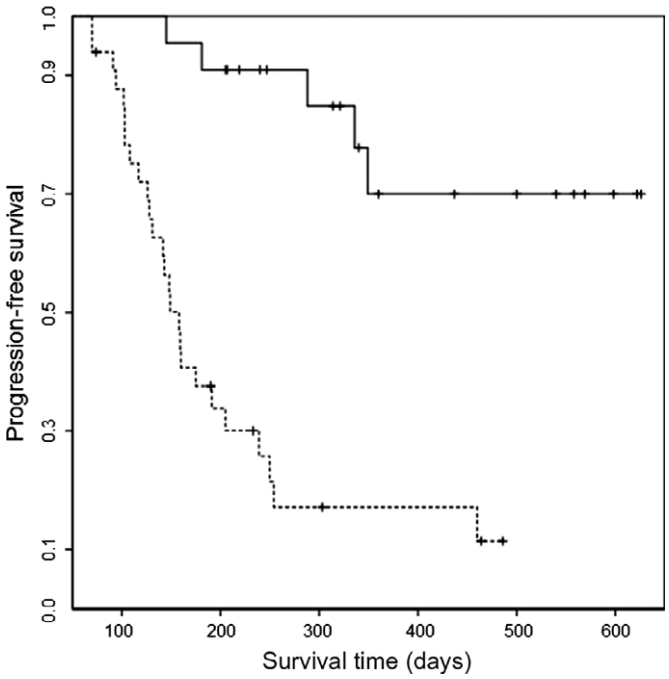

Fig. 3. Kaplan–Meier curves of progression-free survival by the percentage change of the sum of total lesion glycolysis after the last cycle of treatment (cut-off, 66.0%; log–rank test, $P < 0.0001$). The solid line indicates the group showing ≥66.0%; the dotted line is the group showing >66.0%.

PET/CT measurements as an independent predictor of PFS after the last treatment cycle. To the best of our knowledge, this is the first prospective multicenter study comparing various PET/CT measurements reflecting metabolic tumor burden for assessment of treatment response as well as application of the Lugano classification.

Semiquantification as a technique for interpreting PET/CT images has generally been used for analysis of malignant lymphomas. The semiquantification of PET images is useful in defining minimal uptake and a more objective way to interpret therapeutic response than visual analysis alone.[27] Visual dichotomous assessment is subjective and occasionally difficult to make because FDG uptake is a continuous variable. Although scans can be semiquantitated by several PET/CT measurements, which of these measurements would be useful to the community physician is not clear.

The semiquantitative measure ΔSUV may be useful in response assessment. Investigators have reported the utility of ΔSUV on interim PET/CT for early response assessment.[8,28] Although ΔSUV is a simple quantitative parameter and suitable for clinical application with appropriate standardization of PET/CT methodology, whether it can be used in early assessment of aggressive non-Hodgkin's lymphoma remains controversial. False-positive findings occasionally encountered on interim PET/CT in patients treated with rituximab may contribute to the controversy. Wahl *et al.*[25] proposed the use of SUL_{peak} (i.e., SUV corrected for lean body mass) for semiquantitation and to maintain quality control, which is a PERCIST1.0 criterion. However, ΔSUL may be more difficult to measure when tumor volume is decreased by treatment. Moreover, ΔSUL is mathematically equivalent to ΔSUV when the image is smoothed because SUL_{peak} is defined at the hottest point in the tumor focus (1 cm^3 spherical ROI).[25]

As tumor burden may help to define treatment response and clinical outcome, some investigators have evaluated PET/CT volumetric parameters as assessment measures.[9–15] The MTV is a PET/CT volumetric parameter calculated by selecting a tumor with SUV_{max} >2.5 or using a threshold-based method with the liver or mediastinum as a reference.[25] Several studies have reported that absolute baseline MTV of the most intensively labeled lesion is an independent predictor of PFS in DLBCL.[12–14] Tseng *et al.*[14] reported that the ratio of interim to baseline MTV is a prognostic index in Hodgkin's lymphoma. Although MTV could be a prognostic indicator for assessment of malignant lymphoma, the conclusion that MTV is an indicator is based on retrospective analysis of selected datasets. Prospective multicenter studies in homogenous populations receiving the same treatment will be required to determine whether MTV has any advantage over existing methods of visual analysis and ΔSUV.

Total lesion glycolysis (the volume obtained by PET images × the average SUV within the tumor) is another volumetric parameter. The ΔTLG (the ratio of the metabolic rate of the tumor at baseline to its metabolic rate after treatment) was originally called the Larson–Ginsberg Index. It corresponds to the change in cell mass of the target lesion and reflects the global response of the entire tumor to treatment.[26] In a study of patients with DLBCL, ΔTLG was shown to be a strong predictor of survival.[9] Importantly, other investigators showed that ΣTLG reflects treatment response in DLBCL and predicts PFS.[15] However, similar to MTV, TLG will need to be compared to other preexisting PET/CT parameters in a prospective study with homogenous populations receiving the same treatment in order to clarify its prognostic significance. Univariate and multivariate analyses of our data extended the results of previous studies and showed that ΔΣTLG can predict PFS after the last treatment cycle.[9,15]

The accuracy of PET/CT measurements depends on technical and physiological factors that must be standardized for widespread application.[30] In addition, investigators should be attentive to the need for scan parameter adjustment in advance of image acquisition because of variability among PET scanners.[31] Therefore, we carried out a phantom study in all participating institutions to determine the optimal scan parameters appropriate for each institution prior to the clinical study according to routine use recommendations and guidelines.[21–24,29–31]

There is no known relationship between intratumoral FDG metabolic heterogeneity and treatment response in malignant lymphoma. In some studies, the segmentation, intensity–volume histograms, and AUC-CSH have been used to characterize intratumoral heterogeneity of tracer uptake.[16–18] Watabe *et al.*[32] reported that the mean AUC-CSH of lesions in 12 patients with malignant lymphoma was 0.60, but these lesions appeared homogeneous on visual analysis. Brooks and Grigsby suggested that inclusion of tumor volumes below 45 cm^3 could bias comparisons of intratumoral uptake heterogeneity metrics derived from data from the current generation of whole-body PET scanners.[19] The results of the current investigations would suggest that the AUC-CSH has limited power to discriminate between CR and non-CR groups in receiver operating characteristic analysis and is not significantly associated with PFS after two treatment cycles and the last treatment cycle. Although we did not assess the difference between nodal and extranodal target lesions in our AUC-CSH analysis, further study may be needed to confirm the clinical relevance of intratumoral heterogeneity in malignant lymphoma.

One of the potential criticisms of our study might be the lack of intra- and interobserver variability in our various PET/CT parameters. Some investigators have suggested that intra- and interobserver agreement between visual scores and PET/CT parameters should be assessed for accuracy and reproducibility.[27,32] However, we carried out a phantom study prior to collecting patients' data for standardization of PET/CT acquisition. Assessment of variability should be used for quantitative assessment and accurate measurement depending on technical and physiological factors. The segmentation of the ROI for determining SUV_{mean} and derived quantities such as TLG might be required for quantitation.

There are other potential limitations to our study. Our study focused on patients with DLBCL who relapsed after prior treatment and the data may not be extrapolated to untreated cases. Numerically, our study was relatively small (55 patients analyzed) and may not have been sufficiently powered to allow for statistical comparison of some of the covariates. Sample size might have also led to false positives on interim PET/CT, and false positive results should be taken into consideration during therapy.[8]

The phantom studies were carried out to qualify image quality, but we did not qualify the quantitativity of PET images for analysis of AUC-CSH. Further study is warranted to elucidate the feasibility of AUC-CSH in the clinical setting. Furthermore, we used three-way ANOVA with Bonferroni's correction as the demonstrable method in this study population. However, we did not consider enough to be corrected only for this method.

In conclusion, the changes in metabolic tumor burden have prognostic implications in patients with relapsed or refractory DLBCL treated with bendamustine–rituximab therapy. Although further research is required to determine the role of ΔΣTLG as a surrogate marker for survival in this population, use of this measurement may facilitate prioritization of bendamustine–rituximab therapy for patients with relapsed or refractory DLBCL.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

AUC-CSH	area under the curve of the cumulative SUV–volume histogram
CI	confidence interval
CR	complete response
CT	computed tomography
Δ	percentage change
DLBCL	diffuse large B-cell lymphoma
^{18}F-FDG	[F-18] 2-fluoro-2-deoxy-D-glucose
G-CSF	granulocyte colony-stimulating factor
IPI	International Prognostic Index
LD	largest diameter
MTV	metabolic tumor volume
ORR	overall response rate
PFS	progression-free survival
PR	partial response
ROI	region of interest
Σ	sum of
SPD	sum of the products of the maximum perpendicular diameters
SUL	SUVmax corrected for lean body mass
SUV	standardized uptake value
SUVmax	maximum value of SUV
TLG	total lesion glycolysis

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Results of univariate analyses in prediction of progression-free survival (PFS) after the last treatment cycle.