Original Article
Baseline total lesion glycolysis measured with ^{18}F-FDG PET/CT as a predictor of progression-free survival in diffuse large B-cell lymphoma: a pilot study

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Abstract: This pilot study investigates the value of baseline total lesion glycolysis (TLG) in ^{18}F-FDG PET/CT scans for prediction of progression-free survival (PFS) in patients with Diffuse Large B-Cell Lymphoma (DLBCL). We also evaluate the role of other quantitative parameters measured at baseline and interim PET/CT for prediction of PFS. A retrospective review (2003-2010) of patients with DLBCL who underwent ^{18}F-FDG PET/CT before, after cycle two, and after completion of R-CHOP treatment, identified 84 patients. Twenty patients fulfilled the inclusion criteria. Standardized uptake values (SUVmax and SUVmean), total metabolic tumor volume (TMTV), and TLG were measured in baseline and interim PET/CT. Relationship between quantitative parameters and PFS was statistically analyzed using Log-rank test and univariate Cox-regression analysis. Of 20 patients (F/M: 7/13, range: 20-73 years), six patients (30%) developed recurrence after chemotherapy (mean follow-up: 51.35±17.05 months, range: 12-81 months). Results of statistical analysis showed TLG as the only discriminator of recurrence at baseline (cut-point: 704.77 g, HR: 11.21, CI: 1.29-97, $P=0.02$). Among the interim PET/CT parameters, SUVmean (cut -point: 2.07, HR: 6.31, CI: 1.25-31.61), SUVmax (cut-point: 2.3, HR: 6.31, CI: 1.25-31.61), and TLG (cut-point: 96.5 g, HR: 6.38, CI: 1.29 - 31.61) could all help predict PFS ($P<0.05$). Although not routinely reported, high baseline TLG may be a useful index to identify patients with DLBCL who are at increased risk for relapse after conventional R-CHOP. If confirmed in larger prospective studies, this may allow the selection of alternate therapeutic choices at the onset of treatment.

Keywords: Diffuse large B-cell lymphoma, ^{18}F-FDG PET/CT, progression-free survival, quantitative parameters

Introduction

Optimization of the management of patients with Diffuse Large B-cell Lymphoma (DLBCL) is of upmost importance since conventional chemotherapy has been shown to be effective only in 60% of patients [1, 2]. Hence, an accurate predictive tool to identify patients more likely to relapse is needed to allow both for stratification of patients in clinical trials as well as for early implementation of more appropriate treatment strategies.

It has been demonstrated that ^{18}F-FDG PET/CT is an accurate diagnostic tool in detection of neoplastic disease, staging, and early evaluation of tumor response to therapy [3, 4]; the lat-

ter allows for early alteration of ineffective therapy regimens and selection of the patients who can benefit from second line therapies [5]. One such clinical scenario, in which interim monitoring of therapy response using ^{18}F-FDG PET/CT has been shown useful is DLBCL. Considering the substantial recurrence rate of disease in a large group of these patients after standard chemotherapy regimens, it is crucial to identify those at high risk for disease recurrence [6]. Recent clinical trials have demonstrated that interim ^{18}F-FDG PET/CT may be employed to monitor the response to chemotherapy and predict disease recurrence [7-9]. Nevertheless, the role of interim PET for prediction of clinical outcome in DLBCL is still controversial and remains to be fully elucidated [10, 11]. Some groups

Table 1. Patients' inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Negative ^{18}F-FDG-PET scan after completion of chemotherapy	History of previous lymphoma or other malignancies
A record of normal blood glucose level immediately before ^{18}F-FDG injection (<200 mg/dL)	Active infection or granulomatous disease before treatment
At least 12 month of follow-up after completion of chemotherapy	Pregnancy
No regimen other than standard R-CHOP	Age younger than 18 years

have suggested that baseline ^{18}F-FDG PET/CT scans might be as valuable as interim PET/CT scans in the prediction of progression-free survival (PFS) and disease recurrence in various types of neoplasms. Among all quantitative PET parameters, the total glycolytic burden of disease, also known as total lesion glycolysis (TLG), in the baseline ^{18}F-FDG PET/CT scans has been shown to be an independent factor associated with PFS and recurrence in various types of cancer, including lymphoma and thoracic neoplasm [12-15].

The aim of the present study was to investigate the value of baseline TLG in the prediction of PFS in a homogeneous group of patients with DLBCL. The relationship between PFS and various quantitative PET parameters measured at baseline and interim ^{18}F-FDG PET/CT scans was also evaluated.

Materials and methods

Subjects

Records of eighty-four patients with histologically proven DLBCL were retrospectively reviewed. The patients were referred to Massachusetts General Hospital between September 2003 and August 2010. They underwent ^{18}F-FDG PET/CT at baseline, after 2 cycles of standard chemotherapy with cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone, rituximab (R-CHOP), and after completion of chemotherapy. Patients who fulfilled the inclusion criteria and did not have any of the exclusion criteria were then enrolled in the study (**Table 1**). The study protocol was approved by Institutional Review Board (IRB) of the hospital.

Clinical data obtained from all patients included the information about sex, age of disease onset (by the date of diagnosis), presence of B symptoms, number of involved regions, clinical stage of disease according to Ann Arbor staging system, quantitative PET/CT parameters at the baseline and interim PET/CT, duration of treatment and duration of follow-up after completion of therapy, interim PET/CT results, PFS, and occurrence of relapse.

^{18}F-FDG PET/CT acquisition

All scans were performed using a Siemens Biograph PET/CT scanner. Patients were instructed to fast for at least 6 hours and blood glucose level was measured to ensure that it was less than 200 mg/dL before radiotracer injection. Approximately, sixty minutes after intravenous injection of ^{18}F-FDG per standard MGH protocol (555-925 MBq; BMI-based dose), a whole body emission PET scan was performed in 6-8 bed positions (3-5 min acquisition time per bed position based on BMI), covered from base of skull to upper thigh. Non-contrast-enhanced CT with 120-keV, 11-100-mAs (based on BMI), 5-mm collimation and pitch of 0.75 was performed for attenuation correction. The datasets were reconstructed using OSEM algorithm with 2 iterations (BMI < 31) or 3 iterations (BMI ≥ 31), 8 subsets, and 5 mm gaussian filter. The reconstructed images were reviewed in transverse, sagittal and coronal planes, using a dedicated PET/CT fusion workstation with built-in software (Syngo TrueD; Siemens Medical Solutions).

All patients received R_CHOP regimen for six to eight cycles. A baseline ^{18}F-FDG PET/CT scan was acquired before starting R-CHOP treatment. Interim scan was performed within the last 0-3 days before administration of the third cycle of chemotherapy, and the last scan was done 3-6 weeks after completion of treatment. Response to therapy was evaluated one month after the completion of chemotherapy. Pretreatment staging and response evaluation after completion of R-CHOP therapy were based

Table 2. Patients' demographic and clinical characteristics and the qualitative PET/CT results

No	Sex	Age (years)	B symptom	No of Regions	Ann Arbor Stage	Duration of follow- up (months)	PFS (months)	Interim result	Relapse
1	M	60	P	4	3	54	54	N	N
2	F	71	N	3	4	56	56	N	N
3	M	81	N	1	2	49	49	N	N
4	M	62	N	4	3	63	63	N	N
5	F	70	N	3	4	63	63	N	N
6	M	64	N	1	2	62	62	N	N
7	M	55	N	1	1	52	52	N	N
8	M	59	N	4	2	56	56	N	N
9	M	59	P	2	4	59	59	N	N
10	F	60	P	2	3	50	50	N	N
11	F	31	N	1	1	74	74	N	N
12	F	63	N	2	2	32	14	N	P
13	M	53	P	2	2	29	19	N	P
14	M	20	P	2	3	49	32	N	P
15	F	81	P	2	4	48	48	P	N
16	M	76	P	4	4	57	57	P	N
17	M	38	P	1	2	62	62	P	N
18	F	54	N	3	4	81	32	P	P
19	M	42	P	2	3	19	6	P	P
20	M	73	N	4	4	12	4	P	P

N: negative result, P: positive result, PFS: progression-free survival.

on clinical examination, CT scan, bone marrow biopsy, and ^{18}F-FDG PET/CT.

PET quantitative parameters

The PET/CT datasets were reviewed by two radiologists, blinded from patient clinical information. Using the Siemens TrueD workstation, quantitative parameters were measured for each patient at both baseline and interim PET/CT scans.

Any focus of ^{18}F-FDG uptake outside normal physiological whole organ uptake with SUVmax greater than 1.5 liver SUVmean plus 2.5 standard deviation of liver SUV was considered a measurable lesion [16]. When in doubt, the contrast enhanced CT of the patients at the same time point, which was acquired from every lymphoma patient undergoing ^{18}F-FDG PET/CT, was reviewed to evaluate the suspicious focus. We used a relative threshold method for measuring quantitative PET parameters; we created a 3D contour around voxels that were equal to or greater than 50% of the maximum voxel value inside a spherical region. In cases where the relative threshold method resulted in overgrowing of the lesion to include the surrounding background tissue or other organs (based on CT images) an absolute threshold method was employed. In this method, we manually drew a 3D spherical contour within which the voxels equal or greater than absolute value of liver SUVmean plus 2.5 standard deviation of mean liver SUV were defined as tumor [17].

From each baseline and interim PET/CT image, SUVmax, SUVmean, and total metabolic tumor volume (TMTV) were extracted. Metabolic tumor burden (MTB) was measured as the product of SUVmean and MTV for the most ^{18}F-FDG avid lesion. TLG was calculated as the sum of the product of SUVmean and MTV of all lesions (TLG = sum of [SUVmean × MTV]).

Progression-free survival (PFS) was measured as the interval between the initiation of treatment until either disease recurrence or last documented follow-up of the patient if he/she remains disease-free. Disease recurrence was defined as clinical evidence of recurrence or a

Table 3. Univariate analysis using Kaplan–Meier survival curves and Cox-regression analysis

| Parameters | ROC curve & Log-rank test | | | | PFS | Univariate Cox-regression | | |
	AUC	Threshold	Sensitivity - Specificity (%)	P-value[a]	Mean PFS (months)	HR	95% CI	P-value[b]
Baseline SUVmax	0.58	13.84	66 - 72	0.1	51.7 vs. 36.3	3.64	0.66 - 19.98	0.136
Baseline SUVmean	0.47	6.44	66 - 58	0.32	50.8 vs. 40.4	2.26	0.41 - 12.37	0.347
Baseline TLG	0.71	704.77	83 - 79	0.006	56.5 vs. 29.2	11.21	1.29 - 97	0.028
Baseline TMTV	0.66	379.16	66 - 72	0.09	53 vs. 34.5	3.79	0.69 - 20.78	0.124
Interim SUVmax	0.68	2.3	50 - 93	0.01	50.8 vs. 24.7	6.31	1.25 - 31.61	0.025
Interim SUVmean	0.68	2.07	50 - 93	0.01	50.8 vs. 24.7	6.31	1.25 - 31.61	0.025
Interim TLG	0.72	96.5	33 - 99	0.01	50.5 vs. 26	6.38	1.29 - 31.61	0.025
Interim TMTV	0.66	5.95	33- 93	0.16	50.2 vs. 34.8	2.95	0.59 - 14.7	0.185

PFS: progression-free survival, AUC: area under the curve, HR: hazard ratio, CI: confidence interval. [a]P-values showing the level of significance in Kaplan-Meier survival analysis. [b]P-values showing the level of significance in univariate Cox-regression analysis. SUV: standardized uptake value, TLG: total lesion glycolysis, TMTV: total metabolic tumor volume.
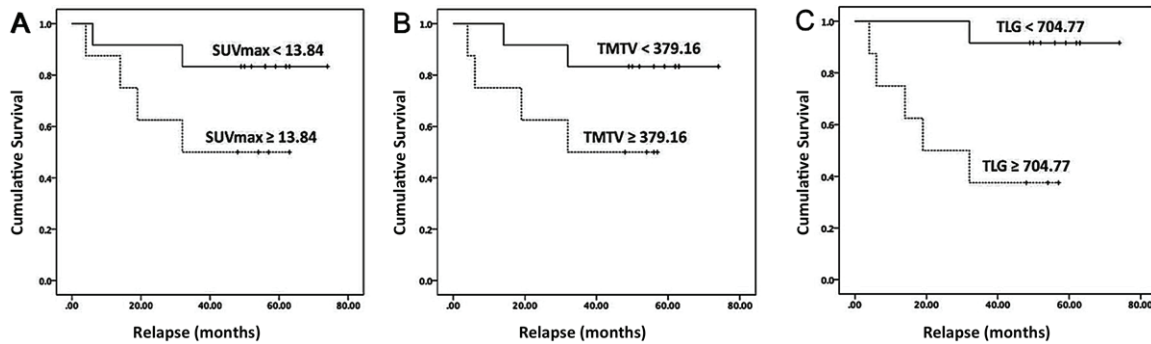

Figure 1. Kaplan-Meier estimate of progression-free survival (PFS) according to the threshold of baseline parameters at their optimal cut point; A. SUVmax was not significantly associated with PFS (cut-point: 13.84, P = 0.1, Sensitivity: 66%, Specificity: 72%). B. TMTV was not significantly associated with PFS (cut-point: 379.16, P = 0.09, Sensitivity: 66%, Specificity: 72%). C. TLG was the only discriminator at baseline of recurrence identified, with the optimal cut-point of 704.77 (P = 0.006, Sensitivity: 83%, Specificity: 79%).

positive follow-up ^{18}F-FDG-PET study. Observations were censored on the date the patient was last known to be alive or the date of death.

Statistical analysis

Descriptive frequencies and relationships between quantitative PET/CT parameters and PFS were statistically analyzed to define demographic and prognostic characteristics of the patients.

The receiver-operating-characteristic (ROC) curve was plotted to estimate the most discriminating decision threshold (cut-off point) for each parameter to maximize the sensitivity and

specificity in predicting the recurrence of disease. By dichotomizing the parameters based on their cut-point, a Kaplan-Meier survival curve was generated and Log-rank test was used to compare PFS between each of the two groups [18]. The estimated hazard ratio (HR) of each parameter at the definite threshold was assessed using univariate Cox proportional hazard analysis [19]. Log-rank test was also used to compare PFS between the negative and positive ^{18}F-FDG uptake at the interim PET/CT using dichotomized visual assessment.

The data were statistically processed using SPSS version 20 for Macintosh (SPSS, Chicago, IL). All quantitative values are reported as mean ± standard deviation (SD) and the tests with a
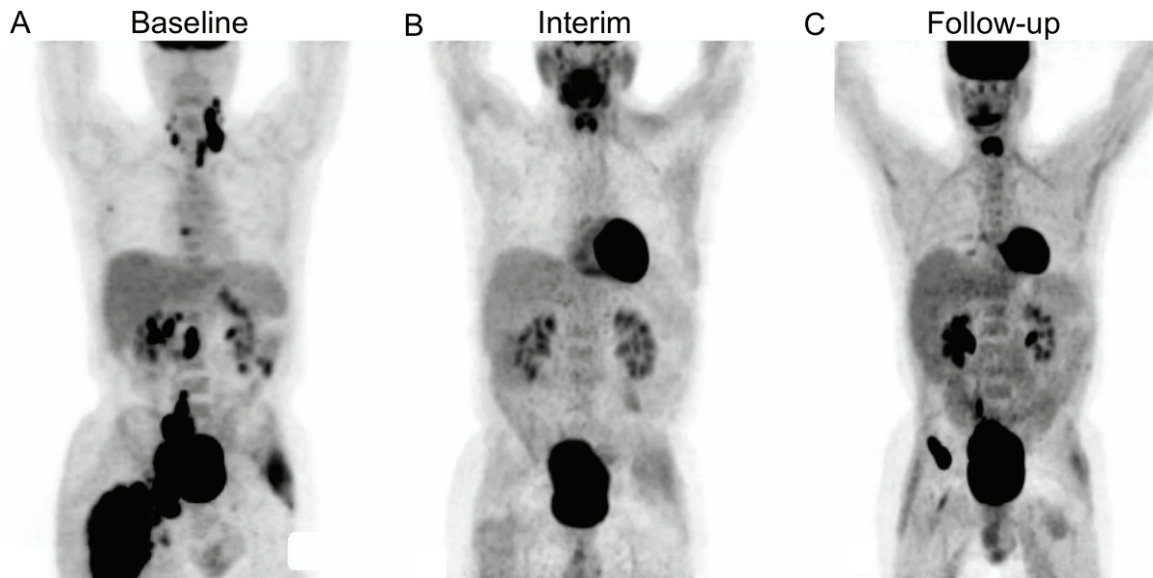
A Baseline B Interim C Follow-up

Figure 2. ^{18}F-FDG PET results from Patient No. 13; The pre-treatment PET image shows high metabolic burden of disease with total TLG of 9028 g (A). Despite showing no ^{18}F-FDG uptake at interim PET (B), the patient experienced relapse 19 months after completion of chemotherapy (C).
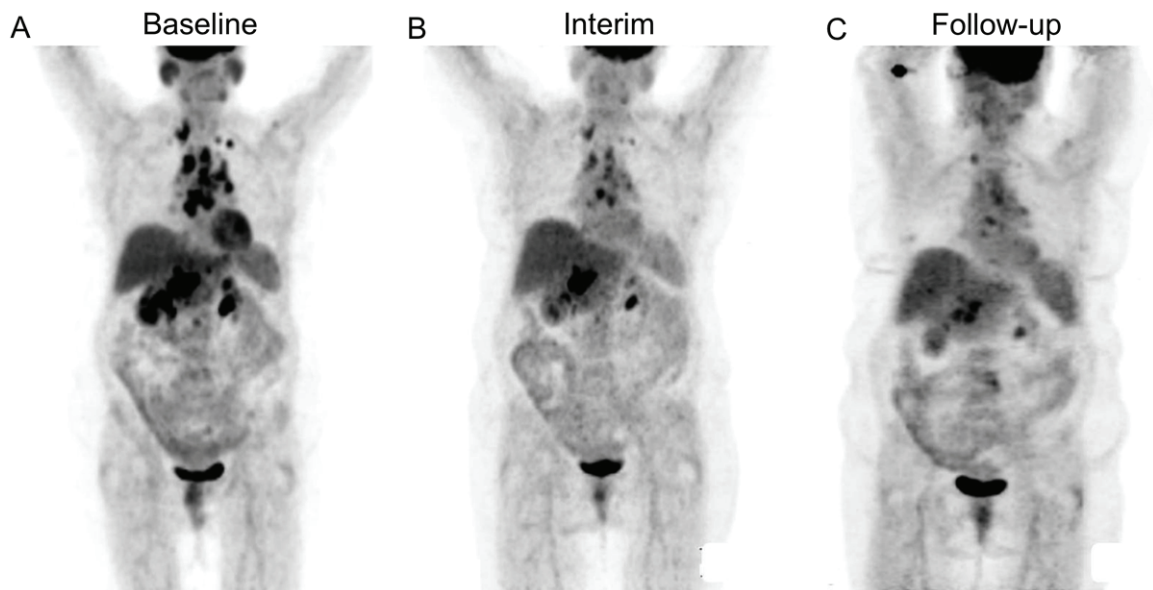
A Baseline B Interim C Follow-up

Figure 3. ^{18}F-FDG PET results from Patient No. 18. Pre-treatment PET image shows high metabolic burden of disease with TLG of 2759 g (A), Interim PET shows positive ^{18}F-FDG uptake with TLG of 942 g (B), the patient experienced relapse 32 months after completion of chemotherapy (C).

P-value <0.05 (two-sided) were considered as statistically significant.

Results

Patients

Twenty patients fulfilled the inclusion criteria including 13 women and 7 men (F/M ratio:

0.54 mean age of the onset 58.6 ± 16.02 years, range 20-73 years). Patients' demographic and clinical characteristics and the qualitative PET/CT results are reported in **Table 2**. Two patients were Ann Arbor stage I (10%), six were stage II (30%), five patients were stage III (25%), and seven were stage IV (35%). After the second cycle of chemotherapy, six patients
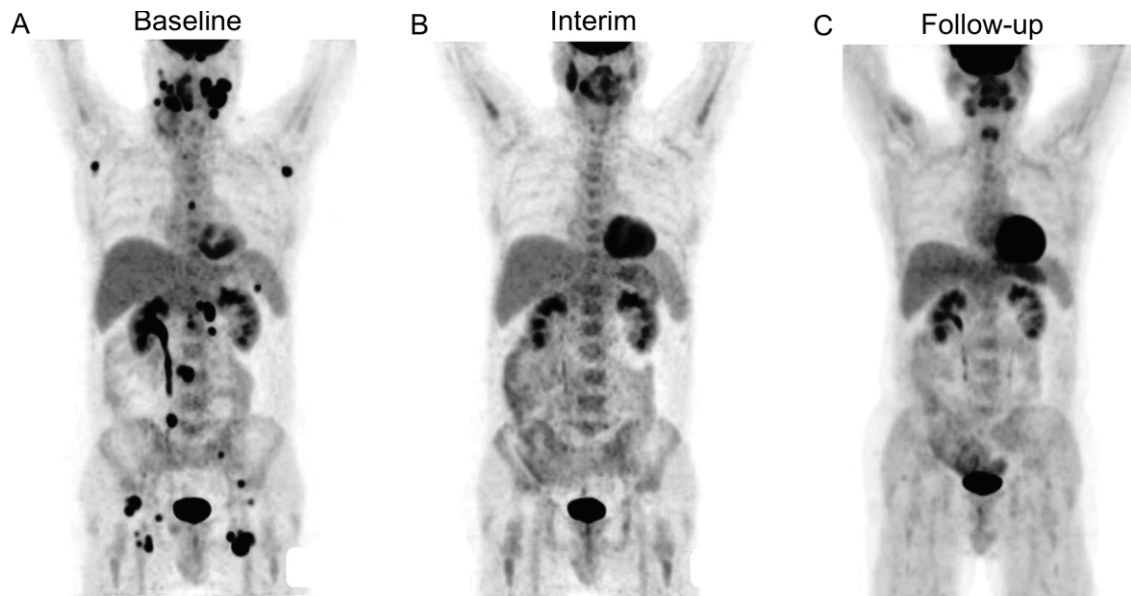
Figure 4. ^{18}F-FDG PET results from Patient No. 4. The pre-treatment PET image shows low metabolic burden of disease with total TLG of 340 g (A). Interim PET shows negative ^{18}F-FDG uptake (B), there was no evidence of relapse during the follow-up period of 74 months after completion of chemotherapy (C).

(30%) had ^{18}F-FDG uptake in at least one site in the whole body PET/CT scan at interim PET/CT (**Table 2**).

Follow-up and progression-free survival

The mean follow-up duration was 51.35± 17.05 months (range: 12-81 months). No patient died as a result of related or unrelated disease by the last follow-up. During the follow-up (i.e. starting from the first cycle of chemotherapy), 14 patients (70%) were in remission with no evidence of disease, while six patients (30%) developed disease recurrence; three of these patients did not have any focus of abnormal ^{18}F-FDG uptake at interim PET/CT images, while the other three had at least one ^{18}F-FDG positive lesion. The mean PFS was 45.6 ± 20.5 months (range -74 months) (**Table 2**).

Results regarding the prognostic and predictive values of all considered parameters using Log-rank test, Kaplan-Meier survival curves, and univariate Cox-regression analysis are reported in **Table 3**.

There was no significant association of PFS with age, gender, or stage of disease. Log-rank test showed baseline TLG as the only predictor of PFS among the baseline PET/CT parameters.

A threshold of greater or equal to 704.77 g was the cut-off point for discrimination of relapse (*P* = 0.006). (**Figure 1**) **Figures 3-6** highlight this concept through examples, in which regardless of the interim PET/CT results, the patients with baseline TLG above the defined cut-point of 704.77g would be at higher risk for progression of the disease (**Figures 2** and **3**), whereas the ones with baseline TLG below this amount would be less likely to experience the relapse (**Figures 4** and **5**).

At interim PET/CT, SUVmax (cut-point: 2.3), SUVmean (cut-point: 2.07), and TLG (cut-point: 96.5 g) were significant predictors of progression of disease (*P* < 0.05). (**Figure 6**) TMTV could not significantly predict the relapse either in baseline or in interim PET/CT images (**Table 3**).

Through the univariate Cox-regression analysis there was a statistically significant association of longer PFS with lower levels of SUVmean (HR: 6.31, CI: 1.25 – 31.61, *P* = 0.025), SUVmax (HR: 6.31, CI: 1.25 – 31.61, *P* = 0.025), and TLG at interim PET/CT (HR: 6.38, CI: 1.29 - 31.61, *P* = 0.025). Similar results were found in the association of PFS with TLG in the pre-treatment phase (HR: 11.21, CI: 1.29 – 97, *P* = 0.028) (**Table 3**).
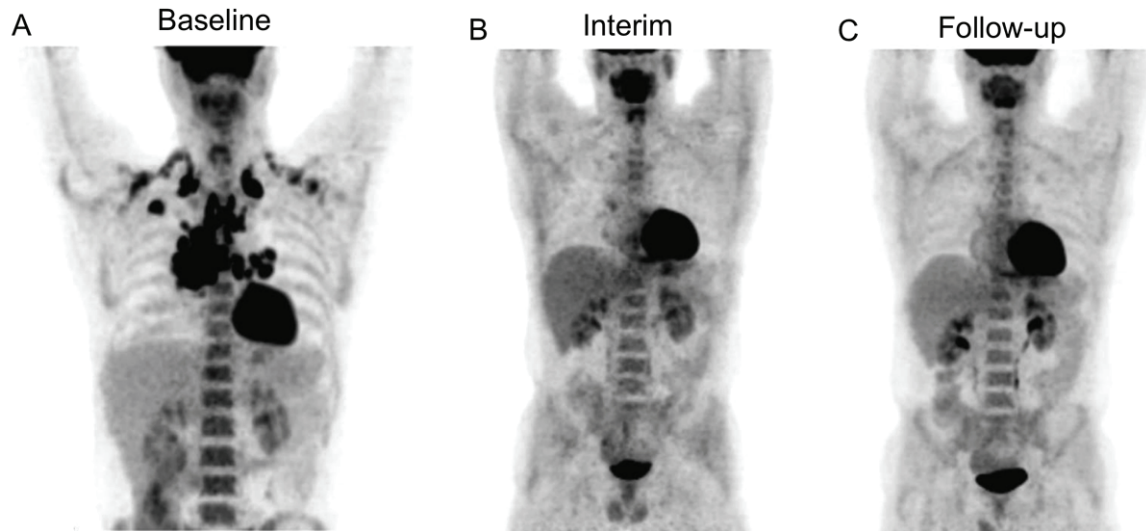
Figure 5. ^{18}F-FDG PET results from Patient No. 17. Pre-treatment PET image shows low metabolic burden of disease with TLG of 686 g (A), Despite showing positive ^{18}F-FDG uptake in mediastinum at interim PET (TLG: 14 g) (B), the patient did not experience relapse during the follow-up period of 62 months after completion of chemotherapy (C).
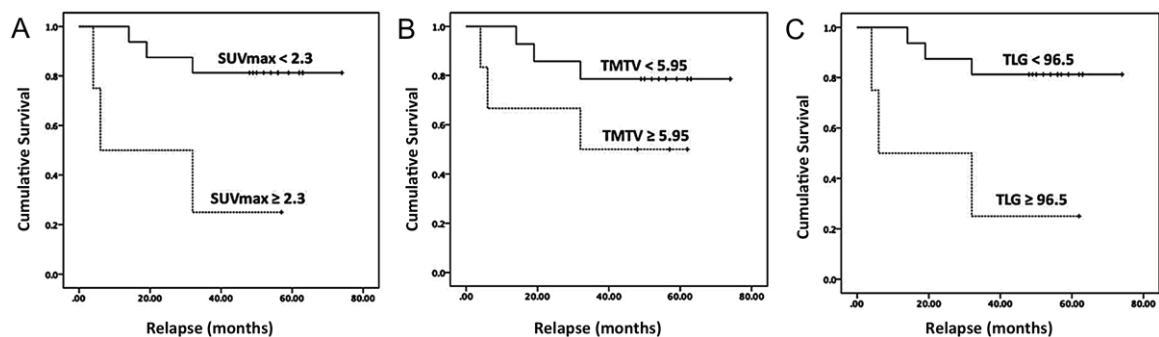

Figure 6. Kaplan-Meier estimate of progression-free survival (PFS) according to the threshold of interim parameters at their optimal cut point; A. SUVmax was significantly associated with PFS (cut-point: 2.3, $P = 0.01$, Sensitivity: 50%, Specificity: 93%). B. TMTV was not significantly associated with PFS (cut-point: 5.95, $P = 0.16$, Sensitivity: 33%, Specificity: 93%). C. TLG was a discriminator of recurrence with the optimal cut-point of 96.5 g ($P = 0.01$, Sensitivity: 33%, Specificity: 93%).

Log-rank test did not show a significant difference in PFS of the patients based on the visual assessment of ^{18}F-FDG uptake at interim PET/ CT (interim PET-negative vs. interim PET-positive groups: 50.2 vs. 34.8 months, Chi square: 1.97, df: 1, $P = 0.16$).

Discussion

Our results show a strong predictive value of baseline TLG on the occurrence of relapse in a homogenous series of patients with DLBCL treated with R-CHOP. TLG represents the metabolic burden of disease that depends on both tumor volume and glucose utilization rate. This index has been considered as a potentially reli-able parameter in providing more details about the status of disease in various types of cancers, especially in lung tumors, oro/nasopharyngeal, and rectal cancers [20-24]. The role of baseline TLG in prediction of PFS in lymphoma has not been routinely reported in the literature. Manohar, et. al. showed a weak but statistically significant association of PFS with baseline TLG and functional tumor volume in a group of patients with high-grade non-Hodgkin's lymphoma, while the SUVmean and SUVmax failed to show any significant correlation with PFS [25]. Another study conducted by Cazaentre, et. al. demonstrated that pre-treatment TLG could be a useful index in predicting response to radioimmunotherapy in patients with non-

Hodgkin's lymphoma, whereas the conventional prognostic indices could not predict the response [26]. To the best of our knowledge, this is the first study in which the value of pretreatment TLG is evaluated in a highly selected group of patients with DLBCL. Our results suggest that the baseline TLG could help identify the patients at the onset of treatment who are at increased risk for relapse.

Previous studies suggested that the visual dichotomized assessment of interim PET results would help in predicting relapse. The patients in whom a positive ^{18}F-FDG uptake was visually detected would be more likely to have relapse after treatment [27]. However, a more recent study published by Prengo, et. al., showed that regardless of the different time point that the interim PET/CT was obtained (after second to fourth cycle), the negative interim PET uptake was associated with favorable clinical outcome, but the positive interim PET uptake was not necessarily associated with a higher risk of relapse [28]. As represented in **Table 2**, our results are in concordance, showing that from the six patients with positive ^{18}F-FDG uptake at interim PET, three of them experienced relapse, while the other three did not. Our Log-rank test result failed to show any significant difference in PSF of patients based on the visual assessment of interim ^{18}F-FDG uptake (50.2 months in positive uptake vs. 34.8 months in negative uptake, Chi square: 1.97, df: 1, P = 0.16). It appears that visual interpretation of interim PET/CT may not be useful in the prediction of clinical outcome.

SUV is the most commonly used quantitative index, having shown its superior role in interpretation of interim images in comparison to visual assessment of ^{18}F-FDG uptake [27, 29, 30]. Since this parameter is commonly affected by various technical and patient-dependent factors, the role of this index is still unconfirmed [31-33]. Results of univariate Cox-regression analysis in our study revealed that the interim SUV measurements have significant prognostic values. However, multivariate Cox-regression analysis could not be done to identify the independent prognostic factor among the parameters that were significant in univariate analysis.

Some recent studies have reported the baseline TMTV as a strong predictor of PFS in patients with lymphoma [34, 35]. Sharma, et.

al. found the TMTV as an independent prognostic factor in pediatric patients with lymphoma [36] and Song, et. al. showed similar results in DLBCL patients with gastrointestinal involvement treated with R-CHOP [37]. Another study conducted by the same group on DLBCL patients with no extranodal involvement showed that higher TMTV values are associated with lower PFS regardless of the stage of disease [38]. Despite the potential value of functional tumor volume reported in recent studies, we did not find any significant association of TMTV with PFS.

Univariate analysis revealed the significant association of TLG with PFS at both baseline and interim PET/CT images; the interim SUV measurements showed significant results as well. However, due to a small sample size and having only six out of twenty patients with relapse, multivariate Cox-regression analysis was not performed, and we could not define the independent prognostic factors among these indices. However, the baseline TLG showed a relatively higher AUC, with higher sensitivity and specificity and higher significance level in the Log-rank test in comparison to the other parameters.

Conclusion

This study showed that the baseline TLG may be used as a predictor of relapse in patients with DLBCL. Baseline predictors such as TLG could be especially of value, since interim ^{18}F-FDG-PET scans for DLBCL patients are still limited, due in part to cost and availability of PET scans. However, the retrospective review of small patient population is a limitation of our study. The role of baseline TLG in prediction of relapse and its association with response to treatment needs to be confirmed in further prospective investigations with larger sample sizes and longer follow-up period.

Conflict of interest statement

None declared.

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