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Original article

BASELINE METABOLIC TUMOR VOLUME PREDICTS PROGRESSION IN DIFFUSE LARGE B-CELL LYMPHOMA

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Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), where a significant number of patients can relapse after receiving first-line immunotherapy. Baseline ^{18}F-FDG PET/CT provides quantitative metabolic parameters that may detect high-risk patients. This study evaluated the association of ^{18}F-FDG PET/CT parameters with progression-free survival (PFS) in patients with newly diagnosed DLBCL treated with first-line immunochemotherapy.

Materials and methods: This retrospective cohort study included 79 adult patients with newly diagnosed DLBCL who underwent baseline and end-of-treatment ^{18}F-FDG PET/CT. We used receiver operating characteristic analysis to determine study-specific cut-off values for baseline PET/CT parameters. PFS was evaluated using Kaplan–Meier analysis, the log-rank test, and univariable and multivariable Cox regression models.

Results: There was a statistically significant difference in PFS between patients with higher and lower values in the PET/CT parameters (tMTV, p=0.001; TLG, p=0.007; SUVmax, p=0.015). In univariable Cox regression, high tMTV (p=0.007), high TLG (p=0.029), high SUVmax (p=0.022), and advanced disease stage (p=0.02) were associated with shorter PFS. After adjustment for disease stage in separate multivariable models, high tMTV remained an independent predictor of shorter PFS (p=0.029), whereas TLG and SUVmax did not retain statistical significance.

Conclusion: Baseline tMTV was independently associated with PFS after adjustment for disease stage and may contribute to the prognostic assessment of patients with newly diagnosed DLBCL. Prospective studies involving larger cohorts and standardized tumor segmentation methods are needed to validate these findings.

Keywords: DLBCL; ^{18}F-FDG PET/CT; tMTV; progression-free survival

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of non-Hodgkin lymphoma (NHL) and accounts for approximately 20-50% of NHLs, depending on the population studied[1]. In these patients, treatment combines both chemotherapy and immunotherapy, using monoclonal anti-CD20 antibodies[2]. A considerable proportion of patients experience disease relapse or progression, mainly occurring in the first two years after diagnosis[3,4]. Patients with recurrence or progression of the disease generally have an unfavorable prognosis and require intensified treatment involving high-dose chemotherapy applied subsequently to the hematopoietic stem cell transplantation[5]. Lymphoma stage is another potential prognostic factor. Disease stage, together with other prognostic factors, forms the International Prognostic Index (IPI)[6] used for risk stratification to distinguish high-risk patients concerning disease relapse or progression. Stage I and II distinguish patients with lymphoma lesions limited to a certain body area, with advanced stage comprising III and IV. Since the introduction of anti-CD20 antibody therapy, there has been a need to determine other predictive factors, because IPI was established in patients treated with chemotherapy based solely on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)[7]. Early distinction of patients at risk is crucial to enable the undertaking of alternative therapeutic regimens.

^{18}FDG Positron Emission Tomography/computed tomography (^{18}FDG PET/CT) is the established method generally used for estimation of disease stage and for evaluation of treatment response in ^{18}FDG -avid lymphomas[8]. Moreover, in addition to qualitative assessment, PET/CT provides quantitative metabolic parameters that may offer prognostic information and serve a promising role in determining disease outcome after treatment with first-line immunochemotherapy. One of them is total metabolic tumor volume (tMTV). tMTV determines the volume of all metabolically active lesions involved during the course of the primary disease[9]. Another relevant indicator is total lesion glycolysis (TLG), determined as the summation of products of MTV for each lesion and mean standardized uptake value (SUVmean). Maximum standardize uptake value (SUVmax) of the most metabolic active lesion has also been investigated, even though its predictive role in DLBCL remains controversial. The aim of this study was to evaluate any correlation between the baseline PET/CT parameters, (tMTV, TLG, and SUVmax), and relapse or disease progression in patients with first-line R-CHOP (monoclonal antibody rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), and to assess whether these parameters provide prognostic information beyond conventional clinical factors.

Materials and methods

An observational retrospective cohort study was conducted in 79 patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL), referred for baseline ^{18}F-FDG PET/CT for disease staging. Patients were followed from May 2018 to March 2025, with the median follow-up of 44 months (range 7-88 months).

Inclusion and exclusion criteria

Inclusion criteria were: age ≥18 years, the presence of metabolically active lesions on baseline ^{18}F-FDG PET/CT, and receipt of first-line immunochemotherapy according to the R-CHOP protocol. Exclusion criteria were: age <18 years, a history of another malignant disease, absence of an end-of-treatment (EOT) ^{18}F-FDG PET/CT examination following completion of first-line immunochemotherapy, and absence of metabolically active lesions on the baseline PET/CT scan. Ethical approval for this study was obtained from the Human Research Ethics Committee at the Faculty of Medicine – Skopje, Ss. Cyril and Methodius University in Skopje (8th of April 2025, number of approval 0905-2181/84).

^{18}F-FDG PET/CT preparation and acquisition protocol

Patient preparation and PET/CT acquisition were performed in accordance with the European Association of Nuclear Medicine (EANM) guidelines. (10). Blood glucose levels measured on the day of the PET/CT examination were <11.1 mmol/L. Following the intravenous administration of ^{18}F-FDG, patients rested for approximately 60 minutes before imaging. PET/CT examinations were performed using a Biograph mCT scanner (Siemens Healthineers, Erlangen, Germany), with an acquisition range extending from the skull base to the upper third of the thigh.

Calculation of PET/CT imaging parameters

The PET/CT examinations were interpreted by a nuclear medicine specialist, who identified all sites of lymphoma involvement. Lesion segmentation was performed using a liver-based threshold defined as 1.5 × liver SUVmean + 2 standard deviations, with a minimum tumor volume of 1 mL. The segmented lesions were included in the calculation of tMTV and TLG. Detected lesions that were not considered to be related to the primary disease were manually excluded.

The metabolic tumor volumes of all lesions were summed using the Syngo.via software platform (Siemens Healthineers), resulting in tMTV values expressed in milliliters (mL). TLG was calculated as the sum of the products of MTV and SUVmean for each individual metabolically active lesion (MTV × SUVmean). In addition, SUVmax was determined for the lesion with the highest metabolic activity by placing a volume of interest (VOI) over the lesion.

Calculation of clinical parameters

Clinical prognostic parameters were also assessed. Patients were classified according to disease stage based on the Lugano criteria (11), IPI risk category, and performance status according to the Eastern Cooperative Oncology Group (ECOG) scale.

Statistical analysis

The Shapiro–Wilk test was used to assess the normality of data distribution. Spearman's rank correlation coefficient was used to evaluate associations between imaging-derived and clinical prognostic parameters. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values for tMTV, TLG, and SUVmax. The cut-off values were identified using the Youden index to maximize the combined sensitivity and specificity. Progression-free survival (PFS) curves and survival estimates were generated using the Kaplan-Meier method, and the groups of interest were compared using the log-rank test. PFS was defined as the time from diagnosis to disease relapse or progression. Univariate Cox-regression analysis was performed for each of the PET and clinical predictors. Those which achieved statistical significance in the univariate Cox-model, which was defined as a two-sided p-value <0.05, were entered in the multivariate Cox regression analysis to identify independent predictors. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

The median age of patients was 58 years (range 22-88); 47(62.0%) patients were men and 32(38.0%) were women. Thirty-four patients (43.0%) had early-stage disease (stage I-II), whereas 45(57.0%) had advanced-stage disease (stage III-IV). Most patients had an ECOG performance status of 0-1 (71 patients, 90.0%), while 8 patients (10.0%) had an ECOG performance status ≥2. The distribution of IPI scores was as follows: score 0 in 7 patients (8.9%), score 1 in 18(22.8%), score 2 in 27(34.2%), score 3 in 21(26.6%), and score 4 in 6 (7.6%) patients. During follow-up, 13(16.5%) patients experienced disease relapse or progression.

The median value for tMTV was 392.22 (range 1.03-6656.50), for TLG was 2628.06 (range 4.91-36984.95) and the median for SUVmax was 18.66 (range 5.21-60.92).

ROC analysis identified study-specific cut-off values aimed at distinguishing between the high- and low-value groups. According to the Youden index, the optimal cut-off values were as follows: 464.6 mL for tMTV (AUC 0.735; sensitivity 84.6%; specificity 33.3%), 2686.78 for TLG (AUC 0.723; sensitivity 84.6%; specificity 42.4%), and 17.22 for SUVmax (AUC 0.629; sensitivity 84.6%; specificity 45.5%) (Figure 1).

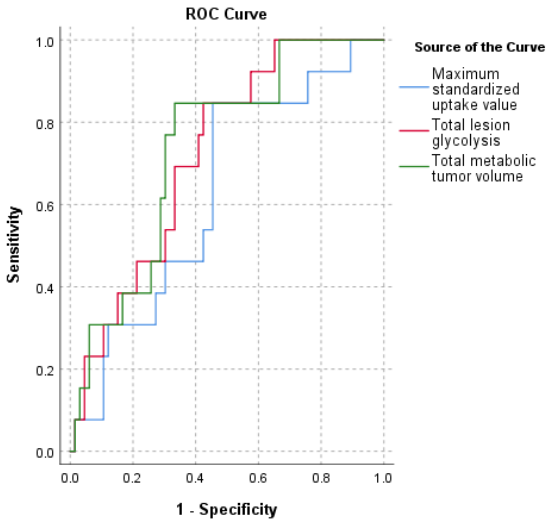

Fig. 1. ROC curves for baseline tMTV, TLG, and SUVmax in relation to PFS

The log-rank test demonstrated statistically significant differences in PFS between patients with high and low values of tMTV (p = 0.001), TLG (p = 0.007), and SUVmax (p = 0.015), with higher values associated with shorter PFS (Figure 2).

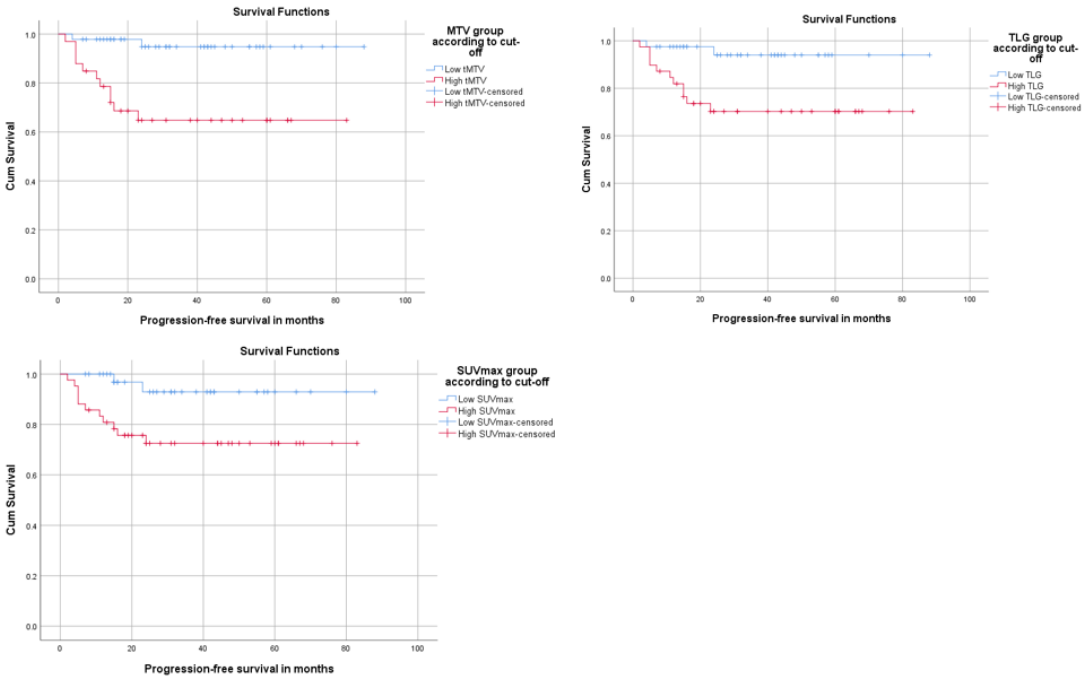

Fig. 2. Kaplan-Meier PFS curve of patients with high and low levels of tMTV, TLG and SUVmax

The association between the PET/CT parameters and patient survival was also assessed. Univariate Cox regression analysis demonstrated that high values of tMTV, TLG, and SUVmax were significantly associated with shorter PFS. Among the clinical parameters, only advanced disease stage was significantly associated with PFS (Table 1).

Table 1. Univariate Cox-regression analysis of the clinical and PET parameters for PFS

Variable	Hazard ratio (HR)	95% Confidence interval (CI)	p-value
tMTV≥464.6 mL	5.883	1.639-21.117	0.007
TLG≥2686.78	4.167	1.161-14.954	0.029
SUVmax≥17.22	5.775	1.292-25.808	0.022
Advanced stage	11.112	1.454-85.087	0.02
High-risk IPI	1.509	0.523-4.353	0.447
ECOG ≥ 2	0.608	0.079-4.647	0.631

Because advanced stage was the only clinical predictor with statistical significance ($p<0.05$), three separate multivariable Cox regression models were constructed, with each baseline PET/CT parameter entered separately together with advanced disease stage. In the model containing tMTV, both high tMTV and advanced stage remained independently associated with shorter PFS. TLG did not retain statistical significance after adjustment for disease stage. In the model containing SUVmax, SUVmax did not show an association with PFS, whereas advanced stage remained statistically significant (Table 2).

Table 2. Multivariable Cox-regression models of DLBCL patients for PFS

Model	Variable	Hazard ratio (HR)	95% Confidence interval (CI)	p-value
Model 1	tMTV ≥464.6 mL	4.210	1.157-15.316	0.029
	Advanced stage	8.011	1.028-62.410	0.047
Model 2	TLG ≥2686.78	2.914	0.803-10.572	0.104
	Advanced stage	8.704	1.119-67.718	0.047
Model 3	SUVmax ≥17.22	4.396	0.978-19.747	0.053
	Advanced stage	8.704	1.147-68.004	0.036

Discussion

This study evaluated the prognostic value of baseline ^{18}F-FDG PET/CT metabolic parameters in 79 patients with newly diagnosed DLBCL treated with first-line R-CHOP. All three evaluated metabolic markers-tMTV, TLG, and SUVmax-were associated with PFS in univariate analyses, tMTV remaining the most reliable predictor of disease progression.

tMTV is regarded as a measurement of the overall metabolic burden of the disease as compared to single lesion-based metrics like SUVmax. In this study, we found an optimal tMTV cut-off value of 464.6 ml, which was comparable to the 444 mL threshold reported by Hanzhen *et al*.,[12] and fell within the broad range of previously published thresholds[13-15].

The difference in PFS between patients in high- and low-tMTV groups was evident, supporting the hypothesis that patients with a high tumor volume at diagnosis are prone to an early relapse or progression. In comparison, although SUVmax and TLG were statistically significant in univariate analysis (with p=0.022 and p=0.029, respectively no higher statistical significance in multivariable Cox regression was kept. This aligns with findings from several studies claiming that SUVmax may not evaluate tumor load or heterogeneity effectively compared to volumetric measures[16,17].

The significant value of disease-specific stage at diagnosis along with tMTV has shown a predictive capability of independently determining the chances of disease progression or early relapse. However, in the multivariable model, advanced disease stage (HR=8.011) and high

tMTV (HR=4.210) remained significant predictors of the occurrence of an event, indicating poorer progression-free survival (PFS). These results confirm our hypotheses that additional metabolic assessment also plays a significant role as important as traditional staging on prediction models of patient outcome.

IPI, although considered the gold standard for risk stratification, was found insignificant at predicting outcome in the univariate analysis of the study. However, this finding should be interpreted cautiously considering the relatively small sample size and the limited number of patients with high IPI scores (only 7.6% of patients were high risk for event). Nonetheless, the present study further reinforces the notion that additional metabolic parameters may complement traditional staging, while also aiding distinction amongst high-risk patients with possible favorable initial staging.

The potential clinical relevance of baseline tMTV lies in its ability to identify patients with a high metabolic tumor burden at diagnosis, thus predicting PFS. It provides an opportunity to individualize treatment options and make treatment modalities even better. Patients with a "high metabolic burden" (tMTV ≥464.6 ml) might consequently receive upfront treatment, which could be more potent, and perhaps closer follow-up based on their metabolic status.
However, this study had some limitations, mainly including: a retrospective cohort study using a relatively small number of cases is considered inadequate representation, hindering the drawing of wide generalizations. The mean follow-up period of nearly 44 months in this study may have influenced the results. The ongoing lack of standardization in tMTV calculation (threshold of measurement either fixed or relative) is also worth consideration. Recently, Boellard *et al.,*[18] suggested a workflow method for segmentation of the lesions, using absolute threshold of SUV>4.0 in order to standardize tMTV measurements in lymphoma, allowing tMTV to be used as a reproducible biomarker. This method should be tested in future clinical trials.

Conclusion

Baseline tMTV is a strong and standalone predictor of PFS in newly defined DLBCL. With tMTV, the addition of prognostic data may provide crucial insight into the accurate grouping of high-risk patients with DLBCL, in connection with clinical disease stage at diagnosis. However, further prospective studies must be carried out to test these metabolic thresholds including larger groups of lymphoma patients, along with evaluation its utility in response-adapted therapeutic trials.

Conflict of interest statement. None declared.

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