To Determine the Prognostic Significance of 18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Scan-Derived Parameters (Total Lesion Glycolysis and Metabolic Tumor Volume) in Patients of Diffuse Large B-Cell Lymphoma with Only Nodal Involvement

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Abstract

Objective: The aim of this study is to evaluate the prognostic significance of 18-fluorodeoxyglucose (^{18}FDG) positron emission tomography/computed tomography (PET-CT) scan-derived total metabolic tumor volume (MTV) and total lesion glycolysis (TLG) in diffuse large B-cell lymphoma (DLBCL) patients with only nodal involvement. **Methods:** Twenty-five (age range: 22–82 years) biopsy-proven patients of DLBCL with only nodal involvement who underwent staging ^{18}FDG PET-CT scan were included in this study. Whole-body PET-CT performed at staging and PET-derived metabolic parameters, namely MTV and TLG of all FDG-avid lesions, were calculated for each patient. Total MTV was computed by summing the volumes of all FDG-avid lesions, the volume of each being calculated at threshold of 42% of the maximum standardized uptake value (SUV) using a semi-automatic software. TLG was calculated by summing the product of volume and SUVmean of each lesion. Patients were followed up to a period of 5 years and data obtained were divided into two groups, with recurrence and without recurrence. **Results:** Six patients developed recurrence on follow-up and 19 patients remained disease free on follow-up. The area under a curve (AUC) for MTV was 0.825 and for TLG was 0.623 suggesting MTV to be a good prognostic indicator and TLG poor indicator for predicting recurrence in these patients. In pairwise comparison of both the receiver operator characteristics, it was found that the difference between the AUCs of MTV and TLG was statistically significant ($P = 0.0349$). Thus, indicating MTV is a statistically better indicator than TLG. **Conclusion:** MTV is a better prognostic indicator than TLG in DLBCL patients.

Keywords: *Diffuse large B-cell lymphoma, metabolic tumor volume, non-Hodgkin lymphoma, positron emission tomography/computed tomography scan, total lesion glycolysis*

Introduction

Lymphomas are a heterogeneous group of disorders involving the lymphatic system, which occurs due to malignant transformation of the B-cell and T-cell lymphocytes. Non-Hodgkin lymphoma (NHL) accounts for 85% cases of lymphomas, in which the most common type is diffuse large B-cell lymphoma (DLBCL), accounting for about 30% of all lymphomas.

The treatment and prognosis of NHL depend on accurate determination of the tumor burden at the time of staging. The usual prognostic criteria used in lymphoma are international prognostic index (IPI), follicular lymphoma international prognostic score and mantle cell lymphoma IPI.

The IPI is the primary clinical tool used to predict prognosis for patients with NHL based on the number of negative prognostic factors at the time of diagnosis. However, due to the higher heterogeneity and hematogeneous pattern of spread seen in NHL relative to contiguous lymphatic spread with HL, the IPI score can be low and tumor burden can be high. Hence, metabolic imaging technique 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) scan-derived parameters have been studied

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as a prognostic tool in NHL and PET-CT have become an important investigation in clinical decisions on therapeutic strategies for treating aggressive NHL, including DLBCL.

FDG PET-CT scan-derived parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are at present being evaluated for determining tumor characteristics such as the metabolic burden of the disease and glycolytic activity to evaluate the prognosis of the patient. Thus, the purpose of this study is to assess the utility of these quantitative indices derived on the pretreatment staging FDG PET/computed tomography (CT) scan, for the prognosis of the patient. Since extranodal involvement leads to poor prognosis, patients with only nodal involvement were included in this study.

Methods

The study included 25 (age range: 22–82 years) biopsy-proven patients of DLBCL with only nodal involvement who underwent staging F18-FDG PET-CT scan. Since DLBCL patients with only nodal involvement were included in this study, if bone marrow biopsy was positive for disease involvement then the patient was excluded from the study. Standard whole-body ^{18}FDG PET/CT was performed using the GE Discovery STE PET-CT system. Fasting for at least 6 h was required before the examination, and the blood glucose level was measured immediately before the administration of ^{18}F-FDG, requiring levels <150 mg/dL. Approximately ~5.55 Mbq/Kg of ^{18}F-FDG was administered intravenously, and the patients rested in a quiet, dark environment for approximately 60 min before scanning. After initial low-dose CT, emission images were obtained from the top of the skull to the middle of the thigh, with acquisition times of 2 min per bed position in the three-dimensional mode. PET images were reconstructed iteratively with CT-based attenuation correction. During follow-up scans, the time between injection and scan and injected activity was kept approximately the same.

Whole-body PET-CT performed at staging and PET-derived metabolic parameters, namely MTV and TLG of all FDG-avid lesions were calculated for each patient. Mean standardized uptake value (SUVmean), normalized to patient body weight, were recorded using a three-dimensional tool placed over sites of nonphysiological FDG uptake. As DLBCL is high FDG-avid disease; thus, SUV cutoff of 2.5 was used to define disease involvement, apart from CT-based characteristics taken into consideration. Metabolic tumor volume of all positive lesions was calculated with maximum (SUVmax) threshold of 42% as the contouring border and all lesions. MTV was added to calculate the total metabolic tumor volume in the baseline PET-CT scan. TLG was calculated by summing the product of volume and SUVmean of each lesion. Patients were followed up to a period of 5 years and data obtained were divided into two groups, with recurrence and without recurrence. Disease recurrence was defined as the appearance of the new lesion on follow-up PET-CT or CT scan and biopsy of the lesion positive for recurrence.

Data analysis

All patients were followed up to 5 years and were evaluated for disease-free status or disease recurrence. Subsequently, high metabolic tumor volume and high TLG correlation with recurrence or no disease recurrence were derived. Disease-free status was considered good prognostic indicator. Statistical analysis was performed using Medcalc 15.8 software. Receiver operator characteristic curve (ROC) [Figure 1] was used to determine the area under the curve for MTV and TLG. Pairwise comparison of both the ROC curve was made, with $P < 0.05$ being considered statistically significant.

Results

A total of 25 patients were included in this study, all treated with chemotherapy were followed up, up to 5 years to evaluate disease-free status or recurrence. Of 25 patients, six patients had recurrence during follow-up, 19 patients remained disease-free during the period of follow-up.

Of 25 patients, 11 patients were female and 14 patients were male. The mean age at diagnosis was 47.5 years (range 22 years to 82 years). Patients were followed up to the period of 5 years postchemotherapy. On analysis, the total metabolic tumor volume mean in recurrence group [Figure 2] (6/24, 24% of patients) was 385.6 ± 420.9 (mean ± standard deviation) ranging from 193.4 to 1326.91 and TLG mean was 2521.2 ± 1432 (mean ± standard deviation) ranging from 1463.1 to 5672.8. In other group, that is patients without recurrence [Figure 3] on follow-up (19/25, 76% of patients) the total metabolic tumor volume mean was 136. 7 ± 144.49 (mean ± standard deviation) ranging from 13.12 to 566.8 and TLG mean was 2400 ± 3147.05 (mean ± standard deviation) ranging from 16.41 to 13629.8 [Table 1].

ROC curve was used to determine the area under the curve for MTV and TLG. Pairwise comparison of both the ROC curve was made, with $P < 0.05$ being considered statistically significant. The estimated area under the ROC curve (AUC) for MTV was 0.825 and for TLG was

Table 1: Metabolic tumor volume mean and total lesion glycolysis mean in 25 patients

	Recurrence group (6/25; 24%)	No recurrence group (19/25; 76%)
MTVmean (range)	385.6±420.9 (193.4-1326.91)	136.7±144.49 (13.12-566.8)
TLGmean (range)	2521.2±1432 (1463.1-5672.8)	2400±3147.05 (16.41-13629.8)

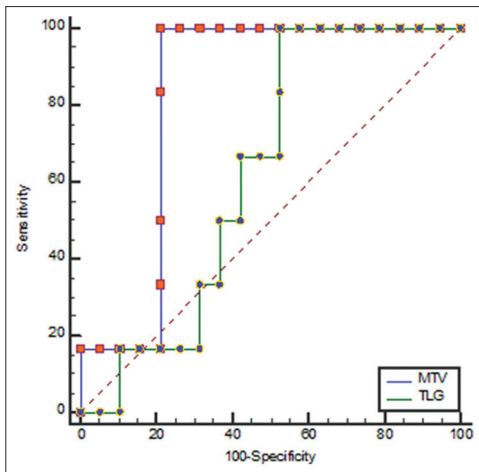MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

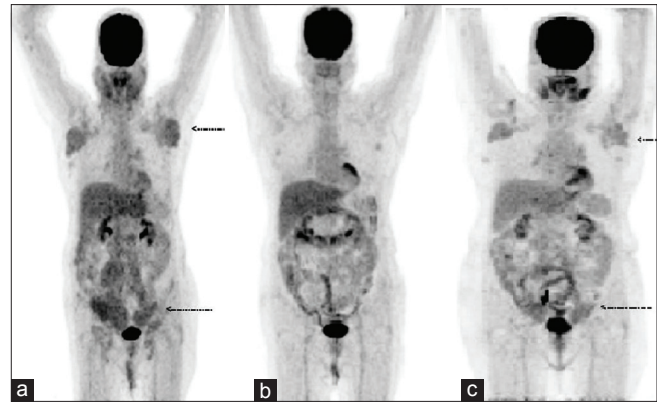Figure 1: Receiver operating characteristic curve

Figure 2: Maximum intensity projection image (a) of positron emission tomography/computed tomography scan at staging demonstrating multiple supra and infradiaphragmatic nodes with total metabolic tumor volume = 1326.8 and total lesion glycolysis = 2342.5. Maximum intensity projection image (b) of posttreatment positron emission tomography/computed tomography scan with the complete metabolic response. Maximum intensity projection image (c) of positron emission tomography/computed tomography scan after 18 months suggestive of recurrence

0.623 suggesting MTV to be a good prognostic indicator and TLG poor indicator for predicting recurrence in these patients. In pairwise comparison of both the ROC curves, it was found that the difference between the AUCs of MTV and TLG was statistically significant ($P = 0.0349$). Thus, indicating that MTV is a statistically better indicator than TLG in predicting prognosis of patients of DLBCL with only nodal involvement.

Discussion

DLBCL is an aggressive NHL with heterogeneous clinical outcomes following treatment with standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). DLBCL is the most common subtype of NHL accounting for approximately 30%–50% of cases.[1] Most relapses occur within the first 2 years, but 10% of all recurrence are seen after 5 years of treatment.[2] The IPI is used for prognostic purposes[3] thus the clinical prognostication of DLBCL relies on IPI and now on its improvised variants, R-IPI, and NCCN-IPI.[4]

However, due to the high heterogeneity of this disease, the IPI system has functional limitations in predicting prognosis for all patients, and there is a need for more accurate prognostic markers. Risk stratification by the cell of origin, double hit, double expressor, and genomic prognostic factors have been developed[5] but have not been adopted broadly in clinical medicine, and these are static factors, recognized at diagnosis that do not take into account the changes that can occur influenced by the management.

The presence of translocations of both c-myc and bcl-2 characterizes double-hit lymphoma (5% of DLBCLs). Patients with high expression of c-myc and bcl-2 by immunohistochemistry constitute a much larger group (29%) who also have a poor prognosis, independently of the IPI score and cell-of-origin subtype.[6] Based on higher sensitivity compared with CT imaging PET-CT scanning is recommended for routine staging and response

assessment of DLBCL. The introduction of PET has resulted in a more accurate assessment of response and can distinguish the persistent disease from residual scar tissue.[7] The semiquantitative parameters of PET-CT scan are SUVmax, SUVmean, MTV, and TLG.

SUV can be based on body weight, lean body mass, and body surface area. It is commonly affected by various technical and patient-dependent factors (time [after injection] dependent– plasma glucose dependent – Bodyweight, BSA, scanning acquisition parameters and PET-scanner). It is a semi-quantitative index of FDG metabolic rate without accounting of total tumor volume, lacks information about tumor burden. The SUVmax reflects the metabolic activity of the most aggressive cells.

MTV is the measure of metabolically active tumor volume of tissues with increased FDG uptake and it is a novel index in FDG-PET. TLG combines the volumetric and metabolic information of FDG PET.

In this study, we studied the prognostic significance of PET-CT-based parameters MTV and TLG in DLBCL patients with only nodal involvement. Of 25 patients, six patients had recurrence on follow-up and 19 patients remained disease free. Of six patients with recurrence, 4 had both supra- and infradiaphragmatic lymph nodes and two patients had lymph nodes on the same side of the diaphragm. Of 19 patients, who remained disease-free, 12 patients had lymph nodes on the same side of the diaphragm and seven patients had both supra- and infradiaphragmatic lymph nodes. ROC curve analysis showed MTV to be a good prognostic indicator and TLG poor indicator for predicting recurrence in these patients. Total metabolic tumor volume takes into account viable fraction of tumor cells. It estimates tumor burden better than anatomical imaging. TLG was not a good prognostic
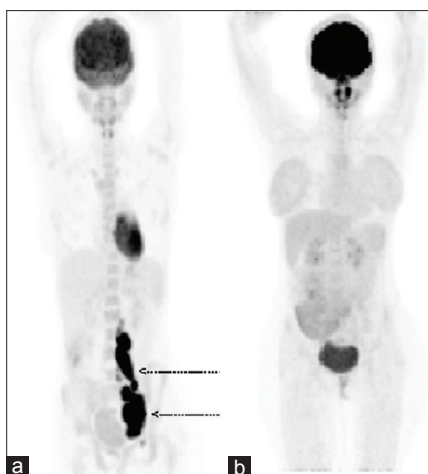
Figure 3: Maximum intensity projection image (a) of positron emission tomography/computed tomography scan at staging demonstrating multiple infradiaphragmatic nodes with total metabolic tumor volume = 108.3 and total lesion glycolysis = 2171.3. Maximum intensity projection image (b) of positron emission tomography/computed tomography scan at 4-year follow-up, showing the absence of fluorodeoxyglucose-avid visible disease

parameter in our study. Since it a product of MTV and SUVmean and many physiological and technical factors affect the computation of SUV. MTV is not dependent on these factors as is calculated from a percentage of maximal uptake.

There are various previous studies that are congruent with ours. A study concluded that baseline metabolic tumor volume is an important prognostic factor in DLBCL treated with RCHOP chemotherapy.[8] Song *et al.* concluded that low MTV group (<220 cm^3) had longer progression-free survival (PFS) and overall survival (OS) compared with the high MTV group (≥220 cm^3). They studied patients without extranodal involvement, which is the same as ours.[9] In another study, by Kim *et al.*, the higher MTV group showed significantly inferior EFS compared with the lower MTV group.[10] Song *et al.* results suggested that MTV is very important and potential prognostic factor compared with SUVmax for predicting the survival of primary GI DLBCL patients with localized lymph node involvement.[11] Two studies by Sasanelli *et al.* showed that MTV is a better prognostic indicator in DLBCL patients and baseline TLG has no prognostic value, which is congruent with our study.[12,13]

Few studies concluded that baseline TLG is the predictor for PFS and OS in DLBCL patients.[14] However, since this study had patients with extranodal disease also, thus the group of patients analyzed is different than ours. Various other studies have also shown that baseline MTV is a strong predictor of prognosis in DLBCL patients, as seen in this study.[15-17] Thus, we can conclude that baseline MTV is a good prognostic factor in DLBCL patients with only nodal involvement. We need to study with a larger number of patients to decide a cutoff of baseline MTV for prognostication of these patients.

Conclusion

In our study of DLBCL patients, MTV was found to be a good prognostic indicator while TLG a poor indicator in predicting recurrence.

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Conflicts of interest

There are no conflicts of interest.

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