CANCER RESEARCH AND TREATMENT (CRT)

Original Article

Prognostic Value of Baseline and Interim Total Metabolic Tumour Volume and Total Lesion Glycolysis Measured on ^{18}F-FDG PET/CT in Patients with Follicular Lymphoma

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Running title: Prognostic Value of TMTV and TLG in FL

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Abstract

Purpose

The purpose of this study was to investigate the prognostic significance of total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG) in patients with follicular lymphoma (FL) at baseline and mid-treatment with ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) scans.

Methods

The study analyzed data from 48 patients with FL who were treated in Jiangsu Province Hospital and reviewed their baseline PET-CT scans. TMTV and TLG were computed by using the absolute value of 2.0, 2.5, and 3.0 thresholding method respectively.

Results

Median age was 53 years, 75.0% of patients had stage III to IV disease, 43.8% had a Follicular Lymphoma International Prognostic Index 1 (FLIPI1) score of 3 to 5 and 20.8% had a FLIPI2 score of 3 to 5. Receiver operating characteristic (ROC) curve analysis showed the optimal cut-off values for TMTV3.0 and TLG3.0 were 476.4 (sensitivity 85.7%; specificity 78.0%; area under the curve [AUC] 0.760; p=0.003) and 2676.9 (sensitivity 71.4%; specificity 78.0%; AUC 0.760; p=0.003). On multivariable analysis, TMTV3.0 and TLG3.0 were independent predictors of both progression-free survival (PFS) (hazard ratio [HR], 5.406; 95% confidence interval [CI], 1.326 to 22.040; p=0.019 and HR, 6.502; 95% CI, 1.079 to 39.182; p=0.042) and overall survival (OS) (HR, 4.111; 95% CI, 1.125 to 15.027; p=0.033 and HR, 5.885; 95% CI, 1.014 to 34.148; p=0.049). ROC curve analysis showed the optimal cut-off values for ΔTMTV3.0 and ΔTLG3.0 were 66.3% (sensitivity, 85.7%; specificity, 63.4%; AUC, 0.774; p<0.001) and 64.5% (sensitivity, 85.7%; specificity, 65.9%; AUC, 0.777; p<0.001).

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Conclusion

Baseline TMTV and TLG are strong predictors of PFS and OS in FL. Furthermore, interim TMTV (ΔTMTV > 66.3%) and TLG (ΔTLG > 64.5%) reduction are valuable tools for early treatment response assessment in FL patients.

Key words Follicular lymphoma, Prognosis, Total metabolic tumor volume, Total lesion glycolysis, The maximum of standard uptake value

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Introduction

Follicular lymphoma (FL) is the second most common lymphoma subtype in Europe and United States and the third most frequent non-Hodgkin's lymphoma (NHL) subtype after diffuse large B-cell lymphoma (DLBCL) and extranodal NK/T cell lymphoma (ENKTCL) in Aisa [1-5]. Although the using of rituximab combined with chemotherapy improves outcome of patients with FL, 20% of patients treated with immunochemotherapy still have disease progression within short time and 50% of them would die within 5 years [6-8]. The Follicular Lymphoma International Prognostic Index (FLIPI1 and FLIPI2) [9,10] and conventional computed tomography (CT) cannot identify them easily and quickly. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography computed tomography scan (PET-CT) not only showed the anatomic location of the lesion but also reflected the level of metabolism. It made the staging, evaluating response and surveillance more accurate. Furthermore, the prognostic value of PET-CT parameter of maximum standardized uptake value (SUV_{max}) has been validated in DLBCL and Hodgkin's lymphoma (HL) [11,12].

Recently studies have shown that total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG) may be useful quantitative parameters for the assessment of treatment response in HL, DLBCL, ENKTL, and peripheral T cell lymphoma (PTCL) [13-19]. Furthermore, date form Meignan et al. [20] also shown that baseline TMTV has strong independent predictive value for high-tumor-burden FL patients. However, the prognostic value of baseline TMTV and TLG using different absolute value thresholding method has not validated in patients form other cohort such as in Asian population and the prognostic value of interim TMTV and TLG has not yet been established in FL patients.

In this study, we attempted to determine whether PET parameters (TMTV and TLG) measured on pretreatment and interim PET-CT using the absolute value of 2.0, 2.5, and 3.0 thresholding method respectively, can predict prognosis in patients with FL in Asia.

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Materials and Methods

1. Subjects

Between August, 2009 and June, 2016, 48 consecutive subjects with newly-diagnosed FL had a pretreatment ^{18}F-FDG PET-CT scan at our centre. Diagnosis was based on the World Health Organization lymphoma classification [20, 21]. Among these 48 patients, there are twenty-two patients had a FDG PET-CT scan for response assessment after 3-4 cycles of treatments. The scores of FLIPI1 and FLIPI2 and the times of progression-free survival (PFS) and overall survival (OS) were calculated according to revised response criteria for malignant lymphoma [22]. Treatment options were recommended according to National Comprehensive Cancer Network (NCCN).

2. ^{18}F-FDG PET-CT image acquisition

PET-CT studies were obtained on the following PET/CT devices: Gemini TF64 (Philips, Netherlands), Gemini GXL (Philips), Gemini TF16 (Philips), Discovery LS (GE Healthcare, USA), and Biograph TP16 (Siemens, Germany). Subjects with fasting serum glucose <7.0 mmol/L received 18F-FDG 3.70-5.55 MBq/kg intravenously for >6 hours. After 60-minute whole-body PET-CT imaging was performed with a whole-body CT scan (120 KV and 140 mA) and a whole-body PET (in 3-dimensional mode, 120s/bed position). Acquisition of CT, PET, and PET-CT fusion images including cross-section, sagittal-section and coronal-section used CT-based attenuation correction in reconstruction image by an iterative method.

3. Image analysis and calculation of TMTV and TLG

All scans were re-examined by two experienced radiologists who were unaware of both clinical and radiological findings of FL. Lesion sites were determined according to visual

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assessment with PET images scaled to color table and a fixed SUV by two experienced nuclear medicine physicians [24]. The workstation automatically calculated SUV_{max} with drawing the region of interest (ROI) along the edge of the enrichment spot. The absolute value of 2.0, 2.5, and 3.0 threshold methods were used for the metabolic tumor volume (MTV_L)/glycolysis of any local lesion (LG_L) computations through the MEDEX software. They were recorded as $MTV_L2.0/LG_L2.0$, $MTV_L2.5/LG_L2.5$, and $MTV_L3.0/LG_L3.0$, respectively. TMTV2.0/TLG2.0, TMTV2.5/TLG2.5, and TMTV3.0/TLG3.0 were obtained by summing $MTV_L2.0/LG_L2.0$, $MTV_L2.5$ /$LG_L2.5$, and $MTV_L3.0$ /$LG_L3.0$ of all local lesions respectively. Bone marrow (BM) and spleen with diffuse uptake were generally excluded in the lesions unless there was focal uptake. Spleen was also considered as involved if there was diffuse uptake increased more than 150% of the liver background.

For interim scans, we recorded the changes in TMTV and TLG, which were defined as ΔTMTV3.0 and ΔTLG3.0. and ΔTMTV3.0 and ΔTLG3.0 were calculated as

$$\Delta\text{TMTV3.0}=\frac{\text{TMTV3.0 at pretreatment-TMTV3.0 at mid-treatment}}{\text{TMTV3.0 at pretreatment}}$$

$$\Delta\text{TLG3.0}=\frac{\text{TLG3.0 at pretreatment-TLG3.0 at mid-treatment}}{\text{TLG3.0 at pretreatment}}$$

4. Statistical analysis

We used the Epidata 3.10 to establish datasets and verify validity of data-entry twice. The discriminative ability of the PET-CT parameters (SUV_{max}, TMTV, and TLG) was determined according to the time-dependent receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) were calculated to assess the predictive accuracy of the model [25]. The difference of AUCs was tested by a non-parametric approach developed by DeLong et al. [26]. Survival curves were constructed by the Kaplan-Meier

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method. Log-rank test was used to compare survival time of different groups categorized by the selected best predictive model. Prognostic significances of PET parameter and clinical variables were assessed by univariate analyses. Variables with significant associations were included in multivariate Cox proportional hazards regression analyses. All the statistical analyses used STATA statistical software (ver. 11.1, StataCorp, College Station, TX) and R software (ver. 3.2.1, The R Foundation for Statistical Computing, Vienna, Austria). Two-sided $p \leq 0.05$ was considered significant.

5. Ethical statement

The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University and done according to the guidelines of Nanjing Medical University. Subjects provided informed consent in accordance with requirements of the Declaration of Helsinki. Subjects provided informed consent in accordance with requirements of the Declaration of Helsinki.

Results

1. Clinical variables

Clinical variables are outlined in Table 1. Thirty-seven subjects were male. Median age was 53 years (range, 30 to 83 years). Thirty-six (75.0%) were Ann Arbor stage III/IV and 31 subjects were grade 1-2. There were 23 patients with BM involvements. Twenty-one patients (43.8%) were estimated as FLIPI1 score of 3-5 while 10 patients (20.8%) were FLIPI2 score of 3-5. Three patients received radiotherapy only, five patients didn’t receive treatment due to no indications, 38 patients received immunochemotherapy with rituximab, cyclophosphamide,

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epirubicin, vindesine and prednisone (R-CHOP), two patients received rituximab alone. Median follow-up is 35 months (range, 16 to 98 months).

2. Comparison of the SUV_{max}, TMTV, and TLG at staging

Median value of baseline SUV_{max}, TMTV2.0, TMTV2.5, TMTV3.0, TLG2.0, TLG2.5, and TLG3.0 were shown in Table 2. We evaluated the predictive accuracy of these models in time-dependent ROC curves which showed optimal cut-off values for SUVmax, TMTV2.0, TMTV2.5, TMTV3.0, TLG2.0, TLG2.5, and TLG3.0 of 7.0 (sensitivity, 85.7%; specificity, 46.3%; AUC, 0.650; p=0.141), 505.5 (sensitivity, 85.7%; specificity, 63.4%; AUC, 0.774; $p < 0.001$), 391.2 (sensitivity, 85.7%; specificity, 65.9%; AUC, 0.777; $p < 0.001$), 476.4 (sensitivity, 85.7%; specificity, 78.0%; AUC, 0.760; p=0.003), 3,259.7 (sensitivity, 71.4%; specificity, 75.6%; AUC, 0.763; p=0.002), 3,080.0 (sensitivity, 71.4%; specificity, 78.0%; AUC, 0.770; p=0.001), and 2,676.9 (sensitivity, 71.4%; specificity, 78.0%; AUC, 0.760; p=0.003).

Pair-wise comparisons of ROC curves in the models are also conducted. There were no significant differences among TMTV2.0, 2.5, and 3.0 ($p > 0.05$) and also no significant differences were observed among TLG 2.0, 2.5, and 3.0 ($p > 0.05$). Taking sensitivity, specificity and AUC into consideration, we selected TMTV3.0 and TLG3.0 for further analyses. Kaplan-Meier PFS and OS cures for the TMTV3.0 (476.4) and TLG3.0 (2,676.9) using the optimal cut-off value are shown in Fig. 1.

3. Prognostic impact of baseline TMTV3.0 and TLG3.0

By univariate analysis (Table 3), we found that BM involvement, FLIPI2 score of 3-5, TLG3.0 > 2,676.9 and TMTV3.0 > 476.4 were both significantly associated with inferior PFS and OS in our cohort. Furthermore, we found that the two PET-CT parameters of TLG3.0 >

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2,676.9 and TMTV3.0 > 476.4 were significantly related to each other (r=0.952, p < 0.001). Therefore, the two PET-CT parameters were entered into multivariate analysis with other clinical variables respectively (Table 4). And we found that both TLG3.0 > 2,676.9 and TMTV3.0 > 476.4 were significantly related to PFS (hazard ratio [HR], 6.502; 95% confidence interval [CI]; 1.079 to 39.182; p=0.042 and HR, 5.406; 95% CI, 1.326 to 22.040; p=0.019) and OS (HR, 5.885; 95% CI, 1.014 to 34.148; p=0.049 and HR, 4.111; 95% CI, 1.125 to 15.027; p=0.033).

To further analyse the prognosis of TMTV3.0 combined with conventional prognosis indices of FLIPI2, patients can divide into four subgroup: (1) FLIPI2 0-2 and TMTV3.0 < 476.4 group: 25 patients (53.1%); (2) FLIPI2 0-2 and TMTV3.0 > 476.4 group: nine patients (18.7%); (3) FLIPI2 3-5 and TMTV3.0 < 476.4 group: eight patients (16.7%); (4) FLIPI2 3-5 and TMTV3.0 > 476.4 group: six patients (12.5%) (S1 Table). We found that patients with both FLIPI2 0-2 and TMTV3.0<476.4 has the superior PFS (p < 0.001) and OS (p=0.010) then other three groups while no significant differences of PFS and OS were observed among the other three groups (Fig. 2).

4. Prognostic impact of interim TMTV3.0 and TLG3.0

Twenty-two patients underwent FDG PET-CT scans after 3-4 cycles of immunochemotherapy. The changes between baseline parameter and interim PET-CT parameters (defined as ΔTMTV3.0 and ΔTLG3.0) of every patient were calculated. We evaluated the predictive accuracy of ΔTMTV3.0 and ΔTLG3.0 in time-dependent ROC curves which showed optimal cut-off values for ΔTMTV3.0 and ΔTLG3.0 of 66.3% (sensitivity, 85.7%; specificity, 63.4%; AUC, 0.774; p < 0.001) and 64.5% (sensitivity, 85.7%; specificity, 65.9%; AUC, 0.777; p < 0.001). Kaplan-Meier PFS and OS cures for the

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ΔTMTV3.0 (66.3%) and ΔTLG3.0 (64.5%) using the optimal cut-off value are shown in Fig. 3.

Among the 24 patients with interim PET-CT scan, we found that patients (n=10) with baseline TMTV3.0 < 476.4 and FLIPI2 0-2 were all with ΔTMTV3.0 > 66.3% while there were only 6 patients with ΔTMTV3.0 > 66.3% out of the 14 patients with either TMTV3.0 > 476.4 or FLIPI2 3-5 (S2 Table). Furthermore, for these patients with either TMTV3.0 > 476.4 or FLIPI2 3-5, patients with ΔTMTV3.0 > 66.3% had superior PFS and OS (Fig. 4).

Discussion

The prognostic value of PET-CT parameters (SUV_{max}, TMTV, and TLG) has been investigated in different various subtypes of lymphoma, such as HL, DLBCL, and ENKTL [12-17,24,27]. Recently, a pooled analysis of 185 patients with high-tumor-burden FL reported that baseline TMTV was independent predictor of PFS. It could identify patients with high risk of early progression and help to guide clinicians to adjust treatments [20]. In the present study, we also investigated the prognostic value of TMTV and TLG at pretreatment and mid-treatment using different absolute threshold in our cohort. We found that both baseline TMTV3.0 and TLG3.0 were independent risk factors of PFS and OS for patients with FL. Furthermore, patients with ΔTMTV3.0 > 66.3% and ΔTLG3.0>64.5% have superior PFS and OS for the 24 patients whose interim PET-CT scans were available.

Similar to the report by Meignan et al. [20], we also found that not only baseline TMTV3.0, but also TLG3.0 which were not evaluated in other study, were independent risk factors for FL patients. Further analysis showed that the PET-CT parameter of TMTV3.0 can add the risk-stratification capacity of FLIPI2. For patients with FLIPI 0-2, there were nearly 20% patients with higher TMTV3.0. Actually, these patients might have inferior survivals

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instead of superior survivals if according to the risk-stratification of FLIPI2 only. Therefore, from our data, we can conclude that patients with any one of the two risk factors (FLIPI2 3-5 or TMTV3.0 > 476.4) had inferior survivals.

In some cases, TMTV was measured by applying a fixed 41% SUV_{max} threshold to every lymphoma lesion [14, 20]. Considering the SUV_{max} of inert lymphomas generally is smaller, it is easy to include some reactive lymph nodes and/or some inflammatory lesions into tumor lesions by 41% SUV_{max} threshold. In this paper TMTV and TLG are computed using absolute values (2.0, 2.5, and 3.0) as the threshold [28, 29]. Actually, ROC curves showed that there were no differences among the three absolute values for TMTV and TLG. Larger cohorts should be included to compare the prognostic value of TMTV and TLG in different absolute threshold.

Furthermore, the prognostic value of MTV and TLG at mid-treatment was first to be evaluated in the present study. We found that ΔTMTV3.0 using a cut-off of 66.3% and ΔTLG3.0 using a cut-off of 64.5% had predictive value in predicting outcome after 4 cycles of therapy in FL patients. That is to say patients who were with higher TMTV3.0 and TLG3.0 at baseline can also achieve superior outcomes if ΔTMTV3.0 > 66.3% and ΔTLG3.0 > 64.5% after four cycles of immunechemotherapy. Therefore, more intensive immunechemotherapy might be considered for these patients in our clinical practice. Because our patients who were available for PET-CT assessment at mid-treatment were small, our conclusion should be tested in other datesets.

In conclusion, baseline TMTV and TLG are independent predictors of PFS and OS for patients with FL. Also, mid-treatment TMTV and TLG are valuable tools for early treatment response assessment in FL patients. Further larger prospective studies are worth performing to validate our conclusions.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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Table 1. Baseline characteristics of the 48 FL patients

Characteristic	No. (%)
Age, median (range, yr)	53 (30-83)
Age > 60 yr	17 (35.4)
Male sex	28 (58.3)
Ann Arbor stage: III-IV	36 (75.0)
FLIPI1 score: 3-5	21 (43.8)
FLIPI2 score: 3-5	10 (20.8)
Follicular grade: I-II	31 (64.6)
BM involvement	23 (47.9)
Treatment regimen	
Radiotherapy	3 (6.3)
Rituximab	2 (4.2)
Observe	5 (10.4)
R-CHOP	38 (79.2)

FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; BM, bone marrow.

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Table 2. Quantity and optimal cut-off value for OS of PET-CT parameters of PET-CT of 48 patients with FL

Variable	Quantity, median (range)	Optimal cut-off value for OS	AUC	Sensitivity (%)	Specificity (%)	p-value
SUV_{max}	8.4 (0-24.3)	7.9	0.650	85.7	46.3	0.141
TMTV 2.0	245.2 (0-3,399.2)	505.5	0.774	85.7	63.4	<0.001
TMTV2.5	178.3 (0-2,864.2)	391.2	0.777	85.7	65.9	<0.001
TMTV3.0	114.3 (0-2,454.3)	476.4	0.760	85.7	78.0	0.003
TLG 2.0	893.1 (0-14,378.9)	3,259.7	0.763	71.4	75.6	0.002
TLG2.5	672.6 (0-13,173.1)	3,080.0	0.770	71.4	78.0	0.001
TLG3.0	594.4 (0-12,056.6)	2,676.9	0.760	71.4	78.0	0.003

OS, overall survival; PET-CT, positron emission tomography computed tomography; FL, follicular lymphoma; AUC, area under the curve; SUV_{max}, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

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Table 3. Univariate analysis for PFS and OS

Variable	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
Male sex	1.093	0.247-4.846	0.906	1.636	0.496-5.404	0.421
Age > 60 yr	0.780	0.152-3.993	0.767	0.971	0.294-3.201	0.961
BM involvement	7.367	1.661-32.671	**0.030**	4.278	1.355-13.503	**0.017**
FLIPI 3-5	3.112	0.701-13.816	0.152	2.779	0.0883-8.749	0.081
FLIP2 3-5	4.878	1.047-22.720	**0.045**	4.756	1.233-18.343	**0.003**
SUV_{max} > 8.1	3.870	0.471-31.811	0.210	7.632	0.994-58.601	0.052
TLG3.0 > 2,676.9	9.322	1.768-49.135	**0.009**	6.445	1.941-21.397	**0.003**
TMTV3.0 > 476.4	8.723	1.645-46.277	**0.011**	5.777	1.731-19.281	**0.005**
R-CHOP regimen	0.669	0.080-5.604	0.711	0.320	0.041-2.481	0.275

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; FLIPI, Follicular Lymphoma International Prognostic Index; SUV_{max}, maximum standardized uptake value; TLG, total lesion glycolysis ; TMTV, total metabolic tumor volume.

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Table 4. Multivariate analysis of TLG and TMTV after adjusting for FLIPI score

Variable	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
TLG						
BM involvement	4.497	0.516-39.184	0.176	3.698	0.408-33.549	0.247
FLIP2 3-5	5.342	1.000-28.553	0.051	5.557	1.038-29.747	0.046
TLG3.0 > 2,676.9	5.885	1.014-34.148	0.049	6.502	1.079-39.182	0.042
TMTV						
BM involvement	2.608	0.673-10.109	0.168	1.941	0.456-8.266	0.372
FLIP2 3-5	4.643	1.390-15.503	0.013	5.221	1.531-17.803	0.010
TMTV3.0 > 476.4	4.111	1.125-15.027	0.033	5.406	1.326-22.040	0.019

TLG, total lesion glycolysis; TMTV, total metabolic tumor volume; FLIPI, Follicular Lymphoma International Prognostic Index; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; BM, bone marrow.

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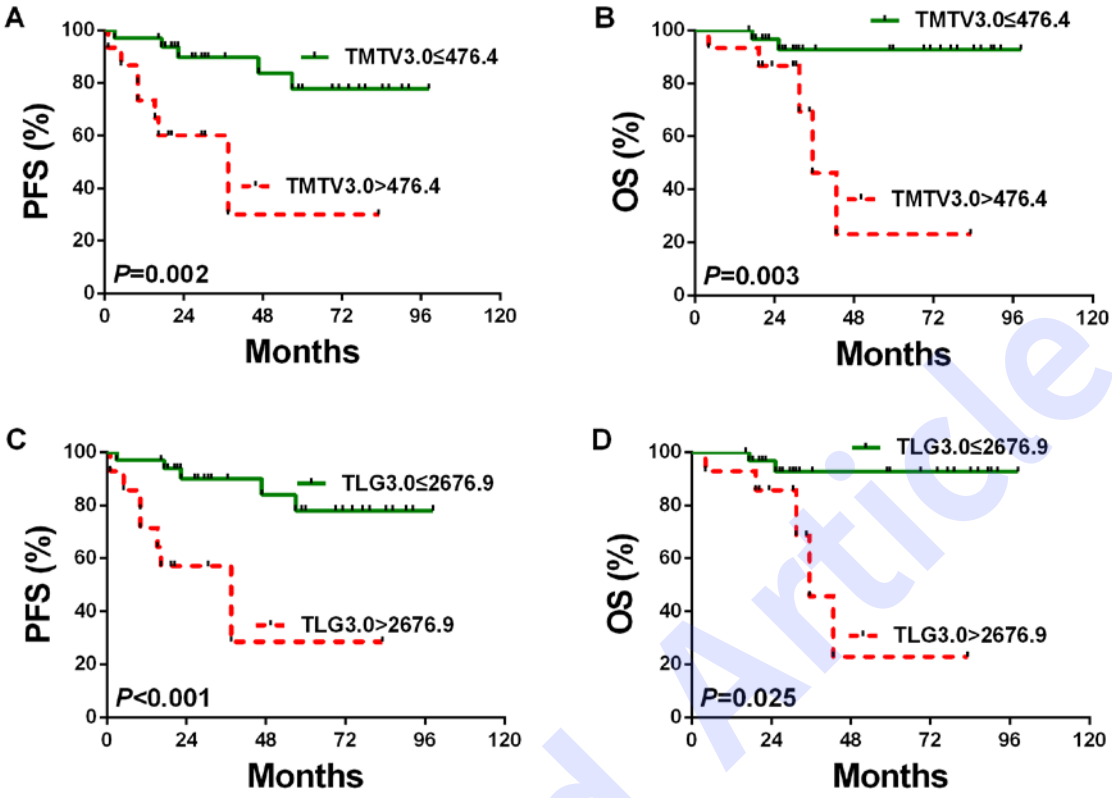

Fig. 1. Progression-free survival (PFS) and overall survival (OS) according to baseline TMTV3.0 and TLG3.0. TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

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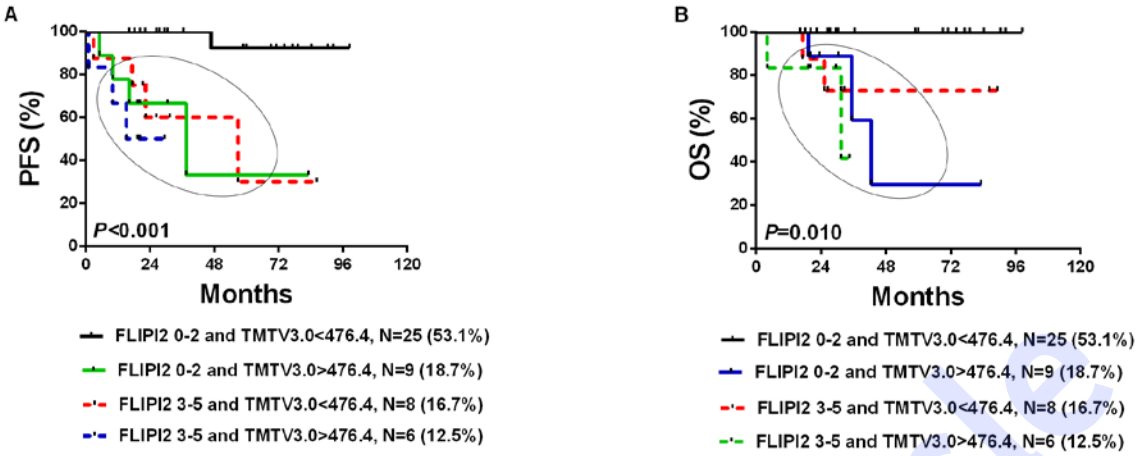

Fig. 2. Progression-free survival (PFS) and overall survival (OS) according to baseline TMTV3.0 and FLIPI2 score. FLIPI, Follicular Lymphoma International Prognostic Index; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

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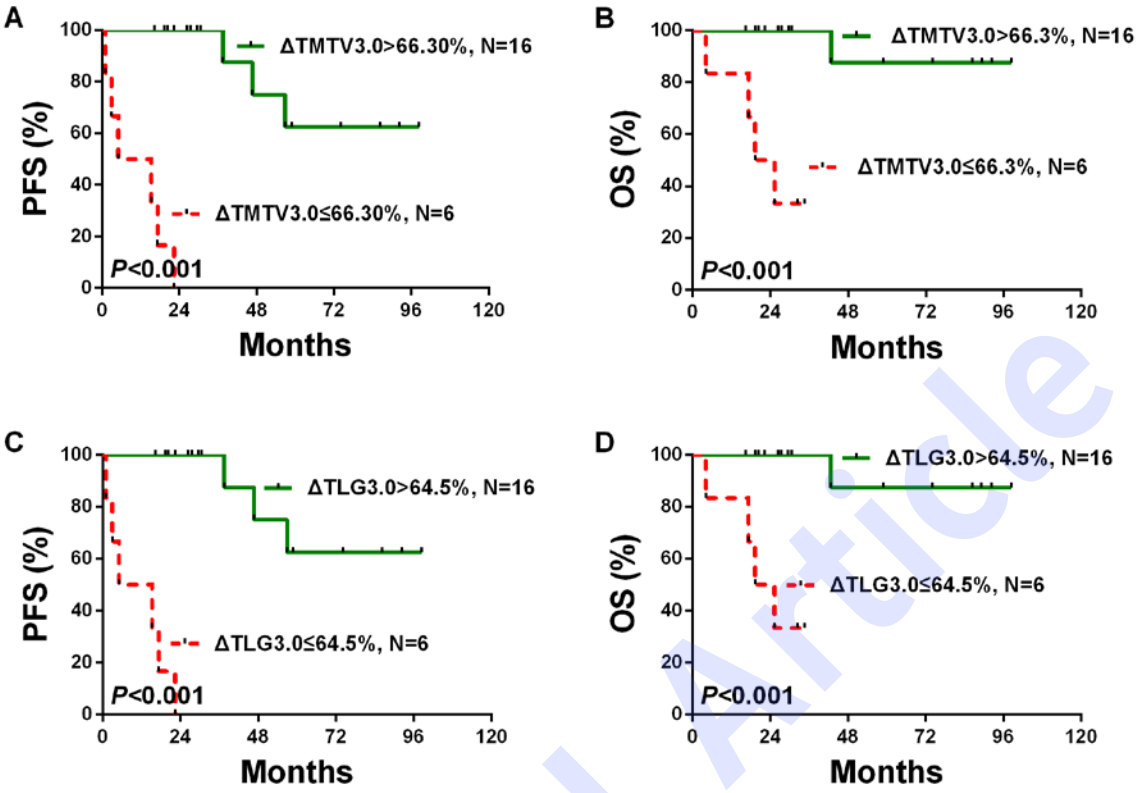

Fig. 3. Progression-free survival (PFS) and overall survival (OS) according to ΔTMTV3.0 (66.3%) and ΔTLG3.0 (64.5%). TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

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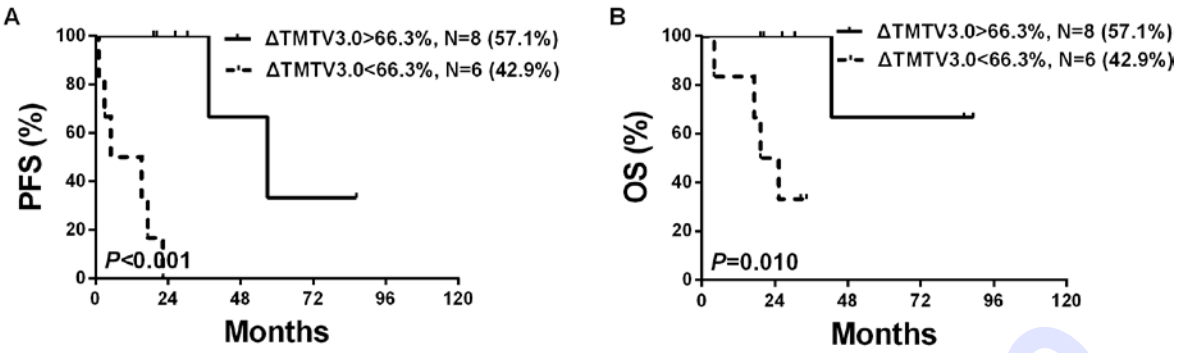

Fig. 4. Progression-free survival (PFS) and overall survival (OS) according to ΔTMTV3.0 for the 14 patients with either TMTV3.0 > 476.3 or FLIPI2 3-5. TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

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S1 Table. The distribution of 48 FL patients according to baseline TMTV status and FLIPI2 score

	TMTV3.0<476.4	TMTV3.0>476.4
FLIPI2 0-2	25 (53.1%)	9 (18.7%)
FLIPI2 3-5	8 (16.7%)	6 (12.5%)

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S2 Table. The distribution of 24 FL patients according to interim TMTV status and FLIPI2 score

	TMTV3.0<476.4 and FLIPI2 0-2 (n=10)	TMTV3.0>476.4 or FLIPI2 3-5 (n=14)
ΔTMTV3.0>66.3%	10	6
ΔTMTV3.0<66.3%	0	8

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