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The effect of 18F-FDG PET/CT findings on prognosis in patients with diffuse large B cell lymphoma

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ABSTRACT

Aims: 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT), plays an important role in both staging at the time of diagnosis and follow-up of treatment response in lymphoma. Our aim was to investigate the effect of different quantitative metabolic parameters, which are not used in routine practice, on treatment response and overall survival (OS) in patients with diffuse large B-cell lymphoma.

Methods: A total of 26 patients were included in our retrospective cohort study. Deauville 5-point scale (5-PS), and cut-off values for changes in maximum standardized uptake value (SUVmax), peak SUV (SUVpeak), metabolic tumor volume (MTV) (2.5-%41- PERCIST -aort) and total lesion glycolysis index (TLG) (2.5-%41- PERCIST-aort) effect of metabolic parameters on treatment response and OS was investigated.

Results: Metabolic parameters did not predict treatment response, while TLGPERCIST (p=0.034), TLGAORT (p=0.040), MTV41 (p=0.040) and TLG41 (p=0.034) parameters were statistically significant for OS. Median OS (months) was statistically significant in TLGPERCIST groups (p=0.047). While the median OS (months) in the TLGPERCIST <4411.90 group was inaccessible, the median OS in the ≥4411.90 group was 32.00 (95%CI: 0.00-87.43) months. Median OS (months) was statistically significant in MTV41 groups (p=0.047). While median OS (months) was inaccessible in the MTV41<376.10 group, median OS in the ≥376.10 group was 32.00 (95%CI: 0.00-87.43) months.

Conclusion: The MTV41 and TLGPERCIST appear to be the best parameter to predict OS in patients diagnosed with DLBCL by 18F-FDG PET/CT.

Keywords: Diffuse large cell lymphoma, metabolic tumor volume, overall survival, PET response, total lesion glycolysis

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and is an aggressive malignancy with heterogeneous disease morphology, biology, clinic and treatment response.[1-2] Clinical risk scores are used for prognosis.[3-5] The generally preferred treatment is rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) and a recent study showed a 2-year progression-free survival (PFS) of 75% and overall survival (OS) of 85%.[6] Positron emission tomography/computed tomography with 18F-fluorodesoxyglucose (18F-FDG PET/CT) is a favourable imaging modality for pre-treatment staging.[7] In addition, 18F-FDG PET/CT showed a high predictive value for both PFS and OS at end-of-treatment evaluation.[8] Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are the most commonly used volumetric parameters that best reflect metabolic tumor burden. In some studies, MTV and TLG have been shown to be significantly associated with clinical parameters such as OS and PFS in DLBCL patients, and tumors with high metabolic volume have been shown to have more progression or disease-related mortality.[9-12] Although volumetric parameters have prognostic significance in DLBCL patients, there is no standardized method for their calculation. Our aim was to investigate the prognostic predictive effect of different parameters in 18F-FDG PET/CT, such as clinical risk scores at diagnosis.

METHODS

Study Design

A retrospective, analytic study was performed following approval from University of Health Sciences Hamidiye Faculty of Medicine Ethics Committee (Date: 01.09.2023, Decision No: 2023/16-12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Study Population

The data of patients with diffuse large B-cell lymphoma admitted to the adult hematology outpatient clinic between 2020 and 2022 were retrospectively analysed. Twenty-six patients who had 18F-FDG PET/CT before and after treatment were included in our study. Clinical symptoms and findings at the time of diagnosis, complete blood and biochemical parameters, tissue pathology data, and 18F-FDG PET/CT findings at the time of diagnosis and at the end of treatment were analysed retrospectively. International prognostic score (IPI), which has a predictive value in terms of OS and relapse-free survival in aggressive non-Hodgkin lymphoma, was calculated.13 Age >60 years, serum lactate dehydrogenase (LDH) concentration greater than normal, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, clinical stage III or IV and >1 extranodal disease site were scored. It was classified as low risk IPI score of zero or one, low-intermediate risk IPI score of two, high-intermediate risk IPI score of three, high risk IPI score of four or five.

Study Techniques: Radiotracer, Imaging and Processing Protocol

Patients with DLBCL were referred to the Nuclear Medicine Department for 18F-FDG PET/CT scanning before treatment. Patients were advised to fast for at least 6 hours before the scan. Patients with blood glucose levels less than 200 mg/dl were included in the study. Patients were injected intravenously with 40 MBq 18F-FDG per kilogram. After radioisotope injection, the patients were kept in a room for 55-60 minutes to rest. Meanwhile, iodinated contrast medium was administered orally. Patients were asked to empty their bladder to reduce the physiological activity of the bladder before the scan. PET/CT scanning was performed on a Siemens Biograph Horizon device. The PET/CT scan was obtained in the cranio-caudal direction, covering the region from the top of the head to the proximal third of the thigh.

Parameters Used

- **Threshold 2.5:** Contains tumor tissue with SUV greater than 2.5 in the drawn area of interest.
- **Threshold 41%:** The plotted area of interest contains tumor tissue with metabolic activity higher than 41% of the SUVmax of the lesion.
- **PERCIST threshold:** This value was calculated by adding 2 standard deviations to the mean SUV value of a 3 cm diameter sphere centered on the eighth segment of the right liver lobe.
- **Threshold value aorta:** This value was calculated by adding 2 standard deviations to the mean SUV value of a cylinder 2 cm long in the vertical plan and 1 cm in diameter in the axial plan in the thoracic section of the descending aorta.
- **MTV2.5:** Tumor volume with metabolic activity greater than 2.5 was automatically calculated by the programme (in cm^3).
- **TLG2.5:** The MTV was automatically calculated by the programme by multiplying 2.5 by the mean SUV measured within the lesion.
- **MTV41:** Tumor volume with metabolic activity greater than 41% of the SUVmax of the lesion was automatically calculated by the programme (in cm^3).
- **TLG41:** MTV was automatically calculated by the programme by multiplying 41% by the mean SUV measured within the lesion.
- **MTVPERCIST:** The tumor volume with metabolic activity higher than the PERCIST threshold was automatically calculated by the programme (in cm^3).
- **TLGPERCIST:** MTV was calculated automatically by the programme by multiplying the PERCIST threshold and the mean SUV of the lesion.
- **MTVAORT:** The tumor volume with metabolic activity higher than the aortic threshold was automatically calculated by the programme (in cm^3).
- **TLGAORT:** MTVAORT calculated by aortic threshold was automatically calculated by the programme by multiplying the mean SUV measured within the lesion.

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as n and % for categorical variables and Median (IQR) for continuous variables. ROC curve was used to analyse the predictive value of various clinical parameters for mortality. Kaplan Meier method was used to compare survival times between various clinical parameter groups. $p<0.05$ was considered statistically significant.

RESULTS

When the international prognostic score (IPI) of 26 patients included in our study was evaluated, 4(15.3%) had an IPI score of 1, 4(15.3%) had an IPI score of 2, 6(23%) had an IPI score of 3, 11(42.3%) had an IPI score of 4, and 1(3.8%) had an IPI score of 5. ECOG performance status was ≥2 in 19 (73%) patients. The median follow-up period was 22,19±23,50 months. Sociodemographic and clinical characteristics were summarised in Table 1. Among the participants, 14 (53.8%) were in stage 4, 5 (19.2%) in stage 3, 1 (3.8%) in stage 2, and 6 (23%) in stage 1, and 3 (11.5%) had bulky disease and 10 (38.4%) had bone marrow involvement on biopsy. Among the patients, 22 (84.6%) were DLBCL of non-germinal center cell origin. Ki-67 proliferation index was ≥90 in 4 (15.3%), immunohistochemical myc expression was positive in

4(15.3%), myc expression was negative in 10 (38.4%), and myc expression was not evaluated in 12 patients. Myc expression and Ki-67 proliferation index were not correlated with metabolic parameters (p>0.05). R-CHOP chemotherapy was given to 23 (88.4%) of the participants and response was achieved in 21(80.7%) of them. Recurrence was observed in 2 (7.7%). No statistically significant difference was found between metabolic parameters and response to treatment (p>0.05) (Table 2).

Table 1. Sociodemographic and clinical characteristics data

Variables	N	%
Follow-up time (months), Mean±SD	22.19±23.50	
Age (years)		
Mean±SD	56.38±14.00	
Median (min-max)	55 (22-87)	
≤60	15	57.7
>60	11	42.3
Gender		
Female	15	57.7
Male	11	42.3
Comorbidity		
No	13	50.0
Yes	13	50.0
Relapse		
No	20	76.9
Yes	2	7.7
Response		
No	5	19.2
Yes	21	80.8
Mortality		
Lives	21	80.8
Exitus	5	19.2
Laboratory Parameters	**Mean±SD**	
WBC (10^3/µl)	7.36±3.24	
Neutrophil (10^3/µl)	5.23±2.95	
Lymphocyte (10^3/µl)	1.58±0.81	
Hemoglobine (g/dl)	11.47±2.61	
Platelet (10^3/µl)	253.19±92.35	
Creatinine (mg/dl)	0.75±0.18	
Uric acid (mg/dl)	4.86±1.72	
Calcium (mEq/L)	9.06±0.66	
Potassium (mmol/L)	4.45±0.56	
Beta2 mikroglobuline (ng/ml)	3.98±2.58	
D-dimer (µg/ml)	1.47±1.27	
INR	1.29±0.54	
aPTT (sn)	23.61±2.85	
Fibrinogen (g/L)	4.18±1.38	

Table 2. Comparison of various clinical parameters with responses to treatment

Variables	Response to treatment		p
	Yes (N=5) Median (IQR)	No (N=21) Median (IQR)	
SUVmax	20.3 (21.5)	27.1 (19.2)	0.205
SUVpeak	18.5 (18.5)	23.7 (16.1)	0.229
MTV2.5	628.0 (1926.3)	522.7 (463.8)	0.626
TLG2.5	2656.1 (9781.1)	4782.8 (10489.7)	0.313
MTV PERCIST	490.8 (804.5)	447.1 (582.1)	0.770
TLG PERCIST	2157.6 (8403.0)	3740.0 (4403.0)	0.495
MTVAORT	845.4 (2269.9)	982.8 (815.4)	0.416
TLGAORT	3498.0 (10175.2)	4312.5 (4684.1)	0.820
MTV41	256.2 (481.3)	302.0 (1062.2)	0.720
TLG41	1726.0 (5382.4)	2452.4 (3356.3)	0.770
AORT	2.1 (0.5)	1.6 (1.2)	0.329
LIVER	3.3 (1.1)	2.9 (1.2)	0.229

Mann Whitney U test, p<0.05 statistically significant

A total of 21 (80.7%) of the participants are alive. TLGPERCIST (p=0.034), TLGAORT (p=0.040), MTV41 (p=0.040) and TLG41 (p=0.034) parameters were statistically significant with mortality. In the ROC analysis designed to discriminate mortality by TLGPERCIST values, the AUC was 0.819 (95% [CI], 0.660-0.978). In case of exitus, the sensitivity and selectivity of TLGPERCIST values with a cut-off value of ≥4411.90 were 80.0% and 76.2%, respectively. In the ROC analysis designed to discriminate mortality by TLGAORT values, the AUC was 0.800 (95% [CI], 0.626-0.975). In case of exitus, the sensitivity and selectivity of TLGAORT values with a cut-off value of ≥5394.25 were 60.0% and 66.7%, respectively. In the ROC analysis designed to discriminate mortality by MTV41 values, the AUC was 0.800 (95% [CI], 0.603-0.997). In case of exitus, the sensitivity and selectivity of MTV41 values at a cut-off value of ≥376.10 were 80.0% and 76.2%, respectively. In the ROC analysis designed to discriminate TLG41 values for mortality, the AUC was 0.810 (95% [CI], 0.637-0.982). In case of exitus, the sensitivity and selectivity of TLG41 values with a cut-off value of ≥3371.20 were 60.0% and 66.7%, respectively. Summarized in Table 3.

TLGPERCIST and MTV41 were statistically significant in terms of median OS (p=0.047 for both). While median OS was inaccessible in the TLGPERCIST <4411.90 group, it was 32.00 (95%CI: 0.00-87.43) months in the ≥4411.90 group. While median OS was inaccessible in the MTV41 <376.10 group, median OS was 32.00 (95%CI: 0.00-87.43) months in the ≥376.10 group (Table 4). Figure 1A-C shows the Kaplan-Meier curves for OS.

Table 3. Analysis of predictive values of various parameter values in differentiating mortality

Variables	AUC	%95 CI	Cut-off	Sensitivity (%)	Specificity (%)	p
TLGPERCIST	0.819	0.660-0.978	≥4411.90	80.0	76.2	0.029
TLGAORT	0.800	0.626-0.975	≥5394.25	60.0	66.7	0.040
MTV41	0.800	0.603-0.997	≥376.10	80.0	76.2	0.040
TLG41	0.810	0.637-0.982	≥3371.20	60.0	66.7	0.034

AUC, Area under the curve; 95%CI, Confidence interval

Table 4. OS comparisons of patients

OS (months)	2 years %	5 years %	Median (%95 CI)	p
OS	88.5	59.0	- (-)	
TLG PERCIST				0.047
<4411.90	100.0	66.7	- (-)	
≥4411.90	66.7	44.4	32.00 (0.00-87.43)	
TLGAORT				0.379
<5394,25	93.8	62.5	- (-)	
≥5394,25	80.0	53.3	- (-)	
MTV41				0.047
<376.10	100.0	66.7	- (-)	
≥376,10	66.7	44.4	32.00 (0.00-87.43)	
TLG41				0.379
<3371,20	93.8	62.5	- (-)	
≥3371,20	80.0	53.3	- (-)	

Kaplan Meier curve, Long rank test, p<0.05 statistically significant

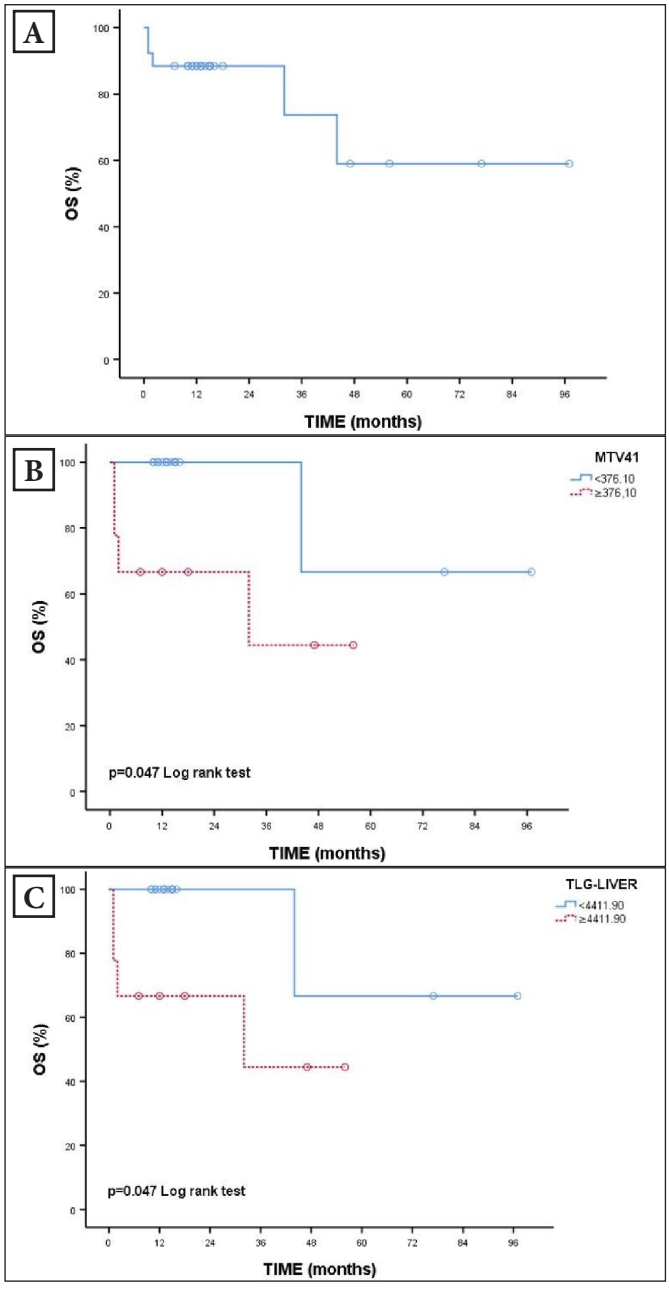

Figure 1A-C. Kaplan-Meier curves for OS.

DISCUSSION

In our study, no correlation was found between metabolic parameters and treatment response in patients with DLBCL, while TLGPERCIST and MTV41 were found to have predictive value for OS. The small number of patients, partial lack of pathological data and retrospective study are the limitations of our study. Whether these parameters are guiding in terms of both treatment response and the type of treatment remains a matter of curiosity. As a result of studies with a larger patient population, measurement of these parameters may provide additional contribution to the routine SUVmax, Deauville score.

The current approach is to define the high-risk subtype of DLBCL and to consider different treatment regimens instead of the standard regimen of R-CHOP. Genetic features, myc expression, cell origin, 18F-FDG PET/CT are used to define the subtype with poor prognosis.[14] In many lymphoma subtypes, MTV predicts the total tumor burden more accurately than the simple size of the tumor, Ann Arbor stage, or even the clinical risk score.[15,16] High pretreatment MTV results in shorter PFS and OS.[17-20] High total MTV and TLG were associated with both worse OS and incomplete response.[21] In another study, it was also defined as a marker of relapse.[15] In our study, MTV and TLG were not found to be associated with treatment response. This may be due to the small number of patients. However, higher MTV and TLG were associated with worse OS. In a study evaluating various methods to measure tumor volume, although the parameters used predicted both PFS and OS, the use of SUV2.5 was recommended because it was easier for clinicians to evaluate with the method.[22] In another study, in univariate Cox regression analysis, whole-body MTV was found to be a significant determinant of OS, but in the multivariate Cox proportional hazards model, neither MTV nor TLG was identified as predictive factors. So, to put it simply, "whole-body MTV" and "whole-body TLG" do not offer any additional prognostic information compared to what is already available through NCCN-IPI in DLBCL.[23]

In clinical practice, there are several challenges associated with the calculation of MTV in lymphomas. First and foremost, there is no consensus on which threshold value to use for the delineation of lymphoma lesions and the calculation of MTV. In our study, with the aim of reducing this limitation somewhat, we utilized four different threshold values for MTV calculation: MTV2.5, MTV41, MTVPERCIST, and MTVAORT, and endeavored to demonstrate which threshold value contributed more effectively. Secondly, measuring MTV using existing software programs can be time-consuming. To surpass this limitation, the development of automated software programs can facilitate easier measurements and save time. Thirdly, the contribution of MTV calculations in DLBCL to prognostic information beyond what is determined by

commonly used clinical risk scores is a subject of debate in the field of research.

Imaging interpretation analyses with the evaluation of different metabolic volumetric parameters are improving day by day. We believe that predictive risk analyses developed by combining these parameters with pathological and clinical data will be useful in predicting treatment response, recurrence and OS.

CONCLUSION

High tumor burden is associated with poor survival. We believe that extending the pre-treatment volumetric-metabolic parameters and evaluating whether they have a predictive value not only in terms of OS but also in terms of treatment response should be evaluated with studies involving a larger patient population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Hamidiye Faculty of Medicine Ethics Committee (Date: 01.09.2023, Decision No: 2023/16-12)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Yin X, Xu A, Fan F, et al.I ncidence andmortality trends and risk prediction nomogram for extranodal diffuse large B-cell lymphoma: an analysis ofthe surveillance, epidemiology, and end results database. *Front Oncol.* 2019;9:1198.
2. Kurz KS, Ott M, Kalmbach S, et al. Large B-Cell lymphomas in the 5th edition of the WHO-classification of haematolymphoid neoplasms-updated classification and new concepts. *Cancers (Basel).* 2023;15(8):2285.
3. Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010;28(14):2373-2380.
4. Salles G, de Jong D, Xie W, et al. Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the lunenburg lymphoma biomarker consortium. *Blood.* 2011;117(26):7070-7078.
5. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood.* 2014;123(6):837-842.
6. Bartlett NL, Wilson WH, Jung SH, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the phase III Intergroup Trial Alliance/CALGB 50303. *J Clin Oncol.* 2019;37(21):1790-1799.
7. Gómez León N, Vega G, Rodríguez-Vigil Junco B, Suevos Ballesteros C. Evaluation of diffuse large B-cell lymphoma patients with 64-slice multidetector computed tomography versus 18FDG positron emission tomography/computed tomography in initial staging and restaging after treatment. *Med Clin (Barc).* 2018;151(7):255-264.
8. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [18F]FDG-PET a valid alternative to conventional diagnostic methods?. *J Clin Oncol.* 2001;19(2):414-419.
9. Zhang Y-Y, Chen W-Y, Cui Y-P, et al. Value of 18F-FDG PET/CT scan quantization parameters for prognostic evaluation of patientswith diffuse large B-cells lymphoma. *Zhongguo Shi Yan Xue Ye Xue Za Zhi.* 2018;26(5):1249-1342.
10. Chang C-C, Cho S-F, Chuang Y-W, et al. Prognostic significance of total metabolic tumor volume on 18F-fluorodeoxyglucosepositron emission tomography/computed tomography in patients with diffuselarge B-cell lymphoma receiving rituximab-containing chemotherapy. *Oncotar-get.* 2017;8(59):99587-99600.
11. Kostakoglu L, Martelli M, Sehn LH, et al. Base-line PET-derived metabolic tumor volume metrics predict progression-free and overall survival in DLBCL after first-line treatment: results from the phase 3GOYA study. *Blood.* 2017;130(Suppl 1):824-824.
12. Tateishi U, Tatsumi M, Terauchi T, et al. Prognosticsignificance of metabolic tumor burden by positron emission tomogra-phy/computed tomography in patients with relapsed/refractory diffuse largeB-cell lymphoma. *Cancer Sci.* 2015;106(2):93-186.
13. Shipp MA. International non-Hodgkin's lymphoma prognostic factors project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 1993;329(2):987-994.
14. Susanibar-Adaniya S, Barta SK. 2021 Update on Diffuse large B cell lymphoma: a review of current data and potential applications on risk stratification and management. *Am J Hematol.* 2021;96(5):617-629.
15. Cottereau AS, Meignan M, Nioche C, et al. Risk stratification in diffuse large B-cell lymphoma using lesion dissemination and metabolic tumor burden calculated from baseline PET/CT†. *Ann Oncol.* 2021;32(3):404-411.
16. Cottereau AS, Lanic H, Mareschal S, et al. Molecular profile and FDGPET/CT total metabolic tumor volume improve risk classification at diagnosis for patients with diffuse large B cell lymphoma. *Clin Cancer Res.* 2016;22(15):3801-3809.
17. Cottereau AS, Becker S, Broussais F, et al. Prognostic value of baseline total metabolic tumor volume (TMTV0) measured on FDG-PET/CT in patients with peripheral T-cell lymphoma (PTCL). *Ann Oncol.* 2016;27(4):719-724.
18. Meignan M, Cottereau AS, Versari A, et al. Baseline metabolic tumor volume predicts outcome in high-tumor-burden follicular lymphoma: a pooled analysis of three multicenter studies. *J Clin Oncol.* 2016;34(30):3618-3626.
19. Cottereau AS, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. *Blood.* 2018;131(13):1456-1463.
20. Mikhaeel NG, Smith D, Dunn JT, et al. Combination of baseline metabolic tumour volume and early response on PET/CT improves progression-free survival prediction in DLBCL. *Eur J Nucl Med Mol Imaging.* 2016;43(7):1209-1219.
21. Albano D, Dondi F, Mazzoletti A, Bellini P, Giubbini R, Bertagna F. Prognostic impact of pretreatment 2-[18F]-FDG PET/CT parameters in primary gastric DLBCL. *Medicina (Kaunas).* 2021;57(5):498.
22. Ilyas H, Mikhaeel NG, Dunn JT, et al. Defining the optimal method for measuring baseline metabolic tumour volume in diffuse large B cell lymphoma. *Eur J Nucl Med Mol Imaging.* 2018;45(7):1142-1154.
23. Adams HJ, de Klerk JM, Fijnheer R, et al. Prognostic superiority of the National Comprehensive Cancer Network International Prognostic Index over pretreatment whole-body volumetric-metabolic FDG-PET/CT metrics in diffuse large B-cell lymphoma. *Eur J Haematol.* 2015;94(6):532-539.