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ORIGINAL ARTICLE

Prognostic significance of neutrophil/lymphocyte ratio (NLR) and correlation with PET–CT metabolic parameters in small cell lung cancer (SCLC)

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Abstract

Purpose The aim of this study is to detect the prognostic significance of neutrophil/lymphocyte ratio (NLR) in SCLC and to evaluate the relation with 18F-FDG PET–CT metabolic parameters (PET–CT MPs).

Methods Demographic parameters, laboratory values including NLR and other clinical variables were analyzed in 112 patients with small cell lung cancer (SCLC) and 54 of these patients had results of metabolic parameters detected with 18 FDG PET–CT [including SUV_{max}, SUV_{mean}, metabolic tumor volume (MTV), whole body MTV (WBMTV), TLG (total lesion glycolysis), whole body TLG (WBTLG)] were evaluated for survival analyses.

Results Mean and median overall survival (OS) and progression-free survival (PFS) were found to be significantly longer in cases with NLR < 4 compared with NLR > 4 in totally. Also stage, performance status, response to first-line therapy, LDH, and lymphocyte count were found to be prognostic for OS and PFS. MTV, WBMTV and WBTLG were found to be prognostic for both OS and PFS, while SUV_{max} found to be significant for OS. Patients with NLR ≥ 4, MTV ≥ 60.1, WBMTV ≥ 120 and WBTLG ≥ 1000 points had lower OS and PFS. A moderate positive correlation was found between NLR and SUV_{mean} (*r*: 0.36), SUV_{max} (*r*: 0.34), TLG (*r*: 0.39), MTV (*r*: 0.51), WBMTV (*r*: 0.40), and WBTLG (*r*: 0.46).

Conclusion There is relationship between PET–CT metabolic parameters and NLR in SCLC. Highest correlation was found with NLR and MTV, WBMTV, and WBTLG, and evaluation of NLR together with these parameters predicts survival times and tumor biology more clearly in SCLC.

Keywords Small cell lung cancer (SCLC) · Neutrophil/lymphocyte ratio (NLR) · PET–CT · Metabolic tumor volume (MTV) · Whole body metabolic tumor volume (WBMTV) · Whole body total lesion glycolysis (WBTLG)

Introduction

Lung cancer is the most common cause of cancer deaths [1]. SCLC is neuroendocrine tumor consisting of 15% of the lung cancers and cigarette is the most frequent etiologic factor [2]. The most important characteristics of SCLC are rapid tumor growth and metastatic potential, and also dramatic response to first-line treatment but early relapse and/or progression [3]. Although age, sex, performance status, LDH, and albumin are prognostic factors in SCLC, disease stage is the most important prognostic parameter [4]. Classically, SCLC is divided into two stages according to the Veterans administration Lung Study Group (VALSG) as limited disease (LD) and extended disease (ED) [5]. In recent years, TNM classification proposed by International Association for the Study of Lung Cancer (IASLC) is used

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due to its higher sensitivity for tumor burden [2, 6]. Treatment is started with chemoradiation and is finished with prophylactic cranial irradiation in patients with stage I–IIIb disease. Chemotherapy is the initial therapy in cases with stage IV disease and thoracic/cranial radiotherapy is used in good responders. OS is 2–4 months, 16–24 months and 10–15 months in patients with untreated, limited stage and extensive stage disease; respectively [7].

SCLC has high metabolic activity and 18F-FDG PET–CT is used with nearly 100% sensitivity for staging. In a meta-analysis, 28% stage deviation has been detected in cases staged with PET–CT compared with conventional imaging methods [8, 9]. Standardized uptake value ($SUV_{max-mean}$) shows the tumor FDG uptake and this is prognostic in various tumors including lung cancer [10–14]. Other parameters showing tumor metabolic activity and tumor burden are metabolic tumor volume (MTV), whole body metabolic tumor volume (WBMTV), total lesion glycolysis (TLG) and whole body total lesion glycolysis (WBTLG). PET–CT metabolic parameters (PET–CT MPs) predict overall survival (OS) and progression-free survival (PFS) in lung cancer and cannot be measured by conventional imaging techniques [15–20].

The association between systemic inflammation and cancer is not a new concept but its importance has been found to be increased in recent years. This association is related to both microenvironment affected by extrinsic and intrinsic pathways and also tumor migration–invasion and metastasis [21]. Malignant potential of the tumors increases with inflammation and grade. Neutrophil/lymphocyte ratio (NLR) is an important marker for systemic inflammation, has prognostic importance and is a easily detected parameter in clinical practice [22].

There are some reports identifying the prognostic significance of metabolic parameters detected by PET–CT and NLR in SCLC [23–26]. However, there is no report comparing the metabolic parameters and NLR. Here, we wanted to explore the prognostic value of SUV_{max}, SUV_{mean}, MTV, WBMTV, TLG, and WBTLG detected by PET–CT and to compare these parameters with NLR in cases with SCLC.

Patients and methods

The study included 112 patients with SCLC treated in Cukurova University Hospital between May 2007 and February 2017 that evaluated retrospectively. Smoking history, performans score, complete blood count (CBC) parameters including neutrophil, lymphocyte, platelet and mean platelet volume (MPV), ALP, LDH and imaging modalities were recorded. NLR was obtained from CBC at the diagnosis and was calculated dividing the number of neutrophil counts by lymphocyte counts. The subgroup of the study including 54 patients had results of PET–CT imagings before and after treatment.

18F-FDG PET–CT

18F-FDG PET–CT scans were acquired after fasting for 8 h and 60–90 min after intravenous administration of 18F-FDG (350–370 MBq). 18F-FDG PET–CT images were obtained using a combined PET–CT Siemens (Biograph 6, Siemens Medical Systems USA). Both the PET and the CT scans were obtained during normal tidal breathing. The total acquisition time varied between 25 min and 35 min per patient. PET images were reconstructed with CT-derived attenuation correction using the ordered subset expectation maximization (OSEM) algorithm. The attenuation-corrected PET images, CT images, and fused PET–CT images displayed as coronal, sagittal, and transaxial slices were viewed on a Symbia workstation (Siemens Healthcare).

Measurement of metabolic tumor volume and total lesion glycolysis

To measure MTV values, PET–CT data were transferred in Dicom format to an OsiriX MD program. A 3D region of interest including each focal lesion previously localized was drawn and SUV_{max} was determined in the selected volume. The shape and size of the VOIs were adjusted to ensure that they neither included areas of high physiological uptake (bladder, myocardium) nor exceeded the anatomical tumor boundaries seen on CT. MTV was calculated from PET data grouping all spatially connected voxels within a threshold of 40% of the SUV_{max} by OsiriX MD program which also calculates SUV Mean value automatically. The total MTV of each patient was defined as the sum of MTVs of all focal lesions selected. The total lesion glycolysis (TLG) was obtained by multiplying the MTV of each focal lesion for the correspondent SUV_{mean} determined in the selected volume by isocontouring. The global TLG of each patient was defined as the sum of TLGs of all focal lesions selected.

Statistical analyses

PFS was defined as the time between the initial PET–CT examination and disease progression or death, whichever occurred first. OS was calculated as the time between the initial PET–CT examination and death or last follow-up. The correlation between continuous variables was analyzed by Spearman correlation test. Strength of agreement is evaluated by correlation coefficient (< 0.00 is poor; 0.00–0.20 is slight, 0.21–0.40 is fair, 0.41–0.60 is moderate, 0.61–0.80 is substantial, 0.81–1.00 is almost perfect). The predictors of survival were analyzed by the Kaplan–Meier method and compared by the Mantel log-rank test. Cox

proportional-hazard regression model is applied to identify multivariate predictors (forward procedure, Wald method). The results were reported as mean ± SD, median, number (*n*) and percent (%). A p value < 0.05 was considered as significant. Statistical analyses were performed using the statistical package SPSS v 22.0.

Results

Clinical and demographic parameters of the patients are shown in Table 1. Of the total 112, female/male ratio was 20/92, median age was 58 (38–83), and 106 patients had smoking history. Chronic obstructive pulmonary disease (COPD) was approximately 40% and performance status (PS) was good in 62% of the cases. Stage distribution was I–II, IIIa, IIIb and IV in 5.4%, 9.8%, 16.1% and 68.8%, respectively, according to TNM classification. 23% of the cases had LD and 77% had ED according to the VALSG. Initial treatment was cisplatin + etoposide (CE) in 55% of the cases. Chemoradiation (CRT) was given as initial treatment in 31.3% of the cases and 13% did not receive initial treatment. Second-line chemotherapy was topotecan in 47.2% of the cases.

Fifty-four cases staged with PET–CT: female/male ratio was 14/40, median age was 58 (38–83) similar to main group, and 30% had LD and 70% had ED. Metabolic parameters including SUV_{mean}, SUV_{max}, TLG, MTV, WBTLG and WBMTV were evaluated and these parameters are also shown in Table 1.

The most sensitive and specific cutoff values of laboratory parameters such as pretreatment neutrophil, lymphocyte, MPV, ALP, LDH, NLR and metabolic parameters including SUV_{mean}, SUV_{max}, TLG, MTV, WBTLG and WBMTV were detected for OS by ROC analysis. (Fig. 1a, b). AUC was found over 0.70 for all parameters. AUC SUV_{mean} was 0.74, SUV_{max} was 0.76, TLG was 0.70, MTV was 0.76, WBMTV was 0.73, and WBTLG was 0.83 according to ROC analysis.

Median follow-up time was 8.4 months (0.03–69.8 months) and 89 (79.5%) patients died during follow-up period. Relationship of OS/PFS with clinical and demographic data of 112 patients are shown in Table 2. Mean OS was found 10.1 (median: 8) months and PFS 7.3 (median: 7) months in total. OS and PFS were found to be longer in early stage disease compared with advanced stage disease. Pretreatment ALP, neutrophil count and MPV had no prognostic significance for OS times (p: 0.602, p: 0.340, p: 0.097, respectively). Pretreatment lymphocyte count was found to be important for survival times: patients with lymphocyte < 2.11 had shorter PFS and OS compared with > 2.11: 5 months and 6 months vs 8 months and 10 months, respectively (p: 0.002, p: 0.002). Median PFS and OS were 9.7 months and 14.5 months in cases with LDH < 223, respectively, while these survival times were 6.6 months and 8.3 months in cases with LDH > 223 (p: 0.031, p: 0.004). Two different cutoff points were used for NLR; PFS and OS were found shorter in cases with NLR > 4 compared with NLR < 4 (p: 0.002, p: 0.012). Similarly PFS and OS were longer in cases NLR < 3 compared with NLR > 3: 8 months vs 11 months and 6 months vs 7 months, respectively (p: 0.001, p: 0.008) (Fig. 2).

Detailed metabolic parameters and their association with PFS and OS in 54 cases are shown in Table 3. Most specific and sensitive measurements predicting OS were determined and cutoff values were detected; cutoff values for SUV_{mean} were 8.7, SUV_{max} was 14.7, TLG was 610, MTV was 60.1, WBTLG was 1000, and WBMTV was 120. Among these metabolic parameters, SUV_{mean}, SUV_{max}, and TLG were not found to be significant for PFS (p: 0.113, p: 0.113, and p: 0.190, respectively), but only SUV_{max} was found to be significiant for OS (p: 0.100, p: 0.05, p: 0.403). However, MTV with 60.1 cutoff was found to be significant for PFS: 10 months vs 6 months (p: 0.008) and OS: 13 months vs 8 months (p: 0.040). WBMTV with 120 cutoff value was found to be significant for PFS and OS: 12 months vs 6 months (p: 0.002) and 13 months vs 7 months (p: 0.008), respectively. According to the WBTLG 1000 cutoff, PFS and OS were different: PFS 13 months vs 6 months (p: 0.000), OS 17 months vs 7 months (p: 0.001) (Fig. 3).

Cox regression analysis showed that NLR and WBTLG were found to be independent risk factors that were related to prognosis (Table 4). The odds ratio (OR) for NLR was found to be 1.7 (95% CI 1–1.3, $p = 0.050$), 1.0 (95% CI 1.0–1.0, $p = 0.041$) for WBTLG, 1.1 (95% CI 1.0–1.1, $p = 0.036$) for age and 3.4 (95% CI 1.0–11.7, $p = 0.049$) for stage. But gender was not associated with prognosis (p: 0.160; OR: 3.4, 95% CI 0.7–4.8).

Correlation between metabolic parameters detected by PET–CT and laboratory values are shown in Table 5. There were positive correlations between NLR and SUV_{mean} (r: 0.362), SUV_{max} (r: 0.344), TLG (r: 0.388), MTV (r: 0.510), WBMTV (r: 0.400) and WBTLG (r: 460). Also there were positive correlations between pretreatment neutrophil and LDH with MTV, WBMTV and WBTLG, and there was negative correlation between lymphocyte and SUV_{mean}, SUV_{max}, TLG and WBTLG. There were positive correlation between ALP and SUV_{mean}, SUV_{max}, WBMTV and WBTLG but MPV had no any correlation with PET–CT parameters.

Discussion

SCLC is one of the most aggressive malignant tumors and it has many prognostic indicators. Sex, age, smoking history, performance status, stage and LDH are prognostic indicators in SCLC [4]. Poor response to treatment and

Table 1 Patient demographics and clinical characteristics

	All patients ($n=112$)	Subgroup ($n=54$) (PET–CT evaluated)
	n (%)	*n* (%)
Gender		
Female	20 (17.9)	14 (25.9)
Male	92 (82.1)	40 (74.1)
Age		
<65	85 (75.9)	42 (77.8)
≥ 65	27 (24.1)	12 (22.2)
Status		
Alive	23 (20.5)	20 (37)
Dead	89 (79.5)	34 (63)
Stage TNM (AJCC)		
1	3 (2.7)	0 (0)
2	3 (2.7)	4 (7.4)
3a	11 (9.8)	6 (11.1)
3b	18 (16.1)	11 (20.4)
4	77 (68.8)	33 (61.1)
Stage VALSG		
Limited	26 (23.2)	16 (29.6)
Extended	86 (76.8)	38 (70.4)
ECOG		
0–1	69 (61.6)	41 (75.9)
2–3	43 (38.4)	13 (24.1)
Initial treatment		
No	15 (13.4)	9 (16.7)
CRT	35 (31.3)	19 (35.2)
CE	62 (55.4)	26 (48.1)
Second-line treatment		
No	15 (2.8)	35 (64.8)
CE	9 (25)	6 (11.1)
Topotecan	17 (47.2)	9 (16.7)
Other	9 (25)	4 (7.5)
Treatment response (first-line)		
CR	3(3.75)	3 (5.6)
Regression	36 (45)	16 (29.6)
Stable	22 (27.5)	13 (24.1)
Progression	19 (23.75)	7 (13)
Smoking		
Yes	106 (94.6)	2 (3.7)
No	6 (5.4)	52 (96.3)
	Mean ± SD median (min–max)	Mean ± SD median (min–max)
Age	58.7 ± 9.5 58.0 (38–83)	58.1 ± 8.6 58 (38–83)
Neutrophil	7.5 ± 2.8 7.04 (3–22.8)	7.0 ± 2.5 7.0 (3.0–15.7)
Lymphocyte	1.9 ± 0.9 1.8 (0.2–4.1)	2.1 ± 0.8 2.0 (0.8–4.9)
NLR	5.2 ± 5.1 3.8 (1–40.4)	4.1 ± 2.6 3.2 (1.0–15.7)

Table 1 (continued)

	Mean ± SD median (min–max)	Mean ± SD median (min–max)
MPV	8.8 ± 1.6 8.5 (4.8–12.3)	9.3 ± 2.1 9.3 (4.8–18.0)
LDH	416.3 ± 455.4 280.0 (111–2615)	266.5 ± 146.8 241.5 (121–982)
ALP	119.9 ± 117.5 81.0 (21–855)	93.8 ± 63.6 73 (37–453)
SUV_{mean}		9.9 ± 3.7 8.8 (4.9–20.8)
SUV_{max}		16.2 ± 6.1 15.3 (6.4–40.6)
TLG		880.5 ± 785.3 610.4 (11.4–2854.3)
MTV		105.9 ± 83.4 83.0 (2.3–283.9)
WBMTV		244.4 ± 235.3 176.5 (10.6–1144.0)
WBTLG		1764.2 ± 1512.0 1342.5 (60.0–5999.2)

AJCC American Joint Committee on Cancer, *VALSG* The Veterans admistration Lung Study Group, *ECOG* Eastern Cooperative Oncology Group, *CRT* chemoradiation, *CE* cisplatin + etoposide, *CR* complete remission, *NLR* neutrophil/lymphocyte ratio, SUV_{max} maximum standardized uptake value of the highest metabolic lesion, SUV_{mean} average standardized uptake value, *MTV* metabolic tumor volume, *WBMTV* whole body metabolic tumor volume, *TLG* total lesion glycolysis, *WBTLG* whole body total lesion glycolysis

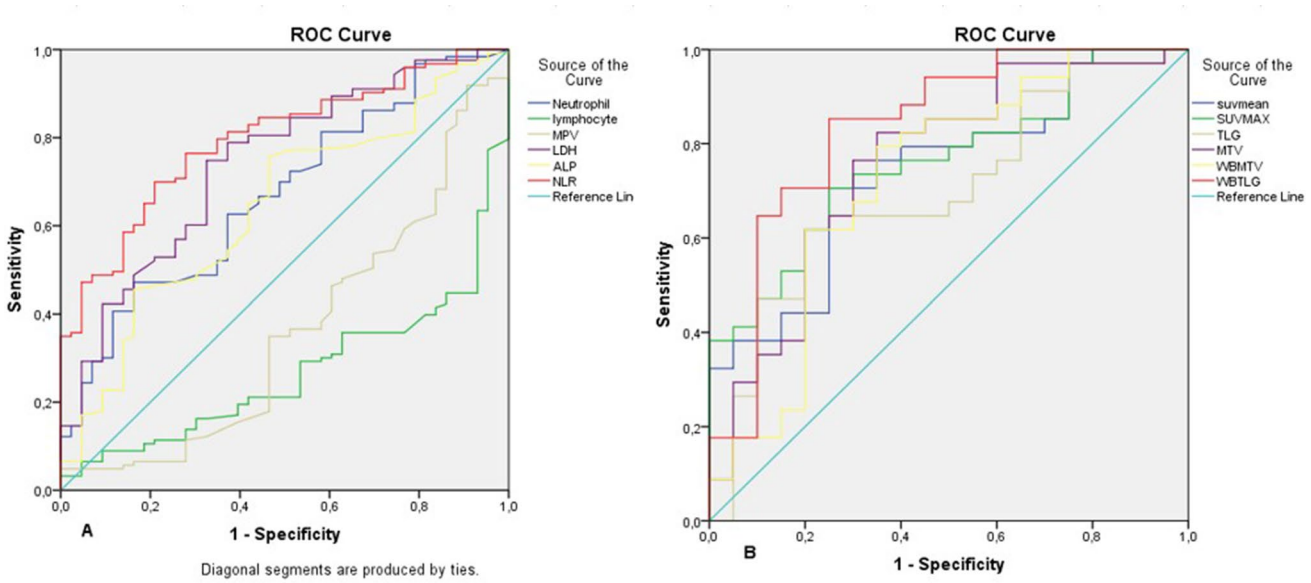

Fig. 1 **a** ROC curves of laboratory parameters, **b** ROC curves PET–CT parameters

difficulty to give optimal treatment due to poor performance status and poor tumor control due to high tumor volume are related with unfavorable outcome. Although good PS, limited stage disease, and lower LDH were found to be associated with better PFS and OS as expected, sex and smoking history were not found to be related with OS in our study group. This may be due to the low number of females and non-smokers in our study group.

NLR is a practical and important prognostic indicator in SCLC as seen in other neoplasias. It has been shown that NLR > 4 is predictive for shorter OS in a review covering 40,559 cases with cancer (not including SCLC) in all stages

Table 2 Relationship of overall/progression-free survival with clinical and demographic and PET–CT metabolic parameters ($n=112$)

	Total (n)	Total (%)	OS			PFS		
			Mean	Median	p	Mean	Median	p
Gender								
Male	92	82.1	9.5	7	*0.132*	7.2	7	*0.115*
Female	20	17.9	13.1	13		9.7	10	
Age								
< 65	85	75.8	11.1	8	*0.050*	8.1	7	*0.178*
≥ 65	27	24.2	7.3	7		6.3	7	
Stage TNM								
1 + 2	6	5.3	28.1	33	*0.0001*	19.8	23	*0.000*
3a	11	9.8	13.2	12		12	11	
3b	18	16	20.3	17		13.4	12	
4	77	68.9	7.3	7		5.5	6	
Stage VALSG								
Limited	26	23.2	18	17	*0.001*	13	11	*0.000*
Extended	86	76.8	8.3	7		6.2	6	
ECOG								
0–1	69	61.6	13.9	13	*0.000*	10.2	10	*0.000*
2–3	43	38.4	4.9	4		4.2	3	
Treatment response								
CR	3	2.6	33	33	*0.000*	23	23	*0.000*
Regression	36	32.1	16.2	13		12	10	
Stable	22	19.6	9.2	8		8.1	8	
Progression	19	45.7	9	7		5.6	6	
ALP								
< 75	50	44.6	10.7	9	*0.602*	7.4	7	*0.878*
≥ 75	62	55.4	9.6	7		7.6	7	
Neutrophil								
< 6.85	46	41	11.1	10	*0.340*	8.9	7	*0.139*
≥ 6.85	66	59	9.3	8		6.7	7	
Lymphocyte								
< 2.11	72	64.2	7.9	6	*0.002*	6.1	5	*0.002*
≥ 2.11	40	35.8	13	10		10.4	8	
MPV								
< 8.9	66	58.9	11.2	10	*0.097*	8.4	8	*0.042*
≥ 8.9	46	41.1	7.5	7		5.6	7	
Overall	112		10.1	8		7.3	7	
LDH								
< 223	36	32.1	14.5	14	*0.004*	9.7	10	*0.031*
≥ 223	76	67.9	8.3	7		6.6	10	
NLR-3								
< 3	39	34.8	13.8	11	*0.008*	10.9	8	*0.001*
≥ 3	73	65.2	8.4	7		6.1	6	
NLR-4								
< 4	58	51.8	12	10	*0.012*	9	8	*0.002*
≥ 4	54	48.2	7	4		5.6	3	

Statistically significant values are in italics ($p < 0.05$)

VALSG The Veterans admistration Lung Study Group, *ECOG* Eastern Cooperative Oncology Group, *CR* complete remission, *PFS* progression-free survival, *OS* overall survival, *NLR-4* neutrophil lymphocyte ratio (cutoff: 4), *NLR-3* neutrophil lymphocyte ratio (cutoff: 3), *PFS* progression-free survival

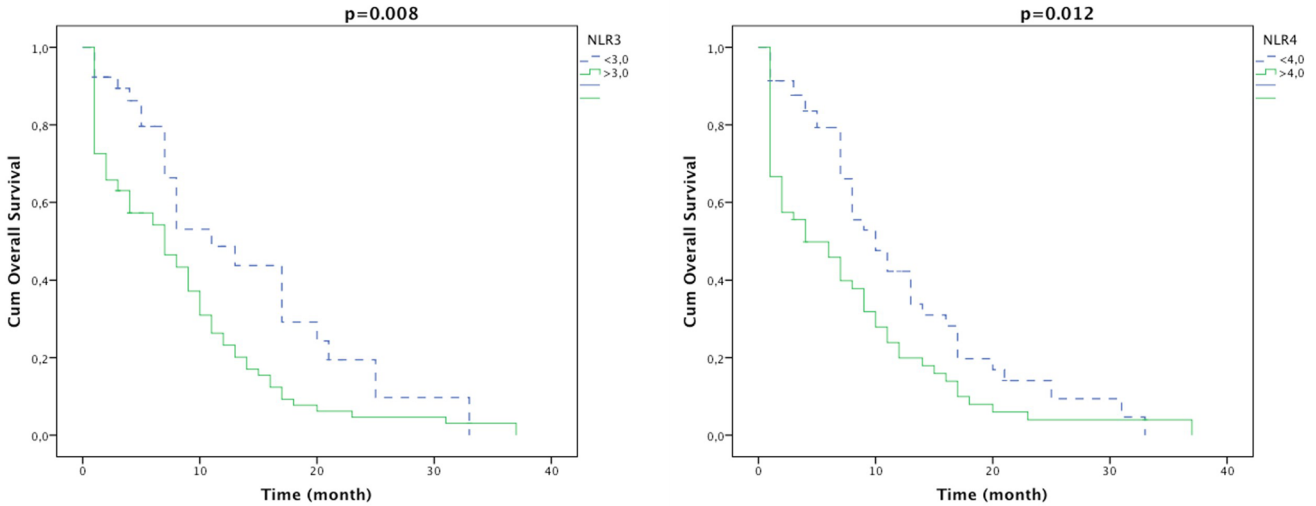

Fig. 2 OS times of the patients according to the different cutoff points of NLR

Table 3 Overall/progression-free survival times according to FDG PET–CT parameters ($n=54$)

	Total (n)	Total (%)	OS			PFS		
			Mean	Median	p	Mean	Median	p
SUV_{mean}								
< 8.7	25	46.3	15.6	12	*0.100*	10.9	9	*0.113*
≥ 8.7	29	54.7	9.1	8		6.9	7	
SUV_{max}								
< 14.7	25	46.3	16	13	*0.050*	10.9	9	*0.113*
≥ 14.7	29	54.7	8.8	8		6.9	7	
TLG								
< 610	27	50	13	10	*0.403*	10.2	7	*0.190*
≥ 610	27	50	8.3	8		6.9	7	
MTV								
< 60.1	22	40.7	16	13	*0.040*	12.2	10	*0.008*
≥ 60.1	32	59.3	8.3	8		6.3	6	
WBWTV								
< 120	22	40.7	16	13	*0.008*	12.1	12	*0.002*
≥ 120	32	59.3	7.6	7		6	6	
WBTLG								
< 1000	21	38.8	19.7	17	*0.001*	14.7	13	*0.000*
≥ 1000	33	61.2	7.4	7		5.5	6	

Statistically significant values are in italics ($p < 0.05$)

FDG PET–CT 18F-fluorodeoxyglucose positron emission tomography–computed tomography, SUV_{max} maximum standardized uptake value of the highest metabolic lesion, SUV_{mean} average standardized uptake value, *MTV* metabolic tumor volume, *WBMTV* whole body metabolic tumor volume, *TLG* total lesion glycolysis, *WBTLG* whole body total lesion glycolysis, *PFS* progression-free survival, *OS* overall survival

(p: 0.001) [27]. In a study covering 187 cases with SCLC, it has been found shorter OS and PFS in cases with NLR > 4 as in our study (11.17 months vs 9.20 months, p: 0.019 and 6.90 months vs 5.49 months, p: 0.005, respectively) [28]. And also in a large study covering 252 cases with SCLC, high NLR has been found to be independent poor prognostic indicator in multivariate Cox model [29]. Although there is not only one definite reason for prognostic significance of high NLR, it is thought that many cases together lead to this result. One of these reasons may be systemic inflammation, which takes place increasingly in the pathogenesis of cancer [30]. Neutrophils which are periphery inflammatory cells

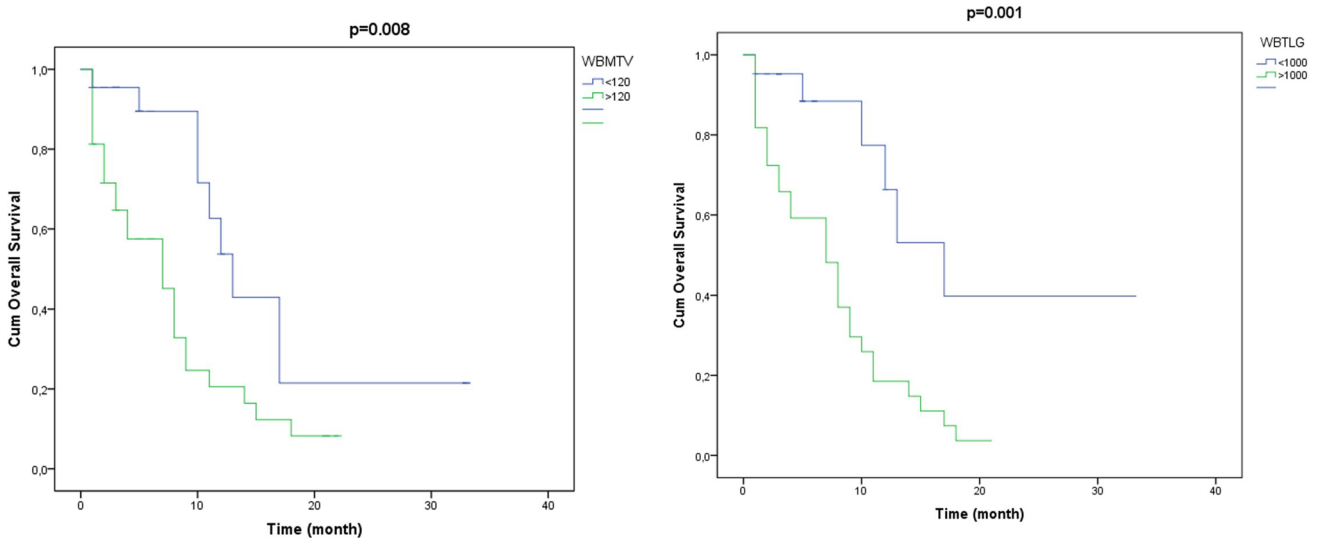

Fig. 3 OS times according to WBTLG and WBMTV

Table 4 Results of Cox regression analyses

	B	SE	*df*	Sig.	OR	95.0% CI for OR	
						min	max
NLR	0.151	0.077	1	*0.050*	1.7	1.0	1.3
WBTLG	0.000	0.000	1	*0.041*	1.0	1.0	1.0
Age	0.038	0.018	1	*0.036*	1.1	1.0	1.1
Gender (male)	0.651	0.464	1	*0.160*	1.9	0.7	4.8
Stage (extended)	1.233	0.626	1	*0.049*	3.4	1.0	11.7

NLR Neutrophil/lymphocyte ratio, *WBTLG* whole body total lesion glycolysis

interact with tumor microenvironment by releasing cytokines and chemokines [vascular endothelial growth factor, matrix metalloproteinase (MMP)] leading to ability of tumor cells to migrate and metastasize by accelerating proliferation and angiogenesis of tumor [31]. On the contrary, lymphocytes have a vital role in the destruction of tumor cells, especially with the CD8+ subtype [32]. From this point, it is normal to see a worsening of the prognosis with a more aggressive course of the tumor with the increase of neutrophil and/or decreasing of lymphocyte. Another cause may be tumor-associated neutrophils (TAN) which are a kind of neutrophil variant formed by neutrophil infiltration of the tumor. These cells both have pro-tumorigenic properties and cause drug resistance by strengthen regulatory T cells [33, 34]. Although TAN has been histopathologically proven to have increased and have prognostic significance in both disease-free survival and OS in renal cell carcinoma, melanoma, colorectal cancer, hepatocellular carcinoma, intrahepatic cholangiocarcinoma, pancreatic ductal carcinoma, head and neck tumor and non-small cell lung cancer cells [35], we did not find a study showing the evidence of increased neutrophils in SCLC tissue samples. As the retrospective nature of our study, TAN is not studied in tumor specimens; further investigation for its prognostic significance is needed.

This is a retrospective analysis and we could not strictly show the inflammation-associated disorders including COPD, obstructive or interstitial pneumonia and other inflammatory diseases. However, it is very well known that smoking is one of the causes of systemic inflammation. In a large study covering 400 cases without lung cancer, 200 smokers and 200 non-smokers, NLR has been found to be statistically higher ($p < 0.031$) in smokers (NLR 2.10 ± 1.42 vs 1.87 ± 0.83 in smokers and non-smokers, respectively) [36]. But in this study, no statistics were made between cigarettes and NLR because only 6 of 112 cases were non-smokers.

PET–CT is an important imaging modality for prognosis in many malignant tumors including SCLC due to its sensitivity for tumor viability and also tumor load [37]. Lee et al. showed shorter survival in cases with higher SUV_{max} in cases with SCLC [38]. On the other hand, Zhu et al. found shorter survival in cases with higher MTV in limited stage disease [39]. We found shorter OS and PFS in cases with higher MTV and only OS related with higher SUV_{max}

Table 5 Correlation between clinical and PET–CT parameters (*n*: 54)

	SUV_{mean}	SUV_{max}	TLG	MTV	WBMTV	WBTLG
NLR						
r	0.36**	0.34*	0.39**	0.51**	0.40*	0.46**
p	*0.007*	*0.011*	*0.004*	*0.000*	*0.003*	*0.000*
Neutrophil						
r	0.124	0.100	0.151	0.358**	0.295*	0.344*
p	*0.371*	*0.471*	*0.275*	*0.008*	*0.030*	*0.011*
Lymphocyte						
r	−0.377**	−0.300*	−0.276*	−0.205	−0.236	−0.267*
p	*0.005*	*0.028*	*0.043*	*0.137*	*0.086*	*0.050*
MPV						
r	0.030	0.001	0.081	0.051	0.221	0.157
p	*0.832*	*0.996*	*0.559*	*0.712*	*0.109*	*0.256*
ALP						
r	0.280*	0.373**	0.144	0.202	0.368**	0.309*
p	*0.041*	*0.005*	*0.297*	*0.142*	*0.006*	*0.023*
LDH						
r	−0.015	0.080	0.207	0.261*	0.582**	0.489**
p	*0.916*	*0.563*	*0.133*	*0.050*	*0.000*	*0.000*

Statistically significant values are in italics ($p < 0.05$)

NLR Neutrophil/lymphocyte ratio, *FDG PET–CT* 18F-fluorodeoxyglucose positron emission tomography–computed tomography, SUV_{max} maximum standardized uptake value of the highest metabolic lesion, SUV_{mean} average standardized uptake value, *MTV* metabolic tumor volume, *WBMTV* whole body metabolic tumor volume, *TLG* total lesion glycolysis, *WBTLG* whole body total lesion glycolysis

*Correlation is significant at the 0.05 level

**Correlation is significant at the 0.01 level

but no association with SUV_{mean}. Our results support the stronger prognostic value of metabolically active tumor volume in comparison with metabolic activity of a single lesion showing FDG uptake. Although MTV and TLG have been found to be similar prognostic significance in that report, we did not find PFS and OS difference in TLG according to these parameters; this may be related the low number of our cases. WBMTV detected by PET–CT shows the total volume of tumor covering primary and its metastases. Stage of the malignant tumors and also metabolically active tumor load are very important and these are detected by PET–CT compared with other conventional imaging methods [40, 41]. However, there are some controversial results about this matter. Oh et al. reported the prognostic significance of stage and WBMTV for PFS and OS in 106 cases with SCLC: WBMTV < 127 cm^3 vs ≥ 127 cm^3, PFS 9.1 months vs 5.4 months ($p < 0.001$) and OS 20.9 months vs 8.7 months ($p < 0.001$). We found similar results with Oh (PFS and OS were found as 12 months vs 6 months and 13 months vs 7 months, respectively, in cases with WBMTV < 120 cm^3 vs > 120 cm^3—*p*: 0.002 and *p*: 0.008).

TLG calculation using a threshold method may be considered as the most important limitation for these kinds of studies. Because the choice of threshold influences the measurement of tumor volume, mean SUV, and whole body TLG, we used a commonly adopted percentage threshold (ie, 40% of maximum SUV) to determine tumor volume due to the lack of no single optimal threshold providing accurate tumor delineation [42]. In previous studies, it has been shown that high FDG accumulation is not limited to malignant tissues and FDG uptake has been found to be higher in tumor-associated macrophages and young granulation tissues than in tumor cells [43]. Thus, whole body TLG may be overestimated; however, whole body TLG proved to be a good indicator of prognosis in this study. Whole body TLG is the summation of individual tumor volume multiplied by its mean SUV.

WBTLG shows volumetric and metabolic activity of the tumor and has better prognostic significance. Chen et al. reported the independent prognostic significance of WBTLG for OS, TNM stage, tumor histology, age, sex and performance status in 105 cases with Non-SCLC. In this study 1-year OS was found as 89% and 42% in cases with lower and higher WBTLG, respectively, and multivariate analyses showed the better predictive role of WBTLG compared with MTV and TNM stage [44]. Similar to Chen's study in our study group, WBTLG was found to be predictive for PFS and OS. Cutoff was 655 in Chen's study while 1000 in our study. This may be due to

different histologic subtypes (SCLC is more aggressive than NSCLC) and we need more studies about this matter.

Our results show that PET–CT MPs including MTV, WBMTV, and WBTLG have better predictive and prognostic significance compared with SUV_{max} or SUV_{mean}.

PET–CT MPs were found to be higher with increased tumor avidity and aggressivity and also relevance with poor prognosis. It is clear that NLR is an inflammation marker and increased NLR is related with poor prognosis. However, association between NLR and PET–CT MPs are not clear enough but reports are increasing to determine this relationship. Sürücü et al. showed an association between NLR and MTV in 52 cases with esophageal cancer [45]. In the study conducted by Jeong et al., 1034 Stage I NSCLC cases were investigated by relationship between tumors FDG uptake and peripheral blood tests, a weak but statistically significant correlation was found between SUV_{max} and leukocyte, neutrophil, lymphocyte, and NLR [46]. We found positive correlation between NLR and PET–CT MPs and also highest correlation was found with NLR and MTV, WBMTV, and WBTLG. While the precise mechanism is currently under investigation, some hypotheses were present on this subject. One of these, inflammatory cells, such as neutrophils, lymphocytes, and macrophages, which infiltrate the tumor, are active and may increase FDG uptake due to more glucose use [43]. Another mechanism may be related to the induction of angiogenesis by inflammation. Tumor needs new angiogenesis to grow. Inflammation makes the microenvironment hypoxic and induces angiogenesis by causing VEGF secretion [47]. As a consequence, the tumor rapidly undergoes a period of new angiogenesis. The amount of tumor FDG uptake is also increased during the new angiogenesis period [48]. These data suggest that increase in tumor FDG uptake as inflammation increases.

NLR as a marker for systemic inflammation is a prognostic factor in various tumors including SCLC. We also found stage, performance status, LDH, NLR and PET–CT MPs have prognostic significance in SCLC. PET–CT is an important imaging method showing both of tumor volume and tumor viability and PET–CT MPs are more informative for stage and tumor behaviour in comparison with conventional imagings. Best of our knowledge, this is the first study evaluating the correlation between NLR and PET–CT MPs such as SUV_{mean}, SUV_{max}, TLG, MTV, WBTLG, and WBMTV in SCLC. Combination of NLR and PET–CT MPs is more informative to determine the tumor biology and can be used as a prognostic factor in SCLC.

There are two important limiting points in this study: one is retrospective nature of the study which limits the detection of possible contribution of inflammatory disorders such as inflammatory lung diseases. The other limitation is the relatively low number of the patients. We need more informative study covering more cases with SCLC and clearly detected accompanying inflammatory lung diseases.

Conclusion

Whole body TLG provides metabolic and volumetric information derived from the whole body and thereby reflects whole body tumor burden. NLR as a marker for systemic inflammation is a prognostic factor in various tumors. The relation between metabolic parameters detected by PET–CT and NLR suggests that the evaluation of pretreatment NLR together with metabolic tumor parameters detected by PET–CT is more useful to detect tumor biology and survival times. However, we need more data to understand the relation between these parameters.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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