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Prognostic value of various metabolic parameters on pre-treatment ^{18}F-FDG PET/CT in patients with stage I-III non-small cell lung cancer

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► ***Original article***

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ABSTRACT

Background: the aim of this study was to investigate the prognostic value of ^{18}Fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) parameters in both overall survival and progression-free survival in Stage I-III non-small cell lung cancer (NSCLC). ***Materials and Methods:*** In this retrospective study, 267 patients who were diagnosed as Stage I-III non-small cell lung cancer and had undergone FDG-PET/CT imaging before treatment were included. PET/CT parameters, maximum and mean standardized uptake values (SUVmax and SUVmean), metabolic tumor volume (MTV), total lesional glycolysis (TLG), and maximum tumor-to-blood standard uptake ratio (SURmax) were calculated. Analyses were performed to evaluate the ability of PET parameters to predict recurrence and death as well as to determine prognostic value. ***Results:*** In predicting both mortality and progression, the area under the ROC curve (AUC) value was highest for TLG (AUC: 0.717, 0.692 respectively). Overall survival was lower in patients with TLG> 214, and progression-free survival was lower in patients with TLG> 194. All PET parameters had a prognostic value in univariate analysis. Age, N1 stage and SUVmean were independent prognostic factors in multivariate analysis. ***Conclusion:*** In predicting death and progression, TLG had the highest predictive value. Age and N1 stage were independent prognostic factors in multivariate analysis, while SUVmean was the most valuable independent prognostic factor.

Keywords: *^{18}F-PET/CT, non-small cell lung cancer, prognosis, survival.*

INTRODUCTION

Lung cancer is the most common type of cancer disease worldwide and the leading cause in cancer-related deaths in men [1].The overall five-year survival rate is approximately 18%. Adenocarcinoma, squamous cell carcinoma (SCC), and small cell carcinoma (SCLC) are the most common types. Adenocarcinoma and SCC account for 85% of lung cancers and are classified as NSCLC [2]. The staging of disease plays an important role in planning treatment and follow-up in patients with NSCLC. Because surgery is recommended as the first-line treatment method in Stage I-III patients, adjuvant chemotherapy and radiotherapy are the preferred treatment modalities in patients with Stage II and III after resection and in patients 1b with a total diameter> 3 cm [3]. ^{18}F-FDG PET/CT is a commonly used imaging modality in almost all phases of lung cancer, including diagnosis, staging, and evaluation of response to treatment. It has been shown that ^{18}F-FDG PET/CT indicates much more accurate staging than CT use [4,5]. Radiotherapy (RT) and chemotherapy (CT) have been used frequently in recent years in NSCLC patients. PET-response criteria for solid tumors (PERCIST) have been

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developed to evaluate treatment response. Response assessment of PERCIST has been shown to be closely related to patient outcomes [6].

Prognostic factors of NSCLC are involved in TNM classification, age, sex, histological type of tumor, and some genetic factors [7].With the increased use of ^{18}F-FDG PET/CT, studies evaluating the prognostic value of PET parameters have increased. According to these study results, PET parameters have been shown to be important prognostic factors in NSCLC. Furthermore, volumetric parameters such as MTV and TLG may predict prognosis better than SUVmax [8].

The aim of this study was to investigate the predictive value of metabolic and volumetric PET parameters in NSCLC in both overall survival and progression-free survival. Also, we aimed to investigate the prognostic value of all PET parameters and to compare with other known prognostic factors.

MATERIALS AND METHODS

Patients

A total of 267 patients included in the study were diagnosed with Stage I-III non-small cell lung cancer and undergone FDG-PET/CT imaging before treatment. The study was performed retrospectively, and all of the patients who has undergone scanning between May 2016 and December 2017 at our clinic enrolled. Inclusion criteries were (a) patients with TNM stage I-III NSCLC, and (b) patients wich PET CT imaging was performed before treatment. TNM staging was performed per the 8th edition of the International Lung Cancer Study Association (IASLC). Patients with distant metastasis were excluded. Eighty patients consisted of operated patients. Of these, 187 had received chemotherapy and radiotherapy treatment only. The median follow-up period was 23 months. Follow-up ranged from 1 to 33 months.

^{18}F-FDG PET / CT imaging and analysis

^{18}F-FDG PET/CT images were obtained using a PHILIPS GEMINI TF 16 Slice PET/CT (Philips Healthcare, Cleveland, OH) device. After fasting at least six hours, patients with blood glucose levels below 200 mg / dL underwent intravenous administration of 8-11 mCi ^{18}F-FDG (Eczacıbası Monrol, Turkey). The body region from the vertex point to the upper femoral region was scanned one hour after injection. CT imaging was performed (140 kV, 100mAs, 5 mm slice), followed by PET imaging. PET emission images were obtained from nine to ten bed positions, depending on the patient's height (1.5 minutes in each position). PET and CT images were uploaded to a workstation and interpreted. On axial images, the volume of interest (VOI) was drawn to include lung tumor tissue semi-automatically. SUVmax of 18F-FDG was measured from VOI. SUVmean and MTV of each lesion were calculated automatically at the workstation, and 41% SUV was accepted as the threshold. TLG was calculated by multiplying SUVmean with MTV. For maximum tumor-to-blood SUV ratio (SURmax), blood SUVmean measurement was measured from VOI in the descending aorta.

Statistical analysis

All statistical analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, IL). The area under the curve (AUC) was evaluated using the Receiver Operator Characteristic ROC analysis to assess the ability of PET parameters to predict recurrence and death. Univariate and multivariate Cox regression analysis was used to evaluate the relationship between age, sex, histopathological parameters, and PET parameters in terms of progression and death. Survival analyses were performed with Kaplan-Meier survival analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Of the 267 patients included in the study, 34 (12.7%) were female and 233 (87.3%) were male. During the follow-up up to 33 months, mortality was seen in 100 (37.5%) patients, and 167 (62.5%) patients were alive. According to

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the TNM stage, 45 (16.9) were stage I, 57 (21.3) were stage II, and 165 (61.8%) were stage III. Mediastinal lymph node metastasis was absent in 84 (31.5%) patients, and 183 (68.5%) patients had lymph node metastasis. Tables 1 and 2 summarize clinic-demographic and FDG-PET/CT parameters of the patients. While the median overall survival was 23 months, the median for progression-free survival was 10 months. PET parameters for primary tumor were as follows: SUVmax; 17.04 ± 8.130, SUVmean; 8,275 ± 2,916, TLG; 693,724 ± 1087,225, MTV; 73, 170 ± 73, 170, SURmax; 9,749 ± 4,466 (table 2).

Table 1. Clinicodemographic characteristics.

	Parameter	Number of patients (%)
Sex	Male	233/267 (87.3%)
	Female	34/267 (12.7%)
T-stage	1a	2/267 (2.07%)
	1b	18/267 (6.7%)
	1c	35/267 (13.1%)
	2a	35/267 (13.1%)
	3	43/267(16,1%)
	4	81/267(30,3%)
N-Stage	N0	84/267 (31,5%)
	N1	65/267 (24,3%)
	N2	118/267 (44,2%)
TNM-stage	I	45/267 (16,9%)
	II	57/267 (21,3%)
	III	165/267 (61,8%)
Histology	Adenocarcinoma	97/267 (36,3%)
	Squamous cell carcinoma	159/267 (59,6%)
	Other	11/267 (4,1%)

Table 2. FDG-PET/CT parameters of primary tumor.

	Minimum	Maximum	Median	Mean	Standard deviation
SUVmax	2	48	16,00	17,04	8,13
SUVmean	1,6	20,80	8,10	8,27	2,91
TLG	0,6	6425,9	268,60	693,72	1087,22
MTV	0,4	591,1	31,40	73,17	102,27
SUR max	1,0	26,2	9,30	9,74	4,46

SUVmax: maximum standardized uptake value; SUVmean: mean standardized uptake value; TLG: total lesion glycolysis; MTV: metabolic tumor volume; SUR max: maximum standard tumor-to-blood.

When a ROC curve analysis was performed to estimate the mortality for the metabolic FDG-PET/CT parameters of the primary tumor of the patients, the area under the highest curve (AUC) belonged to TLG (0.717). The cut-off value for TLG was 214.1, the sensitivity was 66.5%, and the specificity was 63.0%. The ROC curve of the PET parameters to predict death is given in figure 1, and the AUC is shown in table 3.

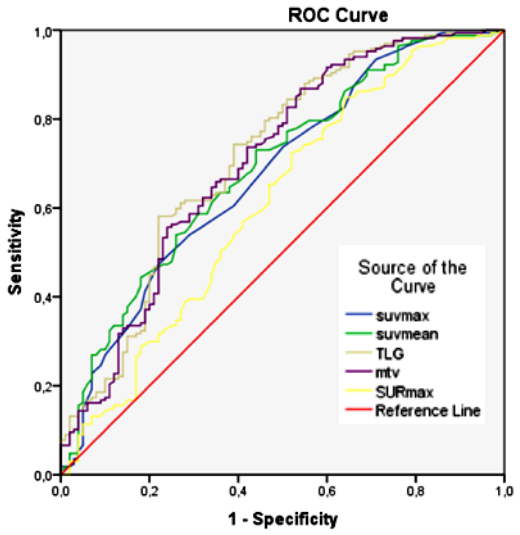


Figure 1. ROC Curve Analysis of PET parameters for predicting death.

Table 3. Area under the ROC curve (AUC) of PET parameters for predicting death.

Parameters	Cutoff	AUC	Sensivite	Spesifite	P value
SUVmax	>15.5	0.677	60.5	61.0	<0.001
SUV mean	>7.95	0,691	63.5	64.0	<0.001
TLG	>214.1	0.717	66.5	63.0	<0.001
MTV	>28.35	0.707	64.7	66.0	<0.001
SUR max	>9.15	0.612	57.0	59.0	0.002

SUR: standard tumor-to-blood SUV ratio; SUVmax: maximum standardized uptake value; SUVmean: mean standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis.

When a ROC curve analysis was performed to predict the progression of metabolic FDG-PET/CT parameters of the primary tumor of the patients, the area under the highest curve (AUC) belonged to TLG (0.692). The cut-off value for TLG was 194.0, sensitivity was 66.0%, and specificity was 62.0%. The ROC curve of the PET parameters to predict progression is given in figure 2, and the AUC is shown in table 4.

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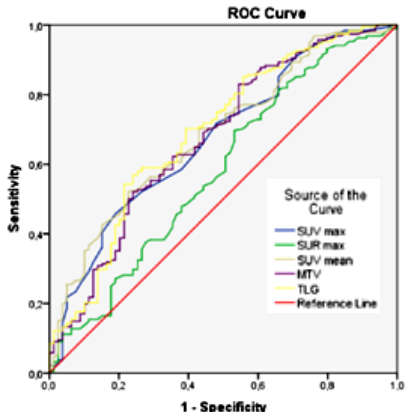


Figure 2. ROC Curve Analysis of PET parameters for predicting progression.

Table 4. Area under the ROC curve (AUC) of PET parameters for predicting progression

Parameters	Cutoff	AUC	Sensivite	Spesifite	P value
SUVmax	>14.5	0.675	64.4	57.0	<0.001
SUV mean	>7.65	0,687	63.3	60.8	<0.001
TLG	>194	0.692	66.0	62.0	<0.001
MTV	>26.9	0.676	62.2	64.6	<0.001
SUR max	>9.0	0.583	54.8	53.2	0.033

The Kaplan-Meier analysis for cut-off values for PET parameters in terms of overall survival is shown in figure 3. There was a significant difference in all parameters in terms of overall survival. P <0.001 for SUVmax, SUVmean, TLG and MTV, and p = 0.009 for SURmax. Median overall survival was 31 months in patients with TLG ≤214.1, while the median overall survival was 15 months in patients with TLG> 214.1.

In univariate analysis, age, T, N and TNM, and all PET parameters had prognostic value in terms of overall survival (table 5). In multivariate analysis, age (HR: 1.031, 95% CI: 1.010 1.053, p = 0.004), N1 stage (HR: 0.416, 95% CI: 0.212-0.814, p = 0.011) and SUVmean (HR: 1.155, 95% CI): 1.005-1.328, p = 0.042) were independent prognostic factors.

The Kaplan-Meier analysis, taking into account the cut-off values of PET parameters for progression-free survival, is shown in figure 4. There was a significant difference in overall survival for SUVmax, SUVmean, TLG, and MTV (p<0.001). There was no significant difference for SURmax (p=0.214). The median progression-free survival was 26 months in patients with TLG ≤194, whereas the median progression-free survival in patients with TLG> 194 was seven months.

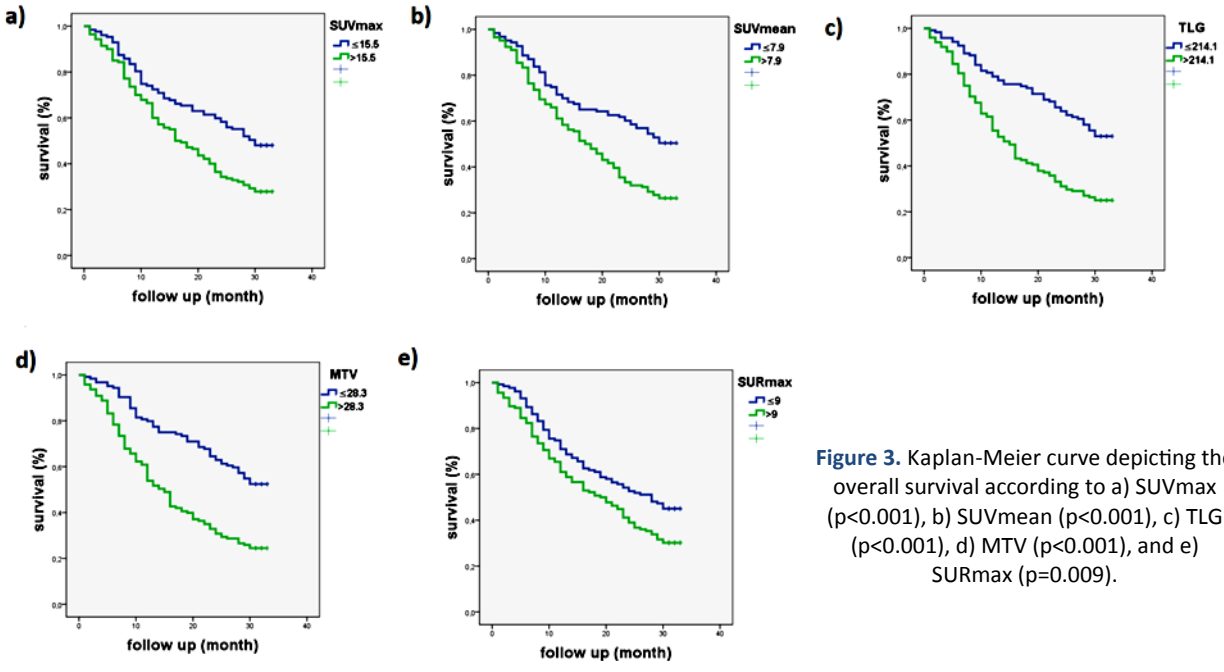


Figure 3. Kaplan-Meier curve depicting the overall survival according to a) SUVmax (p<0.001), b) SUVmean (p<0.001), c) TLG (p<0.001), d) MTV (p<0.001), and e) SURmax (p=0.009).

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Table 5. Univariate and multivariate analysis of overall survival.

			Univarate				Multivariate	
Variables	Wald	HR	95 % CI	P	Wald	HR	95 % CI	P
Sex	0.771	0.811	0.508-1.294	0.367				
Age	7.571	1.026	1.007-1.045	0.006	8.358	1.031	1.010-1.053	0.004
T stage	34,376			<0,001				
T1a	1,213	,329	0,046-2,377	0,271				
T1b	15,263	,099	0,031-,316	<0,001				
T1c	19,172	,251	0,135-,466	<0,001				
T2a	6,884	,527	0,327-,851	0,009				
T2b	4,584	,637	0,421-1.789	0,032				
T3	4,394	,625	0,403-1.331	0,036				
T4	NA	NA	NA	NA				
N stage	34.466			<0.001				
N0	NA	NA	NA	NA				
N1	34,461	0,285	0,187-0,433	<0.001	6,548	0,416	0,212-0,814	0,011
N2	2,427	0,752	0,526-1,076	0,119				
TNM stage	35,502			<0.001				
I	26,856	0,208	0,115-0,376	<0.001				
II	12,933	0,471	0,312-0,710	<0.001				
III	NA	NA	NA	NA				
Histology	2.804			0.452				
Adenocarcinoma	1.804	2.282	0.685-7.603	0.179				
SCC	1.022	1.852	0.561-6.119	0.312				
Other	NA	NA	NA	NA				
SUV_{max}	22.314	1.041	1.024-1.058	<0.001				
SUVmean	26.313	1.130	1.079-1.184	<0.001	4.116	1.155	1.005-1.328	0.042
TLG	32.478	1.000	1.000-1.000	<0.001				
MTV	27.610	1.003	1.002-1.005	<0.001				
SURmax	7.360	1.044	1.012-1.077	0.008				

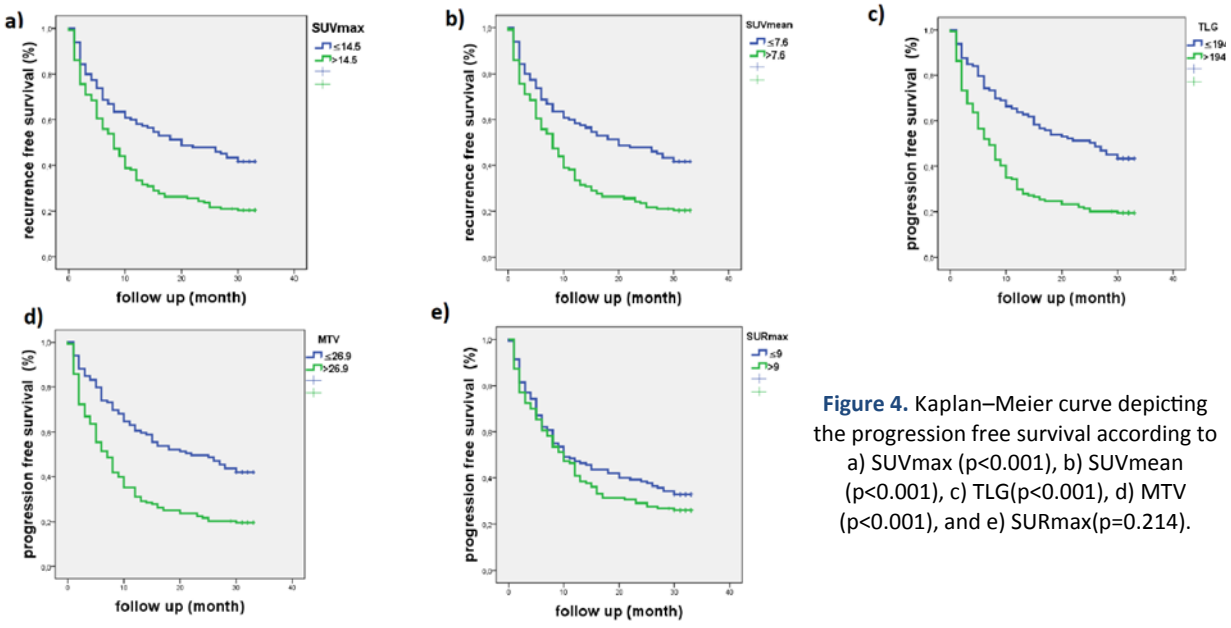


Figure 4. Kaplan–Meier curve depicting the progression free survival according to a) SUVmax (p<0.001), b) SUVmean (p<0.001), c) TLG(p<0.001), d) MTV (p<0.001), and e) SURmax(p=0.214).

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In univariate analysis age, T, N and TNM stage and all PET parameters had prognostic value in terms of progression-free survival (table 6). In multivariate analysis only age (HR: 1.029, 95% CI: 1.009-1.049, p = 0.004), N1 stage (HR: 0.519, 95% CI: 0.283-0.950, p = 0.033) and SUVmean (HR: 1.174, 95) % CI: 1.031-1.337, p = 0.015) were independent prognostic factors.

Table 6. Univariate and multivariate analysis of progression.

			Univarate				Multivariate	
Variables	**Wald**	**HR**	**95 % CI**	**P**	**Wald**	**HR**	**95 % CI**	**P**
Sex	0.478	0.857	0.554-1.326	0.481				
Age	7.863	1.025	1.007-1.042	0.005	8.358	1.031	1.010-1.053	0.004
T stage	35,504			<0.001				
T1a	1,715	0,267	0,037-1,926	0,190				
T1b	16,317	0,178	0,077-,411	<0,001				
T1c	20,371	0,292	0,171-,498	<0,001				
T2a	8,560	0,499	0,313-,795	0,003				
T2b	5,525	0,621	0,418-,924	0,019				
T3	4,778	0,626	0,411-,953	0,029				
T4	NA	NA	NA	NA				
N stage	24,833			<0.001				
N0	NA	NA	NA	NA				
N1	24,814	0,401	0,280-,575	<0,001	4.525	0.519	0.283-0.950	0.033
N2	2,121	0,770	0,542-,575	0,145				
TNM stage	30,257			<0.001				
I	23,930	0,307	0,191-,493	<0.001				
II	10,997	0,523	0,356-,767	0.001				
III	NA	NA	NA	NA				
Histology	3.306			0.191				
Adenocarcinoma	1.404	1.777	0.687-4.600	0.236				
SCC	0.442	1.378	0.536-3.544	0.506				
Other	NA	NA	NA	NA				
SUV_{max}	19.313	1.035	1.019-1.051	<0.001				
SUVmean	24.384	1.116	1.069-1.166	<0.001	5.891	1.174	1.031-1.337	0.015
TLG	27.142	1.000	1.000-1.000	<0.001				
MTV	23.722	1.003	1.002-1.004	<0.001				
SURmax	3.946	1.030	1.000-1.061	0.047				

DISCUSSION

In our study, PET parameters for SUVmax, SUV mean, TLG, MTV, and SURmax were estimated by ROC analysis in predicting death and progression. AUC value was the highest with TLG in both mortality and diseases progression estimation (AUC: 0.717, 0.692 respectively). The cut-off value for TLG was 214 to predict death and 194 to predict progression-free survival. In the Kaplan-Meier analysis using cut-of values, while overall survival was significantly different in all PET parameters, a significant difference was found in all factors except SUR max in progression-free survival. All PET parameters were associated with prognosis in univariate analysis. Age, N1 stage, and SUVmean were independent prognostic factors for death and progression in patients with stage I-III NSCLC.

To determine the predictive value of PET parameters in terms of mortality, significant results were reported in cut-of-values and Kaplan-Meier analyses performed in the literature. Initial studies have investigated the prognostic value of the commonly used SUVmax parameter in routine reporting [9, 10, 11].

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Subsequently, Kohutek *et al.* [9] performed a study of 211 patients with stage I NSCLC, showing that patients with a high SUVmax (SUVmax >3) value had shorter overall survival. In addition, high SUVmax was associated with a higher risk for local recurrence and distant metastasis after Stereotactic Body Radiation Therapy (SBRT). According to the meta-analysis study of Dong *et al.* [12] SUVmax had prognostic value in terms of overall survival, and survival of patients with primary tumors with high SUVmax was significantly lower. In one study, Hsu *et al.* showed that tumor size and SUVmax value can predict post-op results in patients with early stage NSCLC. In addition, overall survival was significantly higher in patients with tumor lengths below 3 cm and SUVmax below 3.1 in this study [13].In the study of Domachevsky *et al.* showed that SUVmax> 8.2 in terms of overall survival is a prognostic factor in patients with stage I-II NSCLC [14]. In our study, SUVmax had predictive and prognostic value in terms of overall survival and recurrence. In addition, overall survival was significantly lower in stage I -III patients with SUVmax of the primary tumor> 15.5. We think that the difference between SUVmax cut of values is related to the stages of patients with NSCLC included in the study.

After the development of new PET parameters, developed in the following years and taking into account the metabolic characteristics of the tumor, studies investigating the prognostic value of these new parameters were published. In the studies in which SUVmax was compared with SUVmean and other metabolic PET parameters, SUVmax has less prognostic significance than other parameters [8,15,16]. In our study, all PET parameters were found to be associated with prognosis. While TLG was a better parameter in predicting death (>214) and progression (>194), SUVmean appears to be an independent prognostic factor in overall survival (HR: 1.155) and progression-free survival (HR: 1.155). It is a parameter obtained by multiplying SUVmean and MTV in TLG. In the literature, researchers have reported that the prognostic value of TLG and SUVmean is higher in most of the ground studies compared to others. All these results suggest that the average uptake in the whole lesion is more important than the maximum uptake of FDG in the lesion in terms of prognosis.

According to a study conducted by Shin *et al.* [17] with 77 NSCLC patient data, SUVmax and SUVmean had the highest AUC (0.812; 0.812) in death prediction, and SURmax and SUVmean had the highest AUC in recurrence prediction (0.759; 0.759, respectively). They also emphasized that, while all PET parameters have prognostic value, the N stage is the most important prognostic factor in multivariate analysis for both death and recurrence. In our study, age and N1 stage were independent prognostic factors in multivariate analysis, while SUVmean was the most valuable independent prognostic factor. SURmax was observed as a prognostic factor in our study, although it did not appear to have a significant effect on progression-free survival. While there is no literature finding to support this situation, the lack of standardization in the manually drawn ROI of the descending aorta in SURmax measurement may be a factor that may affect the SURmax value. In studies, Olivier *et al.* [18] with 17 NSCLC patients, Sharma *et al.* [19] with 60 NSCLC patients, and Salavati *et al.* [20] with 196 NSCLC patients investigated the prognostic value of PET parameters, wherein MTV and TLG were the most important prognostic values among all PET parameters. In addition, Lee *et al.* [21] noted that, among 63 NSCLC patients, MTV and TLG appear to be the most valuable prognostic factors. In a similar study, Steiger *et al.* showed that volume-based PET parameters are associated with progression-free survival and overall survival and can be used for risk assessment in stage I-II NSCLC [22]. In a meta-analysis, Liu *et al.* [23] investigating the prognostic value of PET CT parameters in NSCLC patients, reported that patients with high SUVmax, MTV and TLG have a higher risk of recurrence and death. However, most of the studies included in the meta-analysis consisted only of SUVmax. When these results are evaluated in the literature, PET parameters appear to be valuable prognostic factors and MTV and TLG are more valuable parameters

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than others. According to Wang *et al.* [24], in patients with stage I-III NSCLC, when look at whole body values calculated from the sum of both primary tumor and nodal PET CT parameters, the whole body MTV was significantly associated with overall survival and progression-free survival, and whole body TLG was significantly associated with progression-free survival, in multivariate analysis.

One of the limitations of our study was that it was a retrospective study, and another was that the follow-up period was short.

CONCLUSION

In patients with stage I-III NSCLC, TLG was the most predictive PET parameter for predicting death and progression. Overall survival was lower in patients with primary tumor, greater than 214.1 TLG, whereas progression-free survival was lower in patients, greater than 194. Age and N1 stage were independent prognostic factors in multivariate analysis, while SUVmean was the most valuable independent prognostic factor for overall survival and progression.

Compliance with ethical standards

Approval was obtained from the local ethics committee (No: 19-KAEK-168).

Ethical approval

The study was authorized by the local ethics committee.

***Conflicts of interest*:** *Declared none.*

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