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The prognostic value of PET/CT-derived volumetric parameters for postoperative recurrence in resected non-small cell lung cancer

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ABSTRACT

Aims: Non-small-cell lung cancer (NSCLC) recurrence is high even after complete surgical resection. This study aimed to investigate the relationship between recurrence and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) and to determine prognostic factors.

Methods: Patients with pathologically confirmed stage I-II NSCLC who underwent surgical resection were retrospectively analyzed. Before surgery, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were derived by applying SUV_{max}-based thresholds of 2.5 and 42%. Data regarding demographics, clinicopathological features, and tumor characteristics were gathered. Kaplan-Meier method was used for disease-free survival (DFS) and overall survival rates. Factors associated with recurrence were evaluated using univariate and multivariate Cox regression analysis.

Results: The mean age of the 179 patients included in the study was 61.24 years. The median follow up duration was 50 months. Recurrence occurred in 38.5% of the patients. Prognostic factors for recurrence were larger tumor size, visceral pleural invasion, and PL2 involvement. When stratified by histology, MTV measured using SUV_{max} thresholds of 2.5 and 42% was significantly higher in patients with recurrence in the squamous cell carcinoma subgroup. In univariate analysis, high $MTV_{42\%}$ was associated with shorter DFS. In multivariate analysis, $MTV_{2.5}$ remained independently associated with DFS. SUV_{max} and TLG were not independently associated with DFS.

Conclusion: Larger tumor size and pleural invasion were associated with shorter DFS. $MTV_{2.5}$ was independently associated with DFS; however, its low discriminatory performance limits its current clinical utility, and the finding requires external validation.

Keywords: Disease-free survival, NSCLC, recurrence, SUV_{max}, total lesion glycolysis, metabolic tumor volume

INTRODUCTION

Lung cancer has a high incidence and mortality. Non-small cell lung cancer (NSCLC) is observed in 80-85% of cases, and the most common subtype is adenocarcinoma.[1,2] NSCLC is usually diagnosed at an advanced or metastatic stage, and the 5-year survival rates are low.[3] Even for patients who receive surgical intervention with complete resection (R0), the estimated 5-year survival rate is approximately 73%.[4] Therefore, identifying additional poor prognostic factors remains critically important. The TNM staging system is widely recognized as a critical prognostic factor and the primary guide for treatment decisions.[5] However, it does not always accurately represent the tumor's biological behavior, indicating a need for supplementary prognostic biomarkers.

18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) is a widely used imaging technique for differential diagnosis, staging, monitoring therapeutic responses, detecting recurrent disease, and assisting in radiotherapy planning. In clinical practice, the most commonly used 18F-FDG PET/CT parameter for measuring the metabolic activity of a lesion is the maximum standardized uptake value (SUV_{max}).

In 18F-FDG PET/CT scans, the most commonly used parameter for evaluating lesions is SUV_{max}. This parameter provides a semi-quantitative measurement of the radioactivity concentration within a lesion. SUV_{max} is calculated as the highest standardized uptake value obtained

from the voxel demonstrating the highest activity within the region of interest drawn around the lesion.[6] Several studies have demonstrated an association between elevated SUV_{max} values and poor prognosis in malignancies;[7,8] however, this relation was not confirmed in some studies.[9] In addition to SUV based metrics, total lesion glycolysis (TLG) and metabolic tumor volume (MTV) can be derived from PET/CT and have been suggested to be more reliable parameters for predicting prognosis than SUV.[10-12]

Despite numerous studies evaluating PET/CT-derived metabolic parameters in NSCLC, their prognostic value in patients with completely resected early-stage disease remains controversial. Previous studies have reported inconsistent findings regarding SUV_{max}, MTV, and TLG because of differences in patient populations, tumor stages, histopathological composition, and thresholding methods used for volumetric analysis. Moreover, studies comparing different MTV/TLG thresholding approaches and evaluating these parameters according to histopathological subtype remain limited. The primary aim of this study was to evaluate the prognostic value of PET/CT-derived metabolic parameters for predicting recurrence in early-stage NSCLC. To address these gaps, we evaluated metabolic parameters using two commonly applied thresholding methods and performed histopathological subtype-specific analyses in a homogeneous cohort of completely resected stage I-II NSCLC patients. The secondary aim of this study was to evaluate the relationship between PET/CT-derived parameters across histopathological subtypes and recurrence, as well as to identify other prognostic factors associated with recurrence.

METHODS

Ethics

This study was conducted with the approval of the Ethics Committee for Clinical Researches of the Ankara Keçiören Training and Research Hospital (Date: 12.06.2019, Decision No: 2012-KAEK-15/1915). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data Evaluation

We screened patients diagnosed with NSCLC who underwent surgical resection from January 2012 to December 2016. Follow-up was performed at the same institution, and survival and recurrence data were obtained from hospital records.

Only patients with histologically proven stage I-II NSCLC who underwent complete tumor resection (R0) were included in the study. Surgical procedures consisted of lobectomy or pneumonectomy with systematic lymph node dissection. The study included patients with pathologically confirmed N0 status based on postoperative histopathological evaluation following surgical resection. The 7th edition of the TNM classification system was used to determine pathological staging, because it was in routine clinical use during the study period. Histopathological subtypes of adenocarcinoma, squamous cell carcinoma (SCC), and adenosquamous carcinoma were included. Exclusion criteria included non-R0 resection, limited resection (segmentectomy or wedge resection), surgery performed at another center, stage III-IV NSCLC, oligometastatic disease, second primary malignancy, multiple primary lung cancers, thoracic radiotherapy, unavailable preoperative PET/CT images, and incomplete postoperative follow-up data.

Patient demographic characteristics (age, gender, and presence of comorbidities), histological subtype (adenocarcinoma, SCC, and adenosquamous carcinoma), pathological tumor size and stage, visceral pleural invasion (VPI) and PL2 involvement were recorded. In the modified Hammar system, PL0 is defined as tumor growth restricted to the subpleural lung parenchyma, without invasion beyond the elastic layer of the visceral pleura. Tumor invasion beyond the elastic layer is defined as PL1, invasion reaching the pleural surface is defined as PL2, and invasion into the parietal pleura is defined as PL3. VPI is defined as the presence of PL1 or PL2 invasion.[13]

Locoregional recurrence was defined as recurrence in the ipsilateral lung lobe and/or metastasis to the ipsilateral mediastinal or hilar lymph nodes following lobectomy or pneumonectomy. Distant metastasis was defined as recurrence occurring in sites other than the ipsilateral lung. Recurrence was defined based on clinical evaluation, imaging findings, and histopathological assessment. Patients with clear radiological progression on thoracic CT or 18F-FDG PET/CT were considered to have recurrence based on imaging findings. In cases with suspicious findings, histopathological confirmation was obtained by biopsy.

18F-FDG PET/CT Imaging Protocol

Only preoperative 18F-FDG PET/CT scans performed before initiation of oncologic management were included, with image data sourced from the institutional picture archiving and communication system (PACS). All examinations were performed within a mean of 33±2.5 days before surgery. Primary tumor SUVmax, mean SUV (SUV_{mean}), MTV and TLG were calculated.

An integrated PET-CT scanner (Siemens Biograph-6 Hi-Rez; Siemens Medical Solutions, Knoxville, TN, USA) was used for imaging. According to the standard imaging protocol, all patients restricted food and water intake for at least 6 hours prior to imaging. Patients with peripheral blood glucose values under 180 mg/dl received intravenous 18F-FDG at doses of 370-555 MBq (10-15 mCi). After a standardized uptake period of 60 minutes at rest, imaging was performed. Initially, a low-dose computed tomography (CT) scan was acquired from the vertex to the proximal femur with patients positioned supine and arms raised, using the CareDose protocol (Siemens). PET imaging was performed using 6-8 bed positions, with a scanning duration of 3 minutes for each position. CT-derived data were applied for attenuation correction, and PET datasets were reconstructed via an iterative reconstruction method employing 4 iterations and 8 subsets, with additional Gaussian filtering.

18F-FDG PET/CT Image Analysis

18F-FDG PET/CT images were analyzed using dedicated software by one experienced nuclear medicine physician who was blinded to the clinical data.

SUV_{max} was calculated as follows:

SUV_{max}=tissue concentration (MBq/ml)/injected FDG activity (MBq)/body weight (g). SUV_{mean} within the same region was recorded.

Various methods for calculating MTV and TLG have been described in the literature. In the absence of a universally accepted standard for volumetric PET analysis, two thresholding methods were selected because they represent the most commonly used approaches in NSCLC. Accordingly, MTV was calculated using two different approaches. First, metabolically active tumor volume was defined as the volume of voxels demonstrating an uptake greater than 42% of the primary tumor SUV_{max}.[14] Second, MTV was calculated using a fixed absolute SUV threshold of 2.5, including all voxels with an SUV ≥2.5.8 TLG was derived by multiplying MTV and SUV_{mean}. Parameters calculated using the fixed SUV threshold were termed $MTV_{2.5}$ and $TLG_{2.5}$, whereas those calculated using the 42% SUV_{max} threshold were termed $MTV_{42\%}$ and $TLG_{42\%}$. SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, $MTV_{42\%}$, and $TLG_{42\%}$ values were calculated separately for adenocarcinoma and SCC, and their associations with recurrence were evaluated.

Statistical Analysis

Categorical variables were presented as frequencies and percentages, while continuous variables were reported as mean±standard deviation or median (minimum-maximum). The Shapiro-Wilk test was used to assess normality. Comparisons between groups were performed using the independent samples t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using the Chi-square test or Fisher's exact test.

The prognostic performance of SUV_{max}, MTV, and TLG for recurrence was examined through receiver operating characteristic curve analysis. Threshold values yielding the highest discriminatory power were determined using the Youden criterion, and diagnostic performance metrics including sensitivity, specificity, positive predictive value, and negative predictive value were subsequently calculated. Based on these thresholds, patients were categorized into high and low risk groups according to SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, $MTV_{42\%}$, and $TLG_{42\%}$. Disease-free survival (DFS) and 5 years survival were estimated using the Kaplan-Meier approach, with between-group differences evaluated by the log-rank test. Variables associated with DFS were further explored using univariate and multivariate Cox proportional hazards models. Because the volumetric parameters derived using the fixed and relative thresholding methods were potentially correlated, two separate multivariable models were constructed. Model 1 included SUV_{max}, $MTV_{2.5}$, and $TLG_{2.5,}$ whereas model 2 included SUV_{max}, $MTV_{42\%}$, and $TLG_{42\%}$, together with the selected clinicopathological covariates. Statistical significance was defined as a two-sided p value below 0.05. All analyses were conducted using IBM SPSS Statistics (version 26.0; IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 503 individuals with histologically proven non-small cell lung cancer who underwent curative N0, R0 surgical resection between 2012 and 2016 were initially evaluated. After applying the predefined inclusion criteria, 179 patients were ultimately included in the analysis. The majority of patients were male (n=160, 89.4%). The mean age was 61.24±7.63 years. At least one comorbid condition was identified in 108 patients (60.3%). The median duration of follow-up was 50 (6-94) months. Pathological stage I disease was identified in 131 patients (73.2%), while 48 patients (26.8%) had stage II disease. Histopathologically, 86 patients (48%) had adenocarcinoma, 86 patients (48%) had SCC. During the follow-up period, disease recurrence was observed in 69 (38.5%) patients. The median interval from surgery to recurrence was 19 (4-80) months. Patient and tumor characteristics are summarized in **Table 1**.

Table 1. Patient and tumor characteristics

Patient characteristics	**n (%)**
Gender	
Male	160 (89.4%)
Female	19 (10.6%)
Age (years)*	61.24±7.63
The presence of comorbidities	108 (60.3%)
Follow-up time (months)**	50 (6-94)
Recurrence	69 (38.5%)
Recurrence time (months)**	19 (4 - 80)
Tumor characteristics	
TNM staging	
Stage I	131 (73.2%)
Stage II	48 (26.8%)
Histopathology	
Adenocarcinoma	86 (48%)
Squamous cell carcinoma	86 (48%)
Adenosquamous carcinoma	7 (4%)

*Mean±standard deviation **Median (min-max) TNM: Tumor, node, metastasis, Min: Minimum, Max: Maximum

Association of Demographic Findings and Tumor Characteristics with Recurrence

No statistically significant associations were found between recurrence status and age, gender, or the presence of comorbidities, pathological stages and histopathological subtype. Tumor size was larger in the recurrence group, and this difference was statistically significant (p=0.046). The presence of VPI and PL2 involvement was significantly higher in patients with recurrence than in those without recurrence (p=0.029 and p=0.018, respectively). The association of demographic and tumor characteristics with recurrence is presented in **Table 2**.

18F-FDG PET/CT-Derived Parameters and Association with Recurrence

The overall and histopathological subgroup analyses of SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, $MTV_{42\%}$, and $TLG_{42\%}$ are summarized in **Table 3**. In the overall analysis, SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, $MTV_{42\%}$, and $TLG_{42\%}$ values were not significantly different between the recurrence and non-recurrence groups. When stratified by histopathological subtype, no significant differences were observed in the adenocarcinoma subgroup for any of the evaluated parameters. In contrast, in the

Table 2. Association of demographic findings and tumor characteristics with recurrence

	Without recurrence n (%)	Recurrence n (%)	p
Age*	61.24±7.57	61.25±7.81	
Gender			0.247
Male	96 (60%)	64 (40%)	
Female	14 (73.7%)	5 (26.3%)	
Comorbidity			
Absent	49 (69%)	22 (31%)	0.092
Present	61 (56.5%)	47 (43.5%)	
TNM staging			
Stage I	85 (64.9%)	46 (35.1%)	0.119
Stage II	25 (52.1%)	23 (47.9%)	
Histopathology			
Adenocarcinoma	50 (58.1%)	36 (41.9 %)	0.332
Squamous cell carcinoma	54 (62.8%)	32 (37.2%)	
Adenosquamous carcinoma	6 (85.7%)	1 (14.3%)	
Tumor size (cm)*	3.45±1.53	3.94±1.68	0.046
Visceral pleural invasion (PL1-PL2)			
Absent	81 (66.9%)	40 (33.1%)	0.029
Present	29 (50%)	29 (50%)	
PL2 involvement			
Absent	63 (70%)	27 (30%)	0.018
Present	47 (52.8%)	42 (47.2%)	

p<0.05 statistically significant; * Mean±standard deviation TNM: Tumor, node, metastasis, PL1: Tumor invasion beyond the elastic layer of the visceral pleura, PL2: Tumor invasion to the surface of the visceral pleura

SCC subgroup, $MTV_{2.5}$ and $MTV_{42\%}$ were significantly higher in patients with recurrence compared to those without recurrence (p=0.026 and p=0.016, respectively). No statistically significant differences were found for SUV_{max}, $TLG_{2.5}$ and $TLG_{42\%}$ parameters in either subgroup.

To evaluate the sensitivity and specificity of metabolic parameters in predicting recurrence, ROC curve analysis was performed and optimal cut-off values were determined. The determined cut-off values, sensitivity, specificity, AUC and p value are presented in **Table 4**, and the ROC curve in **Figure 1**. According to the cut-off values, the metabolic parameters were categorized into two different groups as high and low.

Univariate and Multivariate Cox Regression Analysis

Univariate and multivariate Cox regression analysis results are presented in **Table 5**. In univariate analysis, VPI, PL2 involvement, and tumor size were identified as significant predictors of DFS (p=0.009, p=0.011, and p=0.035; respectively). VPI was associated with shorter DFS (HR, 1.902; 95% CI, 1.176-3.077; p=0.009), while PL2 involvement was also associated with shorter DFS (HR, 1.874; 95% CI, 1.154-3.043; p=0.011). $MTV_{42\%}$ was significantly associated with DFS, with lower values (≤30.66) indicating reduced recurrence risk (p=0.036).

In multivariate analysis, $MTV_{2.5}$ remained independently associated with DFS in model 1 (p=0.038), whereas SUV_{max} and $TLG_{2.5}$ were not significant. In model 2, none of the parameters derived using the 42% threshold (SUV_{max}, $MTV_{42\%}$, and $TLG_{42\%}$) were identified as independent prognostic factors.

Survival Analysis

The 5-year survival rate was 87.2%, and the 5-year DFS rate was 63.7%. The 5-year DFS rate was 66.5% at low $MTV_{42\%}$ and

Table 3. 18F-FDG PET/CT metabolic parameters according to recurrence status and histopathology

Parameter	Total median (min-max)	Recurrence median (min-max)	No recurrence median (min-max)	p
SUV_{max}				
Overall	12.22 (2.48-42.92)	12.64 (8.62-16.58)	12.22 (7.75-19.12)	0.458
Adenocarcinoma	10.20 (2.79-26.93)	9.74 (6.80-14.43)	11.00 (5.76-18.60)	0.662
SCC	14.45 (2.48-42.92)	14.45 (11.23-17.60)	14.32 (10.66-21.00)	0.855
$MTV_{2.5}$ (cm^3)				
Overall	21.85 (0.05-347.41)	26.71 (8.45-49.47)	19.28 (5.91-46.64)	0.300
Adenocarcinoma	18.01 (0.05-347.41)	17.06 (4.63-32.33)	18.51 (5.18-47.72)	0.830
SCC	24.28 (0.05-136.57)	35.67(14.44-71.66)	20.98 (8.78-74.10)	0.026
$TLG_{2.5}$				
Overall	113.92(0.12-2504.82)	124.70(35.87-280.11)	108.74(30.20-282.19)	0.512
Adenocarcinoma	94.17 (0.13-2504.82)	86.97 (19.58-245.69)	94.71 (21.02-267.56)	0.707
SCC	143.75 (0.12-923.21)	202.29(79.23-589.26)	115.65(47.98-296.93)	0.068
$MTV_{42\%}$ (cm^3)				
Overall	10.22 (1.03-154.12)	12.38 (3.85-24.03)	9.39 (4.24-19.54)	0.271
Adenocarcinoma	10.83 (1.03-154.12)	9.75 (3.34-19.07)	11.95 (3.30-24.28)	0.612
SCC	10.29 (1.25-54.25)	14.89 (7.70-29.45)	8.42 (4.35-16.51)	0.016
$TLG_{42\%}$				
Overall	73.35 (4.35-1622.88)	76.82 (27.31-195.16)	72.06 (26.96-175.72)	0.461
Adenocarcinoma	68.34 (4.35-1622.88)	67.28 (15.45-171.90)	70.13 (19.40-193.14)	0.720
SCC	88.27 (6.08-596.01)	125.73(66.32-281.11)	74.18 (30.84-175.72)	0.064

Values are presented as median (min-max). p<0.05 was statistically significant. Min: Minimum, Max: Maximum, 18F-FDG: Fluorine-18 fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standardized uptake value, SCC: Squamous cell carcinoma, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

Table 4. Diagnostic performance of SUV_{max}, MTV, and TLG cutoff values for recurrence

Parameter	Cut-off	AUC	p-value	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SUV_{max}	6.56	0.533	0.458	0.449-0.617	88.4	22.7	41.5	75.0
$MTV_{2.5}$ (cm^3)	25.31	0.546	0.300	0.459-0.633	52.17	62.73	46.8	67.6
$TLG_{2.5}$	200.48	0.529	0.512	0.443-0.616	40.60	66.4	44.4	64.7
$MTV_{42\%}$ (cm^3)	30.66	0.549	0.271	0.461-0.637	20.29	90.91	58.3	64.5
$TLG_{42\%}$	139.77	0.533	0.461	0.445-0.620	37.68	72.73	46.4	65.0

SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

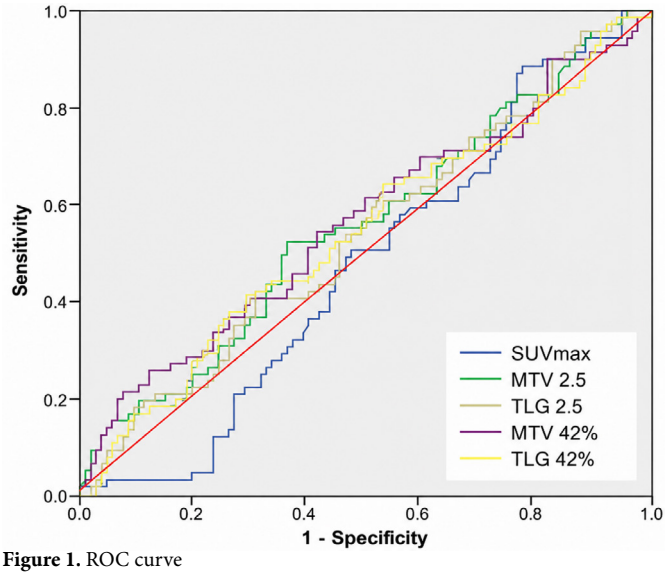

Figure 1. ROC curve
SUVmax: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, ROC: Receiver operating characteristic

45.8% at high $MTV_{42\%}$ (p=0.038). The 5-year DFS according to $MTV_{42\%}$ is shown in **Figure 2**. While $MTV_{42\%}$ $MTV_{42\%}$ was associated with 5-year DFS but not with 5-year survival, it was not associated with 5-year survival. SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, and $TLG_{42\%}$ were not found to be associated with either 5-year survival or 5-year DFS (**Table 6**).

DISCUSSION

In this study, we evaluated the association between PET/CT-derived parameters and recurrence. Histopathological subgroup analyses were conducted to further explore their relationship with recurrence and to identify additional clinicopathological prognostic factors. In this study, larger tumor size and the presence of VPI, particularly PL2 involvement, were significantly associated with recurrence. In the SCC subgroup, $MTV_{2.5}$ and $MTV_{42\%}$ were significantly higher in patients with recurrence, whereas these parameters were not significant in adenocarcinoma. In multivariate

Table 5. Univariate and multivariate Cox regression analysis for disease-free survival

	Univariate Cox regression		Multivariate Cox regression (model 1)		Multivariate Cox regression (model 2)	
Parameter	**Hazard ratio***	**p**	**Hazard ratio***	**p**	**Hazard ratio***	**p**
Gender	0.584 (0.265-1.451)	0.246				
The presence of comorbidity	1.587 (0.956-2.637)	0.074				
Histopathology	0.696 (0.456-1.062)	0.093	0.767 (0.491-1.198)	0.243	0.721 (0.455-1.140)	0.162
Tumor size	1.169 (1.011-1.351)	0.035				
TNM staging	1.555 (0.942-2.567)	0.084	0.954 (0.644-2.271)	0.554	1.071 (0.551-2.083)	0.839
Visceral pleural invasion	1.902 (1.176-3.077)	0.009				
PL2 involvement	1.874 (1.154-3.043)	0.011	1.655 (0.954-2.271)	0.073	1.547 (0.880-2.720)	0.129
SUV_{max}						
Low (≤6.56)	1.854	0.101	1.769	0.165	1.874	0.118
High (<6.56)	(0.887-3.875)		(0.790-3.962)		(0.853-4.119)	
$MTV_{2.5}$ (cm^3)						
Low (≤25.31)	1.534	0.076	2.288	0.038		
High (25.31<)	(0.956-2.460)		(1.046-5.006)			
$TLG_{2.5}$						
Low (≤200.48)	1.208	0.441	0.448	0.051		
High (200.48<)	(0.747-1.955)		(0.201-1.025)			
$MTV_{42\%}$ (cm^3)						
High (30.66<)	1.874	0.036			1.319	0.510
Low (≤30.66)	(1.041-3.373)				(0.579-3.001)	
$TLG_{42\%}$						
Low (≤139.77)	1.428	0.152			0.977	0.948
High (139.77<)	(0.877-2.325)				(0.495-1.930)	

* Values in parentheses indicate the 95% confidence interval. p<0.05 was statistically significant. TNM: Tumor, node, metastasis, PL2: Tumor invasion to the surface of the visceral pleura, SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

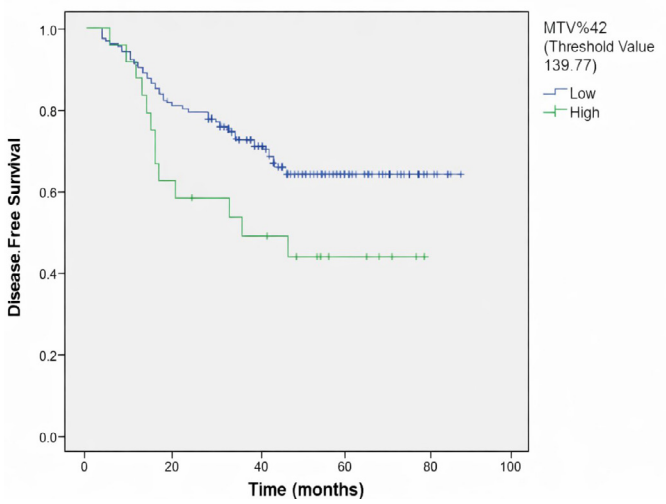

Figure 2. 5-year disease-free survival for $MTV_{42\%}$
MTV: Metabolic tumor volume

Table 6. The relationship between 5-year survival and 5-year disease-free survival with SUV_{max}, MTV, and TLG

	5-year survival		5-year disease-free survival	
	%	p	%	p
SUV_{max}				
Low (≤6.56)	75.8	0.456	75.8	0.147
High (6.56<)	68.5		61.0	
$MTV_{2.5}$ (cm^3)				
Low (≤25.31)	74.5	0.150	69.6	0.073
High (25.31<)	63.6		55.8	
$TLG_{2.5}$				
Low (≤200.48)	71.9	0.488	66.7	0.322
High (200.48<)	66.2		58.5	
$MTV_{42\%}$ (cm^3)				
Low (≤30.66)	72.3	0.058	66.5	0.038*
High (30.66<)	54.2		45.8	
$TLG_{42\%}$				
Low (≤139.77)	73.2	0.154	67.5	0.116
High (139.77<)	62.5		55.4	

*p<0.05 was statistically significant. SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

analysis, $MTV_{2.5}$ remained independently associated with DFS, while $MTV_{42\%}$ was associated only with 5-year DFS.

Demographic Findings and Tumor Characteristics

In studies evaluating postoperative recurrence rates have been reported to range from 25% to 37%. The associations between age, gender, comorbidities, and recurrence were variable across studies.[15-19] Taylor et al.[20] reported a significant association between tumor size, pathological stage, and recurrence in 1.143 patients with NSCLC. Tumors larger than 3 cm had a higher risk of recurrence. Other studies have similarly demonstrated an association between increased recurrence risk and both tumor size and pathological stage.[16,18,21] In our study, the recurrence rate was 38.5%. Age, gender, comorbidities were not significantly associated with recurrence. No significant association was found between pathological stage and recurrence. An unexpected finding of this study was the higher proportion of recurrence observed among patients with pathological stage I disease. This result should be interpreted with caution and is most likely attributable to selection bias inherent to the retrospective study design. However, a significant relationship was observed between tumor size and recurrence. The recurrence group had a larger tumor size. The lack of a significant association with pathological stage, despite the significance of tumor size, may be explained by limitations of the 7th TNM staging system in fully reflecting the prognostic impact of the T factor, which led to modifications of the T descriptor in the 8th TNM staging system.

Hung et al.[22] reported recurrence rates of 29.0% for PL1 and 48.1% for PL2 in 355 N0 patients with non-small cell lung cancer. PL2 involvement was associated with a significantly higher recurrence rate than PL1 involvement. Patients with VPI have significantly higher rates of postoperative recurrence than those without VPI.[19,23,24] In our study, consistent with the literature, the PL2 group showed a higher recurrence rate compared with patients without PL2 involvement. Additionally, the presence of VPI and PL2 involvement was associated with a higher recurrence rate.

18F-FDG PET/CT Findings of Tumor

Previous studies have reported considerable variability in the median values of metabolic parameters among stage I-II NSCLC patients undergoing curative surgery. Hyun et al.[11] reported median values of SUV_{max} 10.9, MTV 15.4 cm^3, and TLG 71.6, whereas Melloni et al.[25] found lower median values (SUV_{max} 6.5, MTV 2.95 cm^3, TLG 9.61). Agarwal et al.[9] reported a median SUV_{max} of 5.9, and Park et al.[12] reported mean values of SUV_{max} 4.55, MTV 5.92, and TLG 14.42 in stage I NSCLC. Previous studies have shown that primary tumor SUV_{max}, MTV, and TLG are significantly higher in patients with recurrence.[18,19,26] In our study, the median values of SUV_{max}, MTV and TLG differed from those reported in previous studies. In the overall analysis, no significant association was observed between PET derived metabolic parameters and recurrence. Several factors may explain this finding.

First, variability in SUV threshold values used to define MTV and TLG may influence the results. MTV can also be calculated independently of SUV threshold values. The most accurate method for determining MTV is manual delineation of tumor boundaries, in which lesion contours are drawn slice by slice to obtain the true tumor volume and achieve highly accurate results, potentially reducing tumor heterogeneity. However, this approach is time-consuming and not practical for routine clinical use. Another possible explanation is the influence of histopathological differences. Previous studies have shown that SCC is metabolically more active and has significantly higher SUV_{max}, MTV, and TLG values.[11,27,28] Based on this, we performed subgroup analyses in our study and observed that PET/CT-derived metabolic parameters differed between adenocarcinoma and SCC groups.

Interestingly, contrary to our expectations, $SUV_{max,}$ MTV, and TLG values were higher in the non-recurrence group among patients with adenocarcinoma, whereas these parameters were higher in the recurrence group in SCC. These differences can be explained by the histopathological characteristics of the tumors. FDG uptake is associated

with overexpression of glucose transporter-1 (GLUT-1), which is higher in SCC than in adenocarcinoma.[29,30] In addition, intratumoral heterogeneity and variations in tumor vascularity may contribute to these differences,[31] as angiogenesis is more pronounced in SCC.[32] Furthermore, heterogeneity within adenocarcinoma subtypes may explain the variability in our findings, as different histological patterns exhibit distinct metabolic behaviors and prognostic profiles.[33] Previous studies have reported that MTV and TLG derived from FDG PET/CT are independent prognostic factors in lung adenocarcinoma patients undergoing curative surgery.[34] In addition, higher SUV_{max}, MTV, and TLG values have been associated with an increased risk of recurrence in pathologically N0 lung adenocarcinoma patients.[18] However, in our study, no significant association was observed between these parameters and recurrence in the adenocarcinoma subgroup. In contrast, in our subgroup analyses, $MTV_{2.5}$ and $MTV_{42\%}$ were significantly higher in patients with recurrence in the SCC subgroup. These findings suggest that histopathological subtype may be relevant when interpreting PET/CT-derived metabolic parameters.

Univariate and Multivariate Cox Regression Analysis

Previous studies have shown that age, stage, tumor size, SUV_{max}, MTV, and TLG are significant prognostic factors for DFS in univariate analyses.[11,35] In univariate analyses, MTV and TLG have superior predictive performance for recurrence risk compared with SUV_{max}.[25,28] In our study, gender, presence of comorbidities, histological type, and pathological stage were not identified as prognostic factors for DFS. In contrast, tumor size, VPI, and PL2 involvement were significant prognostic markers, with recurrence risk increasing with larger tumor size and the presence of pleural invasion. Among the metabolic parameters, only $MTV_{42\%}$ was identified as a prognostic factor for recurrence in univariate analysis, with higher values (>30.66) associated with increased recurrence risk. In contrast to previous reports, SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, and $TLG_{42\%}$ were not significant predictors.

In multivariate analyses, prognostic factors vary across studies. Some studies reported SUV_{max} as an independent prognostic factor,[36] whereas others found MTV or TLG as an independent prognostic factor of recurrence.[25,26,28,35] In our study, only $MTV_{2.5}$ remained independently associated with DFS. SUV_{max}, $MTV_{42\%}$, $TLG_{42\%}$, and $TLG_{2.5}$ were not associated with recurrence.

These findings may be explained by the limited discriminative performance of these parameters in our cohort. The AUC values for SUV_{max}, MTV, and TLG ranged between 0.53 and 0.55, indicating relatively low discriminative ability. These findings suggest that the selected cutoff values may have limited sensitivity and specificity when used alone for predicting recurrence.

Survival

High SUV_{max}, MTV, and TLG patients with high SUV_{max}, MTV, and TLG values had worse overall and 5-year survival rates, as well as recurrence rates.[11,13,21,25-27,34-38] In our study, the 5-year survival and 5-year DFS rates similar to those reported in the literature. However, the cutoff values used for the metabolic parameters varied among studies. In our study, only high MTV42% was associated with worse 5-year DFS. SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$ and $TLG_{42\%}$ were not associated with either 5-year survival or 5-year DFS.

Limitations

First, the retrospective, single-center design may have introduced selection bias. In addition, the absence of mortality in the non-recurrence group may further support the presence of selection bias in the study cohort. Second, standardized uptake values are influenced by various technical and biological factors, including partial volume effects, image resolution, reconstruction algorithms, image noise, the time interval between radiopharmaceutical injection and image acquisition, attenuation correction, normalization procedures, and plasma glucose levels. Third, the lack of standardized methods for calculating MTV and TLG is another limitation. Fourth, heterogeneity in histopathology subtypes may have affected the determination of prognostic factors. Fifth, tumor staging in this study was based on the 7th edition of the TNM classification system, which was the standard in routine clinical practice during the study period. The cohort consisted of patients treated between 2012 and 2016, allowing for adequate long-term follow-up to assess recurrence and survival outcomes. Although newer editions of the TNM classification and evolving treatment strategies have since been introduced, all patients in this study were staged uniformly according to a single system, ensuring internal consistency. Re-staging according to subsequent TNM editions was not feasible due to the retrospective design and limited availability of detailed data required for accurate reclassification. Therefore, the potential impact of temporal changes in staging and management should be considered when interpreting the generalizability of the findings. Finally, several established prognostic factors, including smoking history, lymphovascular invasion, spread through air spaces, molecular alterations (e.g., EGFR and ALK), and adjuvant treatment information, were not consistently available in the medical records and therefore could not be included in the analyses. The absence of these variables may have resulted in residual confounding and should be considered when interpreting the study findings.

CONCLUSION

In this cohort of patients with completely resected stage I-II NSCLC, larger tumor size, VPI, and PL2 involvement were associated with recurrence. $MTV_{2.5}$ was independently associated with DFS in one multivariable model, whereas its discriminatory performance for recurrence was limited. Therefore, these findings should be considered exploratory and require validation in larger, multicenter prospective cohorts before PET/CT-derived volumetric parameters can be incorporated into routine prognostic assessment.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Ethics Committee for Clinical Researches of the Ankara Keçiören Training and Research Hospital (Date: 12.06.2019, Decision No: 2012-KAEK-15/1915).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: EET, ÖÖ; Design: EET, ÖÖ; Control: EET; Data Collection and/or Processing: EET, ÖÖ; Analysis and/or Interpretation: EET; Literature Review: EET, ÖÖ, PAK, ŞMD; Article Writing: EET, ÖÖ, PAK, ŞMD; Critical Review: All Authors.

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