Do Volume-Based and Metabolic 18F FDG PET/CT Parameters Identify Groups at Risk for Poor Prognosis in Patients with Newly Diagnosed Metastatic and Non-Metastatic Non-Small Cell Lung Cancer?

Osman KUPIK[1], Mehmet BOZKURT[2], Sertac ASA[3], Gulnihan EREN[4], Hasan Gundogdu[5], Medeni ARPA[6]

[1] Recep Tayyip Erdoğan University, Faculty of Medicine, Department of Nuclear Medicine, Rize
[2] University of Health Sciences, Faculty of Medicine, Department of Nuclear Medicine, Istanbul
[3] Istanbul University-Cerrahpasa, Faculty of Medicine, Department of Nuclear Medicine, Istanbul
[4] University of Sıtkı Kocman, Faculty of Medicine, Department of Radiation Oncology, Muğla
[5] Recep Tayyip Erdoğan University, Faculty of Medicine, Department of Radiology, Rize
[6] Recep Tayyip Erdoğan University, Faculty of Medicine, Department of Biochemistry, Rize, TURKEY

ABSTRACT

To determine the relationship between ^{18}F FDG PET/CT parameters of the primary tumor/nodal metastasis/distant metastasis and overall survival (OS) of patients with newly diagnosed non-small cell lung cancer (NSCLC). Data from 159 patients with newly diagnosed NSCLC who underwent pretreatment 18F FDG PET/CT were analyzed. The SUV_{max}, SUV_{mean}, the metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of the primary tumor, lymph node metastasis, and distant metastasis were measured. The total MTV and total TLG were calculated. The optimal cut-off values of the ^{18}F FDG PET/CT parameters were determined using receiver operating characteristics curve analysis. Kaplan-Meier curves were used to determine OS. There were a total of 101 deaths during the follow-up (range, 3.7-54.2 months). The median OS was 26.4 months for the entire group, 11.8 months for patients with metastasis, and 41 months for patients with no metastasis ($p< 0.001$). In all patients ($n= 159$), nodal SUV_{max} ($SUV_{max}N$), total TLG, and the presence of distant metastasis were independent predictors. The 2-year OS for patients with TLG ≥ 328 and TLG < 328 were 32% and 80%, respectively. Independent predictors for OS were found as SUVmaxN in the group of patients with distant metastasis, and SUV_{max}, MTV of the primary tumor (MTVT), and lymph node size (LNsize) in the group of patients without distant metastasis. ^{18}F FDG PET/CT may distinguish patients with high risk for poor prognosis in patients with and without metastasis.

Keywords: ^{18}F FDG PET/CT, Non-small cell lung cancer, Metastasis, Prognosis, Survival

INTRODUCTION

Lung cancer is the most common cause of cancer-related mortality worldwide.[1] Non-small cell lung cancer (NSCLC) constitutes approximately 80-85% of all lung cancer cases. Despite the improvements in treatment and imaging methods, lung cancer is associated with poor prognosis. Predicting the prognosis of lung cancer is critically important for treatment management.[2] Treatment and prognosis are determined under the guidance of the Union International Contra la Cancrum (UICC)/ American Joint Committee on Cancer (AJCC) staging system, which is based on the anatomic evaluation of the tumor (T), node (N), and metastasis (M). Accurate staging is essential for proper treatment.[1] Due to the lack of biologic information, the differences in outcomes of similarly staged patients cannot be explained.

Unfortunately, the TNM staging system does not designate tumor-specific and patient-specific characteristics in patients within the same stage of the disease. As a result, patients in the same stage with similar pathologic features have different treatment outcomes and survival rates, despite receiving similar treatment.

^{18}F FDG PET/CT has become the standard imaging modality in nodule characterization, staging, treatment planning, and treatment response assessment, restaging at recurrence, and follow-up in patients with lung cancer.[3-7] The standardized uptake value (SUV) is the most commonly used method for evaluating tumor glucose metabolism. In the literature, studies have reported the predictive and prognostic values of SUV_{max} in patients with NSCLC at the initial diagnosis and after treatment.[8,9] Some authors showed that the pretreatment SUV_{max} was an independent predictor of progression-free survival (PFS) and overall survival (OS) in patients with NSCLC who received chemotherapy.[10] On the other hand, SUVmax, which is the measurement of FDG activity of a single hot pixel in malignant tissue, does not exactly represent the metabolic characteristics of the malignancy. This inadequacy becomes particularly substantial when the tumor tissue shows heterogeneous FDG activity. Besides, SUV_{max} value can change depending on the uptake time, image noise, and methods used for attenuation correction and reconstruction. Volume-based ^{18}F FDG PET/CT parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been suggested to represent the metabolic tumor burden. Although SUV_{max} represents the FDG activity of a single pixel, volume-based ^{18}F FDG PET/CT parameters evaluate FDG activity in malignant tissue as a whole. Initial metabolic tumor burden was identified as a prognostic factor for OS independent of clinical stage.[11]

In this study, we investigated the relationship between metabolic and volume-based parameters of ^{18}F FDG PET/CT and OS in patients with metastatic and non-metastatic NSCLC. These parameters were measured in the whole-body tumor burden, primary tumor, each metastatic lymph node, and distant metastases.

PATIENTS and METHODS

Patient Selection

We retrospectively evaluated the medical records of 219 patients with NSCLC who had undergone baseline ^{18}F FDG PET/CT before their initial therapy between March 2014 and January 2016. Patients with brain metastasis were not included and patients who were diagnosed as having another type of cancer during follow-up were excluded. All patients were staged according to the American Joint Committee on Cancer (AJCC) staging manual, 7th Edition.[1] All procedures performed in studies involving human participants were in conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Clinical Research Ethics Committee in our university faculty of medicine reviewed and approved this retrospective study (Decision number: 2019/07). The study was exempted from the need for informed consent by the institutional review board because this was a retrospective study where the data were de-identified.

^{18}F-FDG-PET Procedures

A positron emission/computed tomography (PET/CT) scanner Biograph mCT (Siemens Healthcare, Erlangen, Germany) was used. After at least 6 hours of fasting, patients with a blood glucose level of < 200 mg/dL were administered an FDG injection at an approximate dose of 3.7 MBq/kg. After a median 64 minutes (min-max 51-87 minutes), imaging was performed of the patients in the supine position with their arms up. PET imaging was adjusted to 2 minutes per bed position. Low-dose CT parameters: voltage, 120 kV; CARE dose 4D mA tube current; and slice thickness, 5.00 mm.

^{18}F FDG PET/CT Analysis and Measurements: Siemens Healthineers Syngo, via a VB30 workstation, MM Oncology, post-processing unit was used for the analyses. Two nuclear medicine physicians and one radiologist who were unaware of the clinical outcomes assessed the ^{18}F FDG PET/CT images. A volume of interest (VOI) was drawn for each lesion, and then corrections were made according to

the FDG uptake of the adjacent tissue. TLG was obtained by multiplying the SUV_{mean} and MTV of the lesion. T-stage, nodal metastasis status (positive or negative) and distance metastasis status (positive or negative) were noted. The SUV_{max} of primary tumor ($SUV_{max}T$), lymph node metastasis ($SUV_{max}N$), and distant metastasis ($SUV_{max}M$); the SUV_{mean} of primary tumor ($SUV_{mean}T$), lymph node metastasis ($SUV_{mean}N$); the metabolic tumor volume (MTV) of primary tumor (MTV_T), nodal metastasis (MTV_N), and distant metastasis (MTV_M); TLG of primary tumor (TLG_T), nodal metastasis (TLG_N), distant metastasis (TLG_M); the total MTV ($MTV_T + MTV_N + MTV_M$); the total TLG ($TLG_T + TLG_N + TLG_M$) and the primary tumor CT volume were measured. The short axis diameters (mm) of the largest metastatic lymph nodes (LNsize) were measured.

Statistical Analyses

For all patients, receiver operating characteristic (ROC) statistics of 18F FDG PET/CT parameters were estimated and threshold values providing the optimal sensitivity and specificity were determined, and those with a $p< 0.05$ were included in the analyses. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to assess the relationship between survival and ^{18}F FDG PET/CT parameters. Any variable with $p< 0.2$ in the univariate model was included in the multivariate Cox proportional hazards regression model. Curves for OS were constructed using Kaplan-Meier survival analysis. Differences between the groups were investigated using the log-rank test. All statistical analyses were performed using the SPSS version 18 software (SPSS Inc., Chicago, IL), and a two-tailed $p< 0.05$ was considered significant.

RESULTS

Patient characteristics: The ^{18}F FGD PET/CT data of 219 patients were evaluated retrospectively. A total of 60 patients were excluded for different reasons (29 patients with SCLC, 15 died with non-malignancy, three patients had secondary malignancies during follow-up [one patient had rectum cancer, one patient had malignant melanoma, one patient had larynx cancer] and 13 patients were lost to follow-up). In total, 159 patients with NSCLC were recruited for the study. The patients' characteristics are summarized in Table 1. A descriptive analysis of the tumors is given in Table 2.

Table 1. The characteristics of the patients (n= 159)

Characteristics	n (%)
Total patients	159
Median age (Range)	66 (36-86)
Sex	
Male	143 (90)
Female	16 (10)
Histologic type	
Adenocarcinoma	79 (49.6)
Squamous cell carcinoma	74 (46.4)
Others	6 (4)
T staging	
T1	14 (8.8)
T2	42 (26.4)
T3	35 (22.0)
T4	68 (42.8)
Nodal stage	
N0	34 (21.4)
N1	17 (10.7)
N2	44 (27.7)
N3	64 (40.3)
M staging	
M0	97 (61)
M1	62 (39)

TNM classified according to the American Joint Committee on Cancer (AJCC) staging system, which is based on the anatomic evaluation of the tumor (T), node (N), and metastasis (M)

Survival Analysis

(a) All patients (n= 159): The median follow-up was 26.5 [95%CI: 21.1- 30.3] months and 101 (63.5%) patients died during follow-up. The median OS was 26.4 (95% CI: 21.6-31.3) months. The results of univariate and multivariate analyses are shown in Table 3. Multivariate analysis revealed that SUVmaxN ($p< 0.001$, HR= 2.873), total TLG ($p< 0.001$ HR= 3.192), and distant me-

Table 2. Descriptive analysis of the tumor

Parameter	All Patients		Metastatic Patients		Non-metastatic Patients	
	Median (Min-max)	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	Mean±SD
SUVmaxT	13.1 (2.4-37.5)	13.9±6.27	13.2 (4.2-37.4)	13.9±6.2	13.1 (2.4-37.5)	13.8±6.37
SUVmeanT	7.4 (2.5-21)	7.89±3.27	7.3 (2.5-21)	7.83±3.26	7.6 (2.6-18.5)	7.93±3.29
MTVT	25 (0.45-424)	13.8±66.7	31.9 (2.6-424)	64.9±74.8	23.2 (0.45-326)	41.7±57.7
TLGT	202.5 (2.2-3381)	423±579	266.6 (11.7-3381)	579±750	194.88 (2.2-2226)	323±410
SUVmaxN	9.4 (2.1-48)	10.4±7.39	10.6 (2.1-28.1)	10.7±6.4	8.5 (2.3-48)	10.1±8.3
SUVmeanN	5.7 (1.6-29.7)	6.07±4.22	6.1 (1.6-29.7	6.93±4.94	4.8 (1.7-18)	5.26±3.24
LNsize	22 (7-48)	22.66±9.18	24 (7-41)	23.5±8.2	20 (7-48)	21.89±10
MTVN	12.2 (0.6-146)	22.1±26.23	17 (0.7-146)	25.5±27.3	9.1 (0.6-127.6)	18.92±24.9
TLGN	63.36 (1.26-1192.5)	149.5±222.6	100 (1.44-1192)	176±255	33.8 (1.26-726)	124.3±186
SUVmaxM	9 (1.5-31.3)	11.13±7.48	9 (1.5-31.3)	11.1±7.5	-	-
MTVM	15 (1-413)	69.22±101.79	15 (1-413)	69.2±101.8	-	-
TLGM	85 (2-4754)	595±1095	81 (2-4754)	595±1106	-	-
Total TLG	386 (2.24-6297)	772±1085	611 (33.3-6297)	1336±1472	247.8 (2.2-2518)	412±472.9
Total MTV	59.4 (0.45-625)	95.2±110	103.5 (15.2-625)	157.9±133.7	33.9 (0.45-382.3)	55.2±67.35
CT volume	41.49 (0.51-1181)	81.44±139.47	50.32 (2.85-1181)	105.6±171.2	28.5 (0.51-676)	66±112.9

Abbreviations: MTVT= metabolic tumor volume (MTV) of primary tumor; MTVM= MTV of distant metastasis; MTVN= MTV of nodal metastasis; SUVmaxM= SUVmax of distant metastasis; SUVmaxN= SUVmax of lymph node metastasis; SUVmaxT= SUVmax of primary tumor; SUVmeanN= SUVmean of lymph node metastasis; SUVmeanT= SUVmean of primary tumor; TLGT= tumor lesion glycolysis (TLG) of primary tumor; TLGM= TLG of distant metastasis; TLGN= of nodal metastasis; LNsize= the short axis diameters (mm) of the largest metastatic lymph node; CT volume= primary tumor CT volume (cm^3).

tastasis status (p< 0.001, HR= 6.717) were independent predictors for OS. Patients were divided into two groups as having a total TLG less than 328 and total TLG equal to or greater than 328 (sensitivity: 81.2%, specificity: 84.5%, AUC = 0.881 p< 0.001). The 2-year OS for the group of patients with a total TLG < 328 and TLG ≥ 328 were 80% and 32%, respectively. The Kaplan-Meier curves for total TLG, $SUV_{max}N$ (with a cut-off value of 7.8, sensitivity: 64.1% specificity: 64.7%, AUC= 0.670, p< 0.001), and distant metastasis status are given in Figure 1. We found high inter-correlation (multicollinearity) between total MTV and total TLG values (correlation matrix of regression coefficient > 0.6), thus total MTV was excluded and only total TLG was counted in the multivariate cox regression model.

(b) Patients with distant metastasis (n= 62): The median OS was 11.8 (95% CI: 8.7-15.0) months in patients with distant metastasis. The results of univariate and multivariate analyses of distant metastases are shown in Table 4. Only $SUV_{max}N$ was established as an independent predictor for OS in the multivariate analysis (p= 0.013, HR=1.080). The Kaplan-Meier analysis of SUV_{max} with the cut-off as 7.8 is shown in Figure 2.

(c) Patients with no distant metastasis (n= 97): The median OS was 41 (95% CI: 37.8-44.1) months in patients without distant metastasis. Data for the univariate and multivariate analyses of these patients are given in Table 5. $SUV_{max}T$ (p= 0.046, HR= 1.068), MTV_T (p= 0.004, HR= 1.009), and LNsize (p= 0.009, HR= 1.057) were independent predictors in the multivariate analysis. When the patients were grouped as MTVT ≥ 23.1 cm^3 and < 23.1 (sensitivity: 80% specificity: 72% AUC= 0.822 p< 0.001), the 3-year OS was 33% and 80%, respectively (Figure 3).

Table 3. Summary of univariate and multivariate analyses (n= 159). As a result of univariate analysis, all parameters were included in the multivariate analysis

	Univariate Analyses			Multivariate Analyses		
Variable	**p value**	**Hazard Ratio**	**95% CI**	**p value**	**Hazard Ratio**	**95% CI**
LNsize (mm) ≥ 20	0.010	1.761	1.148-2.7	0.567	0.741	0.266-2.064
MTVN (cm^3) ≥ 10	0.007	1.807	1.178- 2.771	0.098	0.530	0.250-1.125
SUVmeanN ≥ 4.7	0.002	2.108	1.321-3.363	0.163	2.174	0.730-6.476
TLGN ≥ 33.8	0.002	2.278	1.450-3.581	0.975	0.983	0.334-2.890
MTVT (cm^3) ≥ 19.3	< 0.001	2.960	1.876- 4.671	0.371	1.367	0.689-2.711
SUVmaxT ≥ 13.2	0.074	1.431	0.966-2.120	0.687	1.167	0.550-2.478
SUVmeanT ≥ 8.3	0.055	1.478	0.992-2.201	0.126	1.835	0.843-3.993
TLGT ≥ 193.4	< 0.001	2.934	1.906-4.518	0.188	0.584	0.263-1.300
SUVmaxN ≥ 7.8	0.003	1.933	1.261- 2.964	< 0.001	2.873	1.657-4.979
Total MTV (cm^3) ≥ 32	< 0.001	7.295	3.964- 13.424	*	*	*
Total TLG ≥ 328	< 0.001	6.575	3.912- 11.051	< 0.001	3.192	1.732-5.883
Nodal metastasis status	< 0.001	4.043	2.035 – 8.033	0.973	1.159	0.240-1.761
Distance metastasis status	< 0.001	7.629	4.986-11.673	< 0.001	6.717	4.034-8.712

Abbreviations: CI= confidence interval;
(*) We found high inter-correlation (multicollinearity) between total MTV and total TLG values (correlation matrix of regression coefficient >0.6), thus total MTV was excluded and only total TLG was counted in the multivariate cox regression model

DISCUSSION

Despite aggressive multimodal treatment regimes, the prognosis of lung cancer is still unsatisfactory. Therefore, it is important to determine prognostic factors in order to improve lung cancer survival rates. In our study, we evaluated the metabolic and volumetric parameters of 18F FDG PET/CT for each primary tumor, metastatic lymph node, and metastatic lesion, and investigated parameters that were independent predictors for worse OS in patients with NSCLC.

Lymph node metastasis status and metabolic and volumetric measurements of involved lymph nodes ($SUV_{max}N$, MTV_N, TLG_N) were previously

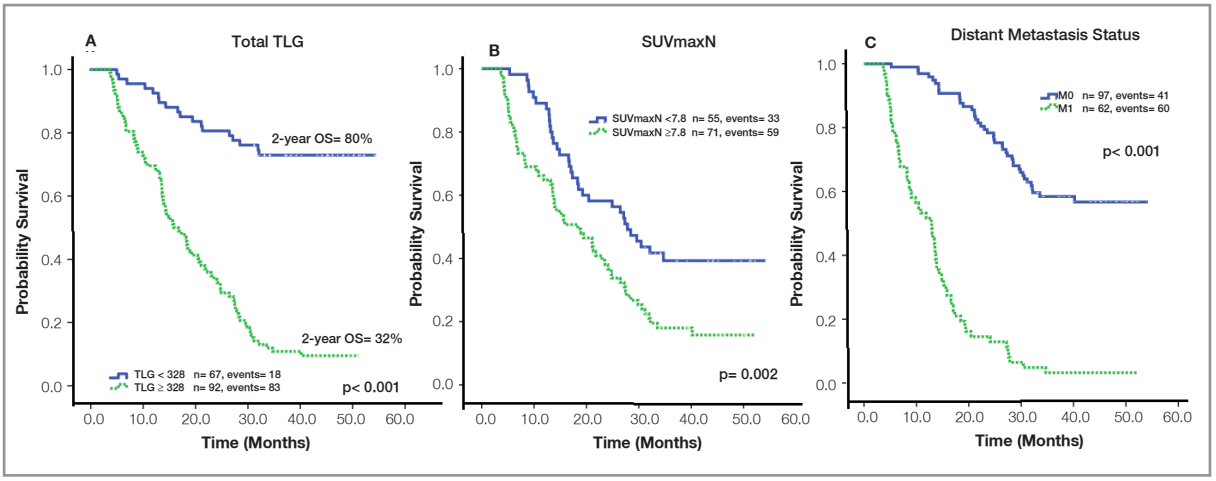

Figure 1. (A) Kaplan-Meier curves for total lesion glycolysis with the cut-off as 328, **(B)** maximum standardized uptake value of lymph node metastasis with the cut-off as 7.8, and **(C)** distant metastasis status

Table 4. Univariate and multivariate analyses for distant metastatic group (n= 62)
(*) Indicates parameters included in multivariate analysis

	Univariate Analyses			Multivariate Analyses		
Variable	**p value**	**Hazard Ratio**	**95% CI**	**P value**	**Hazard Ratio**	**95% CI**
CT volume	0.362	1.001	0.999-1.002		-	- -
SUVmaxT	0.013 *	1.053	1.011-1.096	0.646	1.018	0.944-1.097
SUVmeanT	0.233	1.011	0.993-1.029	-	-	-
MTVT	0.216	1.002	0.999-1.006	-	-	-
TLGT	0.069 *	1.000	1.000-1.000	0.743	1.000	0.999-1.001
LNsize	0.372	1.016	0.985-1.048	-	-	-
MTVN	0.830	1.001	0.993-1.009	-	-	-
SUVmaxN	0.002 *	1.069	1.025-1.114	0.013	1.080	1.016-1.149
TLGN	0.014 *	1.001	1.000-1.002	0.305	0.999	0.997-1.001
SUVmaxM	0.014 *	1.043	1.008-1.079	0.601	0.987	0.939-1.037
MTVM	< 0.001 *	1.007	1.000-1.010	0.206	1.005	0.997-1.012
TLGM	< 0.001 *	1.001	1.000-1.001	0.097	1.000	1.000-1.001
Total MTV	0.001 *	1.004	1.002-1.006	0.944	1.000	0.994-1.006
Total TLG	< 0.001 *	1.001	1.000-1.001	0.917	1.000	0.989-1.003

reported predictors of OS.[12-14] Prior studies showed that the volume of metastatic mediastinal lymph nodes was associated with recurrence as well as survival.[12,13] In a prospective study with 73 patients, a lymph node volume greater than 10.6 cm^3 was associated with an increased locoregional recurrence rate (p< 0.001) and decreased OS (p= 0.04) following neoadjuvant chemoradiation therapy in patients with stage IIIA-IIIB NSCLC.[12] Nwogu et al. showed that lower ratios of positive lymph nodes (LNs) were associated with better survival after NSCLC resection independent of age, sex,

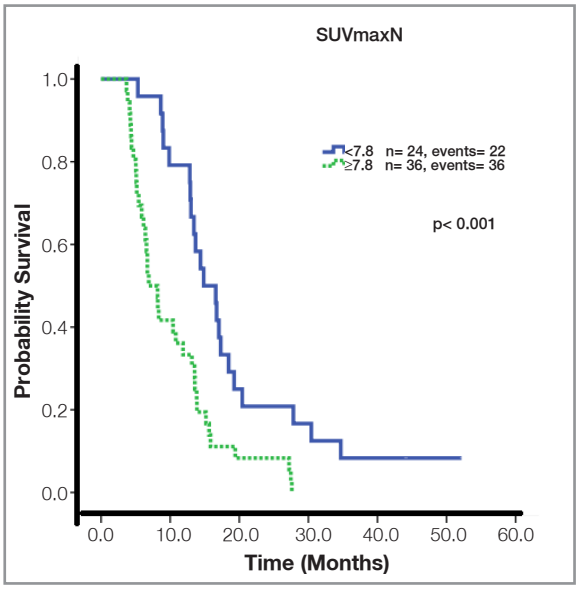

Figure 2. Kaplan-Meier curves for maximum standardized uptake value of lymph node metastasis with the cut-off as 7.8 in patients with TNM stage M1

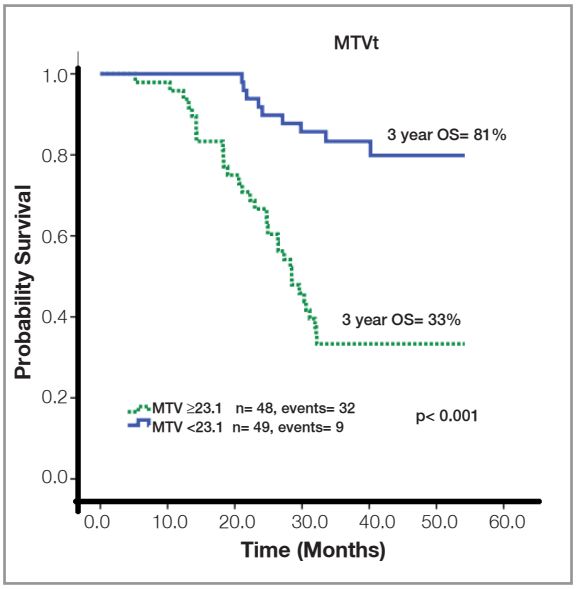

Figure 3. Kaplan-Meier curves for metabolic tumor volume of primary tumor with the cut-off as 23.1 in patients with no distant metastasis

Table 5. Univariate and multivariate analyses for the non-distant metastatic group (n= 97) (*) Indicates parameters included in multivariate analysis

	Univariate Analyses			Multivariate Analyses		
Variable	**p value**	**Hazard Ratio**	**95% CI**	**p value**	**Hazard Ratio**	**95% CI**
Nodal status	0.018 *	2.677	1.185-6.046	0.916	1.087	0.229-5.156
CT volume	< 0.001 *	1.004	1.002-1.006	0.769	0.999	0.995-1.004
SUVmaxT	0.096 *	1.039	0.993-1.086	0.046	1.068	1.003-1.083
SUVmeanT	0.219	1.055	0.969-1.149	-	-	-
MTVT	< 0.001 *	1.009	1.006-1.012	0.004	1.009	1.006-1.012
TLGT	< 0.001 *	1.001	1.001-1.001	0.166	0.999	0.997-1.001-
LNsize	0.002 *	1.057	1.020-1.095	0.009	1.057	1.020-1.095
MTVN	0.001 *	1.019	1.007-1.031	0.574	0.990	0.954-1.026
SUVmaxN	0.179*	1.021	0.990-1.053	0.267	0.954	0.878-1.037-
TLGN	0.012 *	1.002	1.000-1.003	0.268	1.003	0.997-1.010
Total MTV	< 0.001 *	1.009	1.006-1.012	0.640	0.997	0.990-1.030
Total TLG	< 0.001 *	1.001	1.001-1.001	0.112	1.001	0.987-1.003

grade, tumor size, and disease stage.[14] Nappi et al. showed that the metabolic activity of metastatic lymph nodes was related to OS and PFS, also that lymph node metastasis status was associated with poor outcomes, irrespective of SUVmaxT.[15] In our study, the metabolic activity and diameter of lymph nodes were independent predictors of OS, and these findings were in congruence with the literature in this respect.

Our study revealed that total TLG was an independent predictor for OS. The 2-year OS of patients with TLG ≥ 328 and TLG < 328 were 32% and 80%, respectively. Several previous studies reported the prognostic significance of TLG in lung cancer.[16-18] The multivariate analysis showed that metastasis status was the most significant independent predictor for worse OS (HR= 6.717). To exclude the prognostic effect of metastasis status in the non-metastatic group, the patients were divided into two groups in terms of metastasis status.

In the non-metastatic patient group (n= 97), $SUV_{max}T$, MTV_T, and LN_{size} were found to be predictors of OS independent of age, T stage, N stage, and other ^{18}F FDG PET/CT parameters. When the effect of distant metastasis was excluded, the volume-based parameters of the primary tumor and lymph nodes reached statistical significance. Moreover, we found that the enlarged lymph nodes were significantly associated with poorer prognosis; the larger the lymph nodes, the worse was the outcome in the non-metastatic patient group, in agreement with prior literature.[19-21]

Multivariate analysis of the volumetric/metabolic parameters in the distant metastatic patients (n= 62) revealed that $SUV_{max}N$ was the only significant independent predictor value, which was also a statistically significant predictor for OS when all patients were analyzed. To our knowledge, very few studies have evaluated the association of SUV and OS in mediastinal lymph nodes. Okereke et al. investigated the prognostic value of the parameters in the primary tumor and mediastinal lymph nodes of the patients with NSCLC and reported that higher values of SUV in lymph nodes were associated with poorer OS rates, in line with our study, which showed that SUV was associated with worse OS.[22]

As a consequence, $SUV_{max}N$, total TLG, and distant metastasis may be used to further stratify the risk of patients with NSCLC. The prognostic value of ^{18}F FDG PET/CT parameters varies in patients with and without metastatic NSCLC. $SUV_{max}N$ in the metastatic patient group, and SUVmaxT, MTVT, and ND in the non-metastatic group were found to be independent prognostic factors. The prognostic significance of SUV_{max} and/or the diameter of the mediastinal lymph node in both groups was remarkable.

Our study had some limitations. The patients in the same stage did not receive the same treatment protocols. Some patients underwent surgery, whereas others were treated non-surgically. We intended to evaluate the PFS rates in addition to OS rates of the patients. Unfortunately, not all patients were treated and/or followed up in single oncology center. Thus we were unable to acquire accurate recurrence data of the patients.

In conclusion, volumetric and metabolic parameters of ^{18}F FDG PET/CT can distinguish patients with NSCLC with or without metastasis who have a poor prognosis.

REFERENCES

1. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17: 1471-1474, 2010.
2. UyBico SJ, Wu CC, Suh RD, et al. Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls. Radiographics 30: 1163-1181, 2010.
3. Ruilong Z, Daohai X, Li G, et al. Diagnostic value of ^{18}F-FDG-PET/CT for the evaluation of solitary pulmonary nodules: a systematic review and meta-analysis. Nucl Med Commun 38: 67-75, 2017.
4. Huellner MW, de Galiza Barbosa F, Husmann L, et al. TNM staging of non–small cell lung cancer: comparison of PET/MR and PET/CT. J Nucl Med 57: 21-26, 2016.
5. Hicks RJ. Role of ^{18}F-FDG PET in assessment of response in non-small cell lung cancer. J Nucl Med 50 Suppl 1: 31S-42S, 2019.
6. van den Berg LL, Klinkenberg TJ, Groen HJ, et al. Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early stage NSCLC. J Thorac Oncol 10: 826-831, 2015.
7. Sheikhbahaei S, Mena E, Yanamadala A, et al. The value of FDG PET/CT in treatment response assessment, follow-up, and surveillance of lung cancer. AJR Am J Roentgenol 208: 420-433, 2017.
8. Borst GR, Belderbos JS, Boellaard R, et al. Standardised FDG uptake: a prognostic factor for inoperable non-small cell lung cancer. Eur J Cancer 41: 1533-1541, 2005.
9. Jeong HJ, Min JJ, Park J, et al. Determination of the prognostic value of [^{18}F] fluorodeoxyglucose uptake by using positron emission tomography in patients with non-small cell lung cancer. Nucl Med Commun 23: 865-870, 2002.
10. Imamura Y, Azuma K, Kurata S, et al. Prognostic value of SUVmax measurements obtained by FDG-PET in patients with non-small cell lung cancer receiving chemotherapy. Lung Cancer 71: 49-54, 2011.
11. Liao S, Penney BC, Wroblewski K, et al. Prognostic value of metabolic tumor burden on ^{18}F-FDG PET in nonsurgical patients with non-small cell lung cancer. Eur J Nucl Med Mol Imaging 39: 27-38, 2012.
12. Agrawal V, Coroller T, Hou Y, et al. Mediastinal lymph node olvume is associated with locoregional recurrence and overall survival in stage IIIA-IIIB Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 96: E451, 2016.
13. Pöttgen C, Levegrün S, Theegarten D, et al. Value of ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in non–small-cell lung cancer for prediction of pathologic response and times to relapse after neoadjuvant chemoradiotherapy. Clin Cancer Res 12: 97-106, 2006.
14. Nwogu CE, Groman A, Fahey D, et al. Number of lymph nodes and metastatic lymph node ratio are associated with survival in lung cancer. Ann Thorac Surg 93: 1614-1620, 2012.
15. Nappi A, Gallicchio R, Simeon V, et al. [F-18] FDG-PET/CT parameters as predictors of outcome in inoperable NSCLC patients. Radiol Oncol 49: 320-326, 2015.
16. Chung HW, Lee KY, Kim HJ, et al. FDG PET/CT metabolic tumor volume and total lesion glycolysis predict prognosis in patients with advanced lung adenocarcinoma. J Cancer Res Clin Oncol 140: 89-98, 2014.
17. Zhang H, Wroblewski K, Appelbaum D, Pu Y. Independent prognostic value of whole-body metabolic tumor burden from FDG-PET in non-small cell lung cancer. Int J Comput Assist Radiol Surg 8: 181-191, 2013.
18. Chen HH, Chiu NT, Su WC, et al. Prognostic value of whole-body total lesion glycolysis at pretreatment FDG PET/CT in non–small cell lung cancer. Radiology 264: 559-566, 2012.
19. Ding N, Pang Z, Zhang X, et al. Prognostic and predictive effects of positive lymph node number or ratio in NSCLC. Sci Rep 7: 1-9, 2017.
20. Rice SR, Molitoris JK, Vyfhuis MA, et al. Lymph node size predicts for asymptomatic brain metastases in patients with non–small-cell lung cancer at diagnosis. Clin Lung Cancer 20: e107-e14, 2019.
21. Zhang YK, Tan LI, Wang ZY, et al. Association of lymph node involvement with the prognosis of pathological T1 invasive non-small cell lung cancer. World J Surg Oncol 15: 64, 2017.
22. Okereke IC, Gangadharan SP, Kent MS, et al. Standard uptake value predicts survival in non–small cell lung cancer. Ann Thorac Surg 88: 911-916, 2009.

Correspondence:
Dr. Osman KUPIK
Recep Tayyip Erdogan Universitesi
Tip Fakultesi
Nukleer Tip Anabilim Dali
53200 Islampasa, RIZE / TURKEY

e-mail: osmankupik@gmail.com
Tel: (+90-530) 166 34 21
Fax : (+90 464) 217 03 64

ORCIDs:

Osman Kupik	0000-0001-9473-7940
Mehmet Bozkurt	0000-0002-8325-5249
Sertaç Asa	0000-0003-4060-9331
Gülnihan Eren	0000-0002-3315-3893
Hasan Gündoğdu	0000-0003-0858-7304
Medeni Arpa	0000-0001-8321-4829