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Prognostic and Predictive Values of F-18 FDG PET/CT Volumetric Parameters in Small Cell Lung Cancer

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Abstract

Introduction: Volumetric parameters of the 18F-FDG PET/CT can contribute to the treatment decision in high risk patients. In the present study, we aimed to examine the predictive, prognostic, and clinical value of PET/CT by using the two volumetric parameters: metabolic tumor volume (MTV) and total lesion glycolysis (TLG), SUVmax to concurrently evaluate survival data in patients diagnosed with small cell lung cancer (SCLC).

Methods: 244 patients with SCLC, who underwent 18F-FDG PET/CT imaging for staging purpose were enrolled. Primary tumor SUVmax, MTV (40-70%) and TLG (40-70%) obtained from PET/CT were documented.

Results: All lesions (n=244) showed 18F-FDG uptake, mean SUVmax of 19.74±8.71 [range (min – max) = 3.80 - 58.80]. SUVmax was significantly higher in tumors with diameters > 2 cm compared to those with diameters ≤ 2 cm (p=0.000). The mean survival time was significantly shorter in patients with tumor diameter greater than 2 cm, locoregional LN involvement, distant nodal metastasis, or distant organ metastasis (p=0.019, p<0.001, p<0.001 and p<0.001, respectively). Primary tumor SUVmax showed statistically significant positive correlation with tumor size, TLG40/70, and SUVmean40/70. Also, high MTV40 and TLG40 showed statistically significant association with increased tumor diameter and distant organ metastasis.

Conclusion: In our study, volumetric parameters of 18F-FDG PET/CT showed remarkable superiority specifically over metabolic parameters in the detection of distant organ metastasis. Patients with high FDG uptake in primary tumors should be carefully evaluated for poor prognostic and metastatic potential; optimal treatment should be planned accordingly.

Keywords**:** *Volumetric parameters, 18F-FDG PET/CT, Small Cell lung cancer.*

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Introduction

Lung cancer (LC) is the most common type of cancer in both sexes, and it is the most common cause of cancer-related deaths as well (26% and 28% of all female and male cases, respectively). Small cell lung cancer (SCLC) comprises 10-15% of LCs, and is a very aggressive subtype (1). Studies generally do not report marked difference between surgery and radiotherapy/chemotherapy with regard to survival in SCLC, although some studies have reported positive contribution of surgery to the survival in patients with stage I disease. Therefore, as is the case with all types of cancer, accurate staging can contribute to survival and prognosis (2).

^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is widely used for staging, prognostic evaluation, and treatment follow-up of LC. It has proven predictive utility in evaluation of distant organ metastasis, locoregional LN involvement, and recurrence as well. ^{18}F-FDG PET/CT can detect morphological changes of many malignancies well before conventional imaging methods (CT or MRI); and thus, gives the chance to initiate treatment early (3,4,5).

In patients with SCLC, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) can provide valuable information with regard to aggressive tumor behavior, survival, and prognosis, which contributes to disease management (6,7). Some studies have highlighted the shortcomings of metabolic parameters including prognostic and predictive markers in SCLC; some studies have reported that volumetric parameters have superior prognostic value over maximum standard uptake value (SUVmax). They can aid in accurate prediction of survival outcomes (8,9).

In the present study, we used MTV and TLG in conjunction with SUVmax in patients with SCLC to evaluate the predictive, prognostic, and clinical value of ^{18}F-FDG PET/CT imaging and to examine survival data in SCLC.

Materials and Methods

Patients

The study included 244 patients diagnosed with SCLC who underwent whole body ^{18}F-FDG PET/CT scan for staging purpose between February 2010 and October 2018.The retrospective study was approved by the Istanbul Training and Research Hospital local ethics committee (Date: 02.21.2020, No: 2192). All patients provided verbal and written consent for the use of the medical findings for research purposes.

^{18}F-FDG PET/CT Imaging

Prior to the procedure, all patients had blood glucose levels less than 150 mg/dL following at least 6 hours of fasting. Patients received a standard 3.7-5.2 MBq/kg^{18}F-FDG intravenous injection. Starting from the 45th-60th minutes after the injection, whole body PET/CT scans were performed in the supine position from vertex until upper thigh (the first 54 scans were performed with Siemens Biograph 6 HD LSO, and the next 190 scans were performed with Siemens mCT 20 ultra HD LSO PET/CT device) (IL, USA). For calculation of SUVmax, the region of interest (ROI), which encompassed the area of maximum FDG uptake within the primary tumor, was drawn on PET sections. SUVmax was calculated with the formula: *maximum activity within the ROI (MBq/ml) / injected FDG dose (MBq/kg body weight)*. MTV

and TLG were calculated via standard methods that included injected dose, blood glucose level, and body weight. MTV and TLG evaluations were obtained at 40% and 70% thresholds for research at different values. SUVmax, MTV, and TLG results were analyzed with regards to clinical properties, nodal metastasis, locoregional LN involvement, distant organ metastasis and survival data.

Statistical analysis

All the data were analyzed with SPSS (Statistical Package for the Social Sciences) software for Windows (v21.0; IBM, Armonk, NY, USA). Individual and aggregate data were summarized using descriptive statistics including mean, standard deviation, median (min-max), frequency distributions and percentages. The normality of data distribution was verified by Kolmogorov-Smirnov test. Comparison of the variables with normal distribution was made with Student t-test and Paired-Sample t-test. Mann Whitney and Kruskal Wallis tests were conducted to compare non-normally distributed variables between groups. Evaluation of categorical variables was performed by Chi-Square test. Survival rates were estimated by Kaplan-Meier analysis. A p-value of less than 0.05 was considered statistically significant.

Results

The mean patient age was 65.95±9.98 (range = 31-87) years. Of the 244 cases diagnosed with SCLC, 14 (5.7%) were women and 230 (94.3%) were men. Of all cases, 73% (n=178) were 60 years or older, and 27% (n=66) were younger than 60 years of age. All lesions (n=144) showed ^{18}F-FDG uptake, with a mean SUVmax of 19.74±8.71 (median=18.80, range=3.80-58.80). Mean SUVmax did not differ between the group of patients younger than 60 years (n=66) and the group of patients aged 60 years or above (n=178) (20.28±9.14 vs 19.54±8.56, respectively; p=0.696) (Table 1).

Table 1. Relationship between mean±SD SUVmax, survival and clinical and histopathological features of the patients.

	Clinical Variables	**n (%)**	**SUVmax (Mean±SD)**	**P-value (SUVmax)**	**Survival (month) (Mean±SD)**	**P-value (survival)**
Age	< 60 year	66 (27.0%)	20.28±9.14	0.696	30.52±29.95	0.728
	≥ 60 year	178 (73.0%)	19.54±8.56		28.35±28.48	
Tumor Size	< 2 cm	13 (5.3%)	8.85±3.59	**<0.001***	44.11±26.79	**0.019***
	≥ 2 cm	231 (94.7%)	20.36±8.50		28.08±28.77	

Locoregional Nodal involvement	Absent	63 (25.8%)	18.51±9.67	0.181	48.70±30.58	**<0.001***
	Present	181 (74.2%)	20.17±8.33		22.05±24.83	
Distant Nodal involvement	Absent	195 (79.9%)	19.85±8.95	0.791	32.42±29.70	**<0.001***
	Present	49 (20.1%)	19.33±7.72		15.07±20.02	
Distant Organ Metastasis	Absent	162 (66.4%)	19.57±8.92	0.536	36.83±30.42	**<0.001***
	Present	82 (33.6%)	20.08±8.32		13.34±16.87	

***=** $p<0.05$ statistically significant.

Mean tumor size was 5.21±2.56 (range=0.70-16.20) cm. After stratification for tumor size, the mean SUVmax was found to be significantly higher among those with tumor diameter greater than 2 cm (n=231) compared to those with tumor diameter smaller than 2 cm (n=13) (20.36±8.50 vs 8.85±3.59, $p<0.001$) (Table 1).

PET revealed locoregional LN involvement in 74.2% of cases (n=181); however, no significant association was found with primary tumor SUVmax (p=0.181). Distant nodal metastasis was detected in 49 cases (20.1%). Primary tumor SUVmax did not show a statistically significant difference between patients with and without distant nodal metastasis (p=0.791) (Table 1).

Distant organ metastasis was observed in 82 cases (33.6%). The most frequent site of organ metastasis was bone-bone marrow with a rate of 32.9% (n=27), followed by multiple localizations (25.6%, n=21) (Figure 1), contralateral lung (17.1%, n=14), liver (14.6%, n=12), adrenal glands (7.3%, n=6), brain (1.2%, n=1), and muscles (1.2%, n=1). Those with distant metastasis did not show any significantly difference in primary tumor SUVmax compared to those without distant organ metastasis (p=0.536) (Table 1).

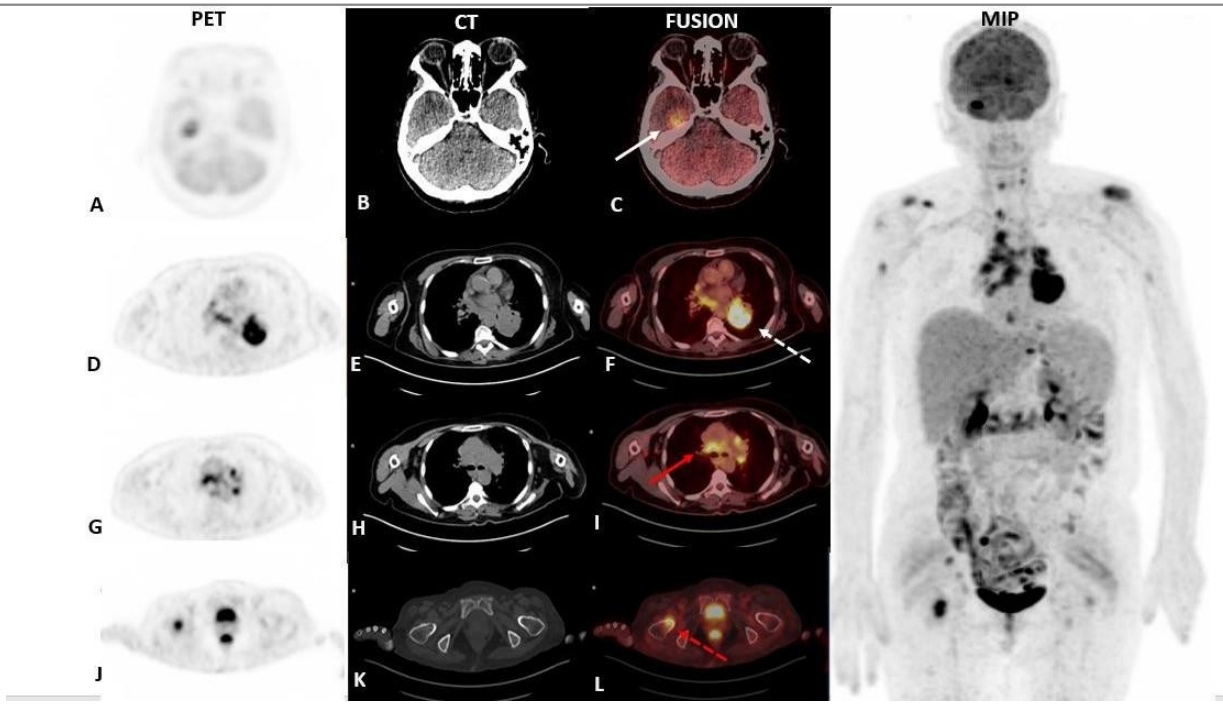

Figure 1. 55 years old woman, (*PET: positron emission tomography, CT: computed tomography, F: Fusion, MIP: maximum intensity projection*), Primary tumor axial diameter : 5.5 cm, Primary tumor SUV max: 14.6, Primary tumor MTV40(%): 34.83, TLG40: 283.05, Primary tumor MTV70(%): 2.79, TLG70: 31.4. Brain metastasis (white arrow), primary tumor (white dash arrow), locoregional LN metastasis (red arrow), bone metastasis (red dash arrow)

The mean follow-up time was 28.93±28.84 months (range=0.17-112.4 months). The mean survival was significantly shorter among those with distant organ metastasis (13.34±16.87 months) compared to those without it (36.83±30.42 months) (p<0.001, Log Rank=0.000) (Figure 2).

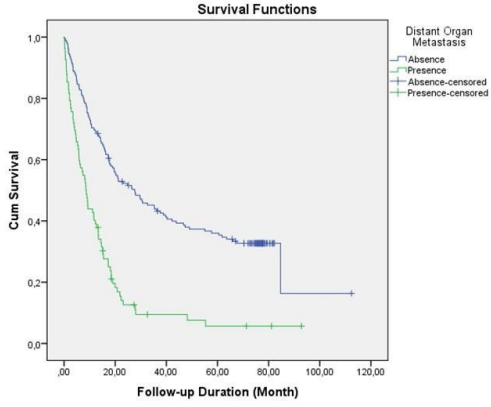

Figure 2. Survival chart according to distant metastasis (**Log Rank=0.000).**

Mean survival was significantly shorter among those with a tumor diameter greater than 2 cm (28.08±28.77) compared to those with a tumor diameter smaller than 2 cm (44.11±26.79 months) (p=0.019, Log Rank=0.097) (Figure 3).

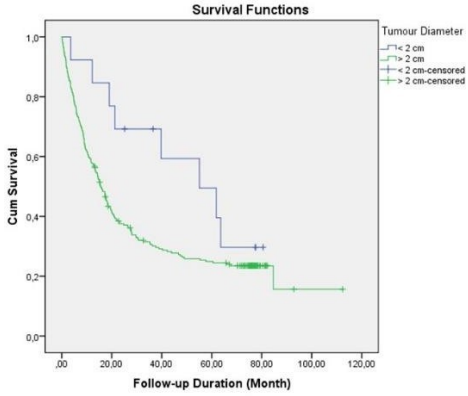

Figure 3. Survival chart by tumor diameters (**Log Rank=0.097).**

Patients with locoregional LN involvement had a significantly shorter mean survival in comparison to those without locoregional LN involvement (22.05±24.83 vs 48.70±30.58 months, p<0.001, Log Rank=0.000) (Figure 4).

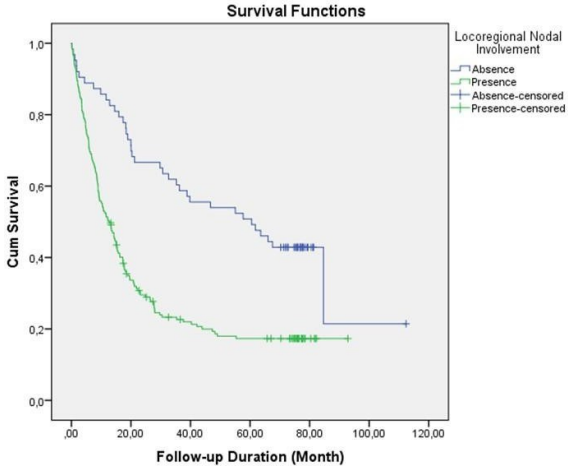

Figure 4. Survival chart according to locoregional LN involvement (**Log Rank=0.000).**

Mean survival was found to be significantly shorter in cases with distant nodal metastasis (15.07±20.02 months) compared to those without it (32.42±29.70 months) (p=0.000, Log Rank=0.001) (Figure 5). No statistically significant association was found between mean survival time and advanced age at the time of diagnosis, gender, or tumor localization (p=0.728, p=0.241, p=0.102 and p=0.590, respectively).

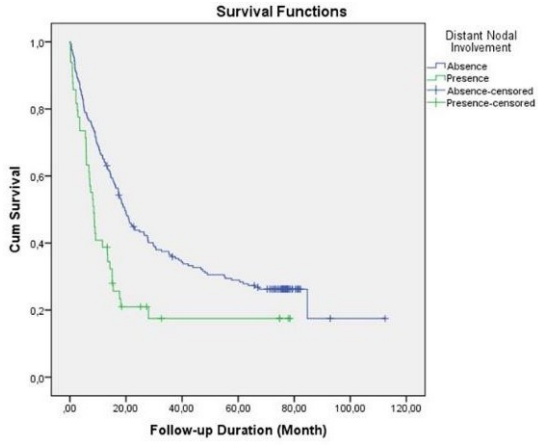

Figure 5. Survival chart according to distant nodal metastasis (**Log Rank=0.001).**

The following mean± SD were calculated for the study sample (n=244): MTV40%: 58.13±90.62, MTV70%: 8.85±14.91, TLG40%: 553.82±741.4, TLG70%: 114.32±171.9, SUVmean40%: 10.76±5.76, SUVmean70%: 14.08±5.32 and SUVpeak: 13.70±5.25. Primary lesion SUVmax value showed statistically significant positive correlation with tumor size, TLG40/70 and SUVmean40/70 (p<0.001, p=0.046, p=0.039, p=0.001, p<0.001 and p<0.001, respectively) (Table 2).

Table 2. SUVmax related correlation analyses.

	SUVmax	
	r	***p***
Age	0.029	0.651
Survival time after diagnosis (Month)	- 0.103	0.166
Tumor Size	**0.438**	**<0.001***

MTV40%	0.120	0.520
MTV70%	0.159	0.393
TLG40	**0.361**	**0.046***
TLG70	**0.372**	**0.039***
SUVmean40	**0.546**	**0.001***
SUVmean70	**0.992**	**<0.001***
SUVpeak	**0.967**	**<0.001***

***=** p<0.05 statistically significant.

High metabolic tumor volume (MTV40%) showed statistically significant association with large tumor diameter and distant organ metastasis (p=0.002 and p=0.015, respectively) (Table 3).

Table 3. Comparison between mean MTV40%-70% and TLG 40-70 values in clinical and histopathological features of the patients.

	MTV 40% (Mean±SD)	**P-value**	**MTV70 % (Mean±SD)**	**P-value**	**TLG 40 (Mean±SD)**	**P-value**	**TLG 70 (Mean±SD)**	**P-value**
Age								
< 60 year	69.49±120.0	0.922	12.08±19.6	0.626	585.3±789.0	0.892	139.2±192.6	0.682
≥ 60 year	47.48±52.22		5.81±7.97		524.2±718.5		90.99±152.4	
Tumor Size								
< 2 cm	3.30±3.28	**0.002***	1.18±1.44	0.091	30.39±42.74	**0.001***	14.64±21.91	0.065
≥ 2 cm	64.00±93.57		9.67±15.48		609.9±759.5		125.0±177.7	

Locoregional Nodal involvement								
Absent								
Present	13.19	0.645	3.73	0.903	159.28	0.823	62.03	0.903
	59.62±91.78		9.02±15.14		566.9±750.4		116.0±174.5	
Distant Nodal involvement								
Absent	31.31±41.41	0.125	5.45±8.21	0.567	371.7±649.8	0.183	90.24±168.8	0.465
Present	77.49±111.0		11.30±18.1		685.3±792.6		131.7±176.8	
Organ Metastasis								
Absent								
Present	13.49±13.39	**0.015***	3.50±3.65	0.448	157.1±160.1	**0.046-***	52.07±54.77	0.643
	68.84±98.04		10.13±16.3		649.0±795.6		129.2±187.3	

***=** $p<0.05$ statistically significant.

A statistically significant association was also found between high total lesion glycolysis (TLG40%) and increased tumor diameter and distant organ metastasis (p=0.001 and p=0.046, respectively) (Table 3).

Discussion

^{18}F-FDG PET/CT imaging technique has become more widespread within the last decades owing to its proven contribution to staging in LC among many other cancer types. Since the early 2000s, a remarkable increase in detection of patients with stage IV LC has been directly proportional to the increasing availability of ^{18}F-FDG PET/CT, as it can detect distant metastasis well before the emergence of disease symptoms. Several studies have aimed to document the prognostic value of FDG uptake in SCLC management (2,10). In one meta-analysis including 1062 SCLC cases, Zhu et al. concluded that increased SUVmax detected in ^{18}F-FDG PET/CT scan performed before treatment had predictive value for prognosis and survival (11). Choi et al. examined 118 SCLC cases and found that increased SUVmax in ^{18}F-FDG PET/CT performed for staging purposes was a statistically significant prognostic factor for mean survival (12). In their study including 66 SCLC cases, Tang et al. found a significant association between increased SUVmax of ^{18}F-FDG PET/CT and high TNM stage and poor survival (p=0.0016 and p=0.006, respectively) (13). Similarly, Ding et al. reported a significant association between increased SUVmax and tumor size in their study including 52 SCLC cases (14).

On the contrary, in their study including 82 SCLC cases, Kim et al. reported that SUVmax in ^{18}F-FDG PET/CT had no significant effect on mean survival time or prognosis, and that it could not be used for prognostic evaluation before treatment (15). In their studies with SCLC cases, Inal et al. (n=54) and Araz

(n=38) et al. reported that FDG uptake and its prognostic significance did not provide remarkable contribution to survival (9,16).

In our study, increased tumor size was found to be significantly associated with mean SUVmax, and a statistically significant positive correlation was present between tumor size and SUVmax. However, the mean SUVmax did not show a significant association with locoregional LN involvement, distant nodal metastasis, or distant organ metastasis among other prognostic factors. Our mean follow-up time was 28.93±28.84 months; and reduced survival was significantly associated with increased tumor size, locoregional LN involvement, distant nodal metastasis and distant organ metastasis.

^{18}F-FDG PET/CT imaging allows evaluation of metabolic activity-related volumetric tumor load with the help of MTV and TLG parameters. Kwon et al. performed imaging to examine metabolic tumor load in 59 SCLC cases. They reported that increased MTV and TLG, in addition to increased SUVmax, had significant predictive value in the evaluation of prognosis, stage, and survival (17). Nobashi et al. evaluated volumetric parameters of ^{18}F-FDG PET/CT according to tumor location in their studies, including 61 SCLC cases, and they found MTV and TLG were independent prognostic factors for peripheral type of tumors ($p<0.0024$) (18). Domachevsky et al. found a significant association between survival data and MTV and TLG parameters in their study with 54 SCLC cases. They also reported that ^{18}F-FDG PET/CT could change staging in 35% (n=19) of patients. The researchers concluded that use of volumetric parameters would be beneficial in tumor staging and prognosis prediction (19). Oh et al. associated high MTV value with poor prognosis in their study including 106 SCLC cases (20). The researchers documented that when used in combination with TNM, MTV had higher predictive value and provided a more accurate prognosis prediction compared to TNM alone or conventional staging. Consistent with these results, we found a significant association between high MTV and TLG values and increased tumor size and presence of distant organ metastasis in the present study. Although SUVmax was found to be positively correlated with TLG (40-70), it was found to be ineffective for the detection of distant metastasis when compared to the volumetric parameters.

In conclusion, only minor improvements have been reported regarding survival data despite recent advances in diagnostic and therapeutic approaches for LC. Accurate and functional imaging has become more important than ever for LC. Unlike other types of cancer, volumetric parameters have apparent major contributions compared to the metabolic parameters of ^{18}F-FDG PET/CT in evaluation of patients with SCLC. Therefore, volumetric parameters (MTV and TLG) of PET/CT should be taken into consideration in the pre-treatment evaluation of patients diagnosed with SCLC. In cases with high ^{18}F-FDG uptake in primary tumor, poor prognosis should be expected and more attention should be given to these patients due to the high metastatic potential and the need for better treatment strategies

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Authorship Contributions

Concept: E.A. , **Design:** E.A. , **Supervision:** E.A., G.A., T.A., Ö.M., S.A. **Data Collection and/or Processing** : E.A., G.A., T.A., Ö.M., S.A. **Analysis and/or Interpretation:** E.A., G.A., T.A., Ö.M., S.A. **Literature Review:** E.A **Writer:** E.A.

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