The relationship between preoperative FDG PET/CT uptake and survival in patients with lung cancer

Ahmet Ulusan, Mehmet A. Ekici, Ilkay Dogan, Maruf Sanli, A. Feridun Isik

Department of Thoracic Surgery, Gaziantep University, Gaziantep, Turkey

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Corresponding author:
Ahmet Ulusan MD
Department of Thoracic Surgery
Gaziantep University
Gaziantep, Turkey
E-mail: draulusan@gmail.com

Abstract

Introduction: Despite all the advances in diagnosis and treatment, lung cancer is the leading cause of cancer death in both sexes worldwide. Because of the different survival rates in lung cancer, additional factors are needed to determine the prognosis. In this study, we aimed to investigate the relationship between survival and clinical data of primary tumor SUV (standardized uptake value) to evaluate the role of [18F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) as a prognostic factor in lung cancer.
Material and methods: The data of patients who underwent anatomic resection and preoperative positron emission tomography/computed tomography (PET/CT) between February 2006 and October 2019 in the Department of Thoracic Surgery, Faculty of Medicine, Gaziantep University were analyzed retrospectively.
Results: In all there were 666 patients, 64 of whom (9.6%) were female and 602 (90.4%) male. The mean age of the patients was 61.91 ±9.6 years. Histologically, there were 369 (55.4%) epidermoid carcinomas and 233 (34.9%) adenocarcinomas. The overall mean survival was 68.2 months and the median survival was 63.6 months. The mean mass SUV value of the patients was 13.73 ±6.65. The effect of histological type, TNM stage, metastasis and recurrence on survival was statistically significant ($p < 0.05$). According to the univariate analysis (Cox regression analysis), it was found that 1 unit increase in SUV value contributed to a statistically significant increase in mortality risk ($p = 0.002$, HR = 1.024, 95% CI: 1.009–1.040).
Conclusions: In our study on 666 patients, unlike the literature, no statistically significant relationship was found between SUV value and survival.

Key words: lung cancer, prognosis, FDG PET, SUV.

Introduction

Lung cancer is a common disease with high mortality. Despite considerable progress in recent years, the 5-year survival rate for lung cancer is around 9.4–14% [1, 2]. Diagnosis of the disease in the late stages is the major cause of high mortality. Five-year survival for stage IA1, IA2, IA3 IB, IIA, IIB, IIIA and IIIB is 88%, 74%, 65%, 60%, 49%, 45%, 40%, and 34% respectively [3, 4].

The stage of the lung cancer at the time of diagnosis is the most important factor affecting survival. However, even in the same stage, there are differences in treatment responses, recurrence rates and survival. Therefore, some laboratory and clinical parameters are needed to determine the treatment strategies, follow-up and prognosis in lung cancer [5].

Although stage, histological subtype, comorbid conditions, tumor differentiation, performance status and some molecular level markers are used as prognostic factors in certain patient groups, additional factors related to the biological behavior of the tumor are being investigated [5, 6]. [I8F]-Fluoro-2-deoxy-D-glucose positron emission tomography FD (FDG-PET) is widely used in clinical staging and restaging processes, detection of recurrence, treatment response as well as conventional imaging tests. In addition to its anatomical features, it is a non-invasive method that is suggested to give an idea about its biological behavior [7, 8].

In recent years, it has been widely discussed whether FDG-PET can be used to determine stage, clinical process and the response to treatment due to its ability to reflect the metabolic activity of the tumor in lung cancer. Some researchers have concluded that there is a relationship between standardized uptake value (SUV), which is an indicator of FDG uptake, and survival of patients with lung cancer [9–13]. In patients with non-small cell lung cancer (NSCLC), when the survival analysis is controlled for the stage, histologic subtype, tumor differentiation and treatment type, some studies have reported that there is a correlation between increased SUV value of the primary tumor and decreased survival time [10, 14, 15]. However, other studies with similar groups of patients reported that there was no relationship between SUV value and survival time of the primary tumor, or that this relationship did not contribute to the information provided by staging [16, 17]. In a meta-analysis, some of these studies were collected and evaluated and it was found that SUV is a powerful factor in determining the prognosis of lung cancer, but these data should be supported by further studies in which prospective, multivariate analyses can be applied [18].

In the light of the studies in the literature, we planned our study to evaluate FDG uptake of the primary tumor as a prognostic factor in lung cancer and the factors affecting it on the SUV parameter. We aimed to investigate the relationship of tumor SUV value with histological subtype, tumor size, TNM stage, and survival in preoperative PET patients with small cell lung cancer (SCLC) and NSCLC subtypes undergoing anatomic resection.

Material and methods

Study participants

In this retrospective study, approval was obtained from the Ethics Committee of Gaziantep University School of Medicine (ethics committee approval no: 2019/413, 23.10.2019). The patients who were diagnosed with lung cancer between February 2006 and October 2019 in the Department of Thoracic Surgery, Faculty of Medicine, Gaziantep University were included in this study.

As inclusion criteria, patients who were diagnosed with small cell lung cancer (SCLC) and NSCLC, who had undergone a PET/CT scan and reported before and underwent anatomic resection were included in the study.

As exclusion criteria, patients who were diagnosed with lung cancer but who did not have anatomic resection, who underwent anatomic resection but had not undergone PET/CT preoperatively, and those whose PET/CT report could not be retrieved during retrospective examination were excluded from the study.

Age, gender, histopathologic diagnosis, tumor location, tumor size, type of operation, stage, and mass SUV value of the patients included in the study, radiotherapy and chemotherapy treatment status, recurrence and final controls were recorded. Survival periods were determined by telephone. Pre-operative staging of all patients was performed according to TNM IASLC 8th edition.

In a minority of cases, adenocarcinoma molecular examination was performed. Unfortunately, we did not add it because there was not enough data. Molecular examination has been performed in our hospital for about 4 years. In the past, especially cases were sent to an external center for molecular examination.

PET/CT imaging

Whole-body PET/CT scans were performed with the Siemens Biograph 2 PET/CT system (Siemens, Munich, Germany) at the Department of Nuclear Medicine, Gaziantep University. Whole body scan was performed 1 hour after intravenous FDG (11-16 mCi) injection and visualized from vertex to thigh. During this 1-hour period, the patients were kept in dark and warm conditions and the patients were asked not to speak. All patients were fasted for at least 6 hours prior to imaging, fasting blood glucose levels were within normal limits during imaging, and no patient used insulin to normalize blood glucose levels. Coronal and sagittal sections' correlations with CT were used to determine the correct location. SUV values for the regions with involvement in the images were determined by calculating the concentration of radioactive material in tissue according to the dose injected and the patient's weight for that region.

Statistical analysis

SPSS Statistics for Windows 25 was used for analysis. The Kaplan-Meier method was used to calculate survival probability. The two life curves were compared with the log-rank method. Haz-

ard regression analysis was used to determine the factors affecting life expectancy. In addition, to determine the best cut-off point for mass SUV values, time-dependent ROC curves with the right censored data method were used for time-dependent measurements. Statistical significance was defined as $p < 0.05$.

Results

In our hospital, *EGFR* mutation is first checked as a molecular profile in adenocarcinoma cases, and if it is negative, *Alk* mutation is checked. If the *Alk* mutation is also negative, the *ROS* and *PD-L1* mutations are checked. Smart drug therapy is applied according to the molecular profile. However, in our country, between 2016 and 2019, smart drug treatment payment was generally applied to patients with stage 4 and gene mutations. The patients we operated on were under-reviewed because of the early stage and high treatment costs. It has been studied especially in young women and non-smokers, since the gene has a high probability of mutation and responds well to smart drugs. In the 4 years between 2016 and 2019, 26 of 81 adenocarcinoma patients were examined for mutation, 2 patients were EGFR (+), 1 patient was ALK (+), 1 patient was ROS (+), and 1 patient was *PD-L1* (+).

All cases were 666 patients, 64 of whom (9.6%) were female and 602 (90.4%) male. The mean age of patients was 61.91 ±9.6 years (Table I).

PET/CT was performed for all patients for distant organ and lymph node metastases. EBUS (endobronchial ultrasonography) or mediastinoscopy was performed in suspected lymph node involvement. All cases underwent R0 resection. According to histological types, 369 (55.4%) patients had squamous carcinoma, 233 (34.9%) had adenocarcinoma, 15 (2.2%) had small cell carcinoma and 49 (7.3%) were from other subtypes of NSCLC. When the tumor is divided into lobes of the lung, the tumor was located in the right upper lobe in 191 patients, the middle lobe in 18 patients, the right lower lobe in 106 patients, the left upper lobe in 146 patients, the left lower lobe in 106 patients, the right hilar zone in 47 patients and the left hilar zone in 52 patients. According to resection types, lobectomy was performed in 436 (65.5%), pneumonectomy in 196 (29.4%) and sublobar resection in 34 (5.1%) of our patients. In terms of lymph node uptake, 200 (30.0%) patients were N1, 156 (23.4%) were N2, and 29 (4.4%) were N3. Those with extensive lymph node involvement were referred to neoadjuvant chemotherapy. At late follow-up, 57 patients (8.6%) had metastasis and 118 patients (17.7%) had local recurrence.

Table I. Demographic data of patients

Parameter	Patients (*N* = 666)
Gender, *n* (%):	
Male	602 (90.4)
Female	64 (9.6)
Age (mean ± SD)	61.91 ±9.6

Table II. Tumor diagnosis, location and SUV values of primary tumor

Parameter	Patients (*N* = 666)
Histological type, *n* (%):	
Squamous epithelium	369 (55.4)
Adenocarcinoma	233 (34.9)
Small cell	15 (2.2)
Others	49 (7.3)
Localization, *n* (%):	
Upper right	191 (28.7)
Right center	18 (2.7)
Lower right	106 (15.9)
Upper left	146 (21.9)
Lower left	106 (15.9)
Right main bronchus	47 (7.1)
Left main bronchus	52 (7.8)
Lymph node uptake+, *n* (%):	
N1	200 (30.0)
N2	156 (23.4)
N3	29 (4.4)
Operation, *n* (%):	
Lobectomy	436 (65.5)
Pneumonia	196 (29.4)
Wedge resection	34 (5.1)
Metastasis, *n* (%):	
No	609 (91.4)
Yes	57 (8.6)
Recurrence, *n* (%):	
No	548 (82.3)
Yes	118 (17.7)
Stage, *n* (%):	
1A1	27 (4.0)
1A2	40 (6.0)
1A3	28 (4.2)
1B	70 (10.0)
2A	59 (8.8)
2B	167 (25.2)
3A	179 (26.8)
3B	39 (5.7)
4A	53 (7.9)
4B	4 (0.6)
SUV values of primary tumor, min.-max. (mean ± SD)	0.00–40.10 13.73 ±6.65

In addition, the stages (T) of patients with lymph node metastasis were found to be 3A and above (Table II). The mean primary tumor SUV value of the patients were 13.73 ±6.65 (Table II).

It was found that primary tumor SUV value did not have a statistically significant effect on survival ($p > 0.05$) (Table III). The effect of histological type on survival was statistically significant ($p < 0.05$). Accordingly, the mortality risk of the squamous epithelium group was 0.534 times lower than that of the other group ($p = 0.003$). The mortality risk of the adenocarcinoma group was found to be 0.578 times lower than that of the squamous epithelium group ($p = 0.011$). The effect of metastasis on survival was statistically significant ($p < 0.05$). According to this, mortality risk of patients with metastasis was found to be 1.96 times higher than in those without metastasis. The effect of recurrence on survival was statistically significant ($p < 0.05$). According to this, mortality risk was 0.616 times lower in patients without recurrence than those with recurrence. There was no statistically significant relationship between operation type and survival time ($p > 0.05$) (Table III). There was a statistically significant relationship between TNM stage and survival time ($p < 0.05$). Accordingly, the mortality risk increases when progressing from Stage 1A1 to Stage 4B (Table III). In addition, according to the univariate analysis (Cox regression analysis), it was found that 1 unit increase in SUV value contributed to a statistically significant increase in mortality risk ($p = 0.002$, HR = 1.024, 95% CI: 1.009–1.040).

In the determination of the most significant threshold value (≤ 8.5) for the primary tumor SUV values, the time-dependent ROC curves with the right censored data method were used for time-dependent measurements. According to this method, it was observed that the distinctive feature of SUV values for survival was not high (AUC = 0.563) (Table IV, Figure 1).

Preop FDG-PET SUV values were statistically significantly different according to TNM stage ($p = 0.001$). It is understood that preop FDG-PET SUV values increase from Stage 1A1 to Stage 4. Preop FDG-PET SUV values were not statistically significant difference according to localization ($p > 0.05$) (Table V, Figure 2).

The total mean survival was 68.2 months and the median survival was 63.6 months. The mean survival and median survival of lobectomy were

Table III. Results of multivariate regression analysis between parameters and survival (mortality)

Parameter	P-value	Hazard ratio Exp (B)	95% CI	
			Lower	Upper
Tumor SUV value	0.860	1.002	0.985	1.019
Histological type:				
Squamous epithelium	**0.003**	0.534	0.354	0.804
Adenocarcinoma	**0.011**	0.578	0.378	0.884
Small cell	0.242	0.590	0.243	1.429
Other	0.184	0.498	0.225	1.389
Metastasis	**0.002**	1.960	1.289	2.979
Recurrence	**0.012**	0.616	0.422	0.899
Operation:				
Lobectomy	0.222	0.734	0.447	1.206
Pneumonectomy	0.413	0.802	0.474	1.359
Wedge resection	0.419	0.845	0.485	1.364
Stage:				
1A1	**0.000**	0.092		
1A2	**0.000**	0.085		
1A3	**0.001**	0.101		
1B	**0.000**	0.120		
2A	**0.004**	0.173		
2B	**0.007**	0.203		
3A	**0.036**	0.292		
3B	0.136	0.402		
4A	0.970	1.044		
4B	**0.031**	0.269		

Table IV. Sensitivity and specificity rates for primary tumor SUV values

Tumor SUV value	Sensitivity	95% CI	Specificity	95% CI
≤ 8.5	30.28	25.3-35.7	84.53	80.3-88.2

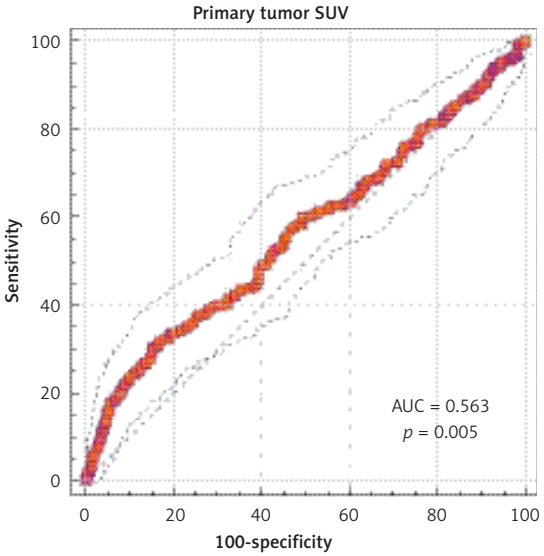

Figure 1. Sensitivity and specificity rates for primary tumor SUV values

69.7 months and 66.7 months, respectively. The mean survival and median survival of pneumonectomy were 65.2 months and 58.2 months, respectively. The mean survival and median survival of sublobar resection were 56.1 months and 53.6 months, respectively (Table VI).

Discussion

In our study, the effect of preoperative FDG-PET SUV values on survival was investigated in 666 patients diagnosed with lung cancer and resection was not found to be statistically significant.

It has been reported in the literature that some factors (histologic type, metastasis, recurrence, operation type, tumor-node-metastasis [TNM] stage) affect the survival time in determining the prognosis in lung cancer [19, 20]. According to current data, the most important factor in determining the prognosis of lung cancer is the stage of the tumor. However, even in the same stage, there are different survival times. In recent studies, the relationship between FDG uptake and TNM stage has been extensively studied [21, 22]. Eschmann *et al*. [23] compared 159 patients with stage IIIA and IIIB, including epidermoid carcinoma, adenocarcinoma, large cell carcinoma, undifferentiated carcinoma, bronchoalveolar carcinoma, and nonspecific NSCLC histology for mean SUV values and survival. According to the results of the study, the researchers suggested that SUV value could be used as a prognostic factor in advanced stages [23]. In our study, the mean survival was 68.2

Table V. Comparison of SUV values according to stage and localization

Parameter	Number	Mean	± SD	*P*-value
Stage:				**0.001**
1A1	27	8.38	5.46	
1A2	40	8.72	4.90	
1A3	28	11.09	5.49	
1B	70	13.31	7.24	
2A	58	14.75	7.06	
2B	168	14.41	6.89	
3A	179	15.43	6.08	
3B	38	15.11	6.82	
4A	53	12.59	5.07	
4B	4	10.25	3.52	
Localization:				0.398
Upper right	191	13.89	6.70	
Right center	18	13.12	7.00	
Lower right	106	12.45	6.74	
Upper left	146	13.91	6.78	
Lower left	106	13.78	7.00	
Right main bronchus	47	14.56	6.10	
Left main bronchus	52	14.73	5.39	

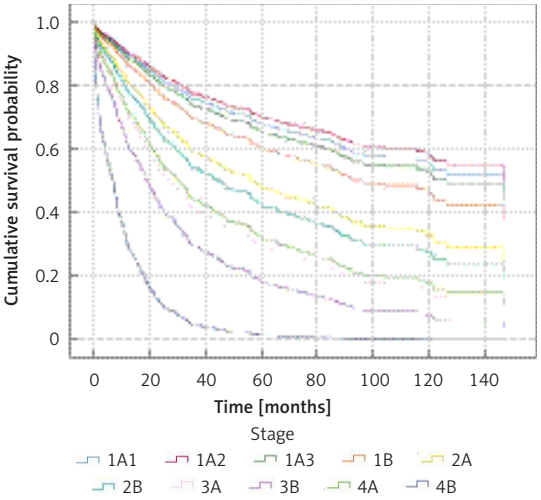

Figure 2. Comparison of SUV values according to stage and localization

months and the median survival was 66.6 months in 666 patients with lung cancer. A statistically significant relationship was found between TNM stage and survival ($p < 0.05$). It is understood that FDG-PET SUV values increase from Stage 1A1 to Stage 4. There was no statistically signif-

Table VI. Mean and median survival for patients undergoing surgery

Operation	Mean				Median			
	Estimate	Standard error	95% CI		Estimate	Standard error	95% CI	
			Lower	Upper			Lower	Upper
Lobectomy	69.776	2.754	64.378	75.174	66.700	3.570	59.703	73.697
Pneumonectomy	65.216	4.434	56.527	73.906	58.233	4.634	49.151	67.316
Sublobar resection	56.166	7.971	40.543	71.788	53.633	8.905	36.180	71.087
Total	68.219	2.269	63.773	72.665	63.633	3.002	57.750	69.517

icant relationship between localization and preop FDG-PET SUV value ($p > 0.05$). However, the effect of metastasis on survival was statistically significant ($p < 0.05$). According to this, mortality risk of patients with metastasis was found to be 1.96 times higher than in those without metastasis.

Recently, PET has been widely used in the diagnosis and staging of lung cancer. It is suggested that PET is a non-invasive method that can provide information about the prognosis of the tumor [9]. FDG-PET is a frequently used method for predicting benign and malignant pulmonary lesions [9]. PET is increasingly used especially in the diagnosis of lung cancer. FDG uptake in PET examination has been suggested to reflect some biological information such as proliferative activity of the primary tumor, tumor doubling time, microvascular density, histological subtype and tumor grade [10, 13]. In the study by Siddique *et al*. [24], an overall significant relationship was found between volume doubling time (VDT) and SUVmax with and without correcting for tumor size [24]. In our study, the effect of histologic type and FDG involvement on survival was statistically significant ($p < 0.05$). Accordingly, the mortality risk of the squamous epithelium group was 0.534 times lower than in the other group ($p = 0.003$). The mortality risk of the adenocarcinoma group was found to be 0.578 times lower than in the squamous epithelium group ($p = 0.011$). The survival time of the SCLC group was not statistically different than that of the adenocarcinoma group ($p = 0.242$).

Several studies have suggested that FDG uptake in PET examination will be important as a prognostic factor. A group of investigators found a correlation between tumor growth rate and FDG uptake [9, 13, 17, 21, 25, 26]. Based on these studies, studies investigating the relationship between FDG uptake and survival as a prognostic factor have come to the fore. In 2019, Kim *et al*. [13] evaluated the data of 130 NSCLC patients between stage I and IV and found that the survival of patients with different FDG involvement at the same stages was different. Accordingly, the survival rate of patients with primary tumor with high FDG involvement is suggested to be shorter. The meta-analysis by Berghmans *et al*. [27] indicated the primary tumor SUV measurement has prognostic value in NSCLC. Kumasaka *et al*. [21] found that SUV values of 112 NSCLC patients were significantly longer than those with a survival of less than 7 than those with a 2-year survival. Similarly, Aktan *et al*. [28] included 46 limited and common stage SCLC patients and found that high SUV values in both stages were associated with short survival time. In a study by Ming *et al*. [29] on 69 patients, they concluded that F-FDG PET/CT with corrected SUVs is of great value for improving diagnostic accuracy in peripheral lung lesions. In our study with our larger patient series compared to those studies, the survival analysis with primary tumor SUV values did not appear to be statistically significant ($p = 0.860$). However, it was observed that every 1 unit increase in the value of the primary tumor SUV increased the risk of death by 1.002 times (HR = 1.002, 95% CI: 0.985-1.019). In our cases, the ideal cut-off point was found to be 8.5 with no significant difference for survival and the highest sensitivity (30.28) and specificity (84.53) for SUV. In determining the most significant threshold value for primary tumor SUV values, it was also found that SUV values were not highly differentiated for survival (AUC = 0.563). However, if the SUV value is high, survival can be low. According to studies in the literature and the results of our study, PET-CT FDG scan and pathological risk factors together are a strongly predictive factor for survival. Although there is a significant relationship between SUV value and survival in many studies in the literature, we think that such a result is due to the small number of patients.

In conclusion, 666 patients with lung cancer who underwent resection had no statistically significant relationship between SUV value and survival. There is a need for prospective, multicenter studies with a large number of patients to investigate the relationship between SUV value of primary tumor and prognosis and parameters affecting FDG uptake in lung cancer.

Conflict of interest

The authors declare no conflict of interest.

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