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Relationship between 18F-FDG PET/CT radiometabolic markers and EGFR mutation, positive ALK Expression in patients with non-small cell lung cancer

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ABSTRACT

Relationship between 18F-FDG PET/CT radiometabolic markers and EGFR mutation, positive ALK Expression in patients with non-small cell lung cancer

Introduction: The aim of this study was to evaluate the association between the presence of EGFR mutations, ALK rearrangement and the standardized uptake value (SUV) of 18F-fluoro-2-deoxy-glucose (18F-FDG) by PET/CT imaging in patients with NSCLC.

Materials and Methods: We retrospectively reviewed NSCLC patients, who underwent EGFR mutation, ALK rearrangement testing and pre-treatment PET/CT. The relationships of EGFR mutation, ALK rearrangement with patient characteristics and three parameters based on 18F-FDG PET/CT, including the maximal standard uptake value (SUVmax) of the primary tumour (tSUVmax), lymph node (nSUVmax) and distant metastasis (mSUVmax) were evaluated.

Results: EGFR mutations were found more frequently in females and non-smokers. tSUVmax was the only PET parameter that was lower in EGFR-positive patients than in EGFR-negative patients (8.7 vs. 11), with a p value of 0.032. There were no differences between nSUVmax and mSUVmax results and EGFR mutation. tSUVmax, nSUVmax and mSUVmax were not significantly different between ALK positive and ALK negative groups in NSCLC. The presence of pleural fluid at the time of diagnosis was significantly associated with positive ALK expression.

Conclusion: We showed that low tSUVmax and primary tumour diameter were associated with mutant EGFR status and could be evaluated with other

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clinical factors to increase the discrimination in EGFR mutation status in some NSCLC patients without EGFR testing. There is a correlation between ALK positivity and the presence of pleural fluid. We also noted that the ALK positivity might be only in the adenocarcinoma group and at a younger age.

Key words: Epidermal growth factor receptor; anaplastic lymphoma kinase; mutation; non-small cell lung cancer; positron emission tomography

ÖZ

Küçük hücreli dışı akciğer kanserli hastalarda 18F-FDG PET/CT radyometabolik belirteçler ile EGFR mutasyonu, pozitif ALK ekspresyonu arasındaki ilişki

Giriş: Bu çalışmanın amacı, Küçük Hücreli Dışı akciğer Kanseri hastalarında EGFR mutasyonun varlığı, ALK yeniden düzenlenmesi ile PET/CT'de 18F-floro-2-deoksi-glukozun (18F-FDG) standardize uptake değeri (SUV) arasındaki ilişkiyi değerlendirmektir.

Materyal ve Metod: EGFR mutasyonu, ALK yeniden düzenleme testi ve tedavi öncesi PET/CT uygulanan NSCLC hastalarını retrospektif olarak inceledik. EGFR mutasyonu, ALK yeniden düzenlenmesi ile hasta özellikleri ve maksimum standart uptake değeri dahil 18F FDG PET/CT'ye dayalı üç parametre arasındaki ilişkiler Primer tümör (tSUVmax), lenf nodu (nSUVmax) ve uzak metastaz (mSUVmax) değerlendirildi.

Bulgular: EGFR mutasyonu kadınlarda ve sigara içmeyenlerde daha sık bulundu. tSUVmax, EGFR-pozitif hastalarda EGFR-negatif hastalara göre daha düşük olan tek PET parametresiydi (8,7'ye 11) ve p değeri 0,032 idi. nSUVmax ve mSUVmax sonuçları ile EGFR mutasyonu arasında fark yoktu. tSUVmax, nSUVmax ve mSUVmax, KHDAK'de ALK pozitif ve ALK negatif gruplar arasında anlamlı olarak farklı değildi. Tanı anında plevral sıvının varlığı, pozitif ALK ekspresyonu ile anlamlı olarak ilişkiydi.

Sonuç: Düşük tSUVmax ve primer tümör çapının mutant EGFR durumu ile ilişkili olduğunu ve EGFR testi olmayan bazı KHDAK hastalarında EGFR mutasyon durumundaki ayrımı artırmak için diğer klinik faktörlerle değerlendirilebileceğini gösterdik. ALK pozitifliği ile plevral sıvı varlığı arasında bir ilişki vardı. ALK pozitifliğinin sadece adenokarsinom grubunda ve daha genç yaşta olabileceğini de belirttik.

Anahtar kelimeler: Epidermal büyüme faktörü reseptörü; anaplastik lenfoma kinaz; mutasyon; küçük hücreli dışı akciğer kanseri; pozitron emisyon tomografisi

INTRODUCTION

Lung cancer is the most frequent reason of cancer-related mortality in the whole world. Surgery, radiotherapy, systemic platinum-based combination chemotherapy, and biological therapies are employed in the treatment of lung cancer (1). Understanding lung cancer biology and molecular changes involved in the carcinogenesis of lung cancer has led to the development of new medications targeting oncogenesis, specifically tumor suppressor genes, growth factor receptors or angiogenesis. This method aims to provide a more effective treatment with fewer side effects by targeting a specific molecule to stop tumor growth.

Although there are no target-specific treatments for each cancer type, several therapies have been included in standard practice. Main molecular changes that may be targeted in NSCLC are epidermal growth factor receptor (EGFR) mutation, Anaplastic Lymphoma Kinase (ALK) translocation and "proto-oncogene tyrosine-protein kinase ROS-1 translocation (2). Multifactorial oncogenes like Kras, EGFR, PI3K, rough domains or EML4-ALK gene fusion mutations have been shown in previous studies; and if not all, most of them have been shown to be present in adenocarcinomas (3). In other words, new drugs that

target a specific pathway and/or population have strong therapeutic indices, low toxicity, and ensure that the patient population that will benefit most from the treatment is selected. These advantages may be achieved especially with therapies intended for tyrosinkinase inhibitor (TKI) (erlotinib and gefitinib) or for ALK (4-7). However, it is difficult to obtain the tumor tie on which sufficient and good-quality mutation examination is possible, and such tests are not yet applicable everywhere.

Positron emission tomography (PET) is a molecular imaging method, which provides physiological information needed for clinical diagnosis based on change in tissue metabolism. Then oncologic PET applications became widespread with the development of computed tomography (CT) and integrated PET scanners (PET/CT). Among the most common PET/CT applications, there are lung cancers. Today, FDG PET/CT is used for diagnosis, staging and evaluation of response to treatment, re-staging, radiotherapy planning and determining prognosis in lung cancer. With PET that is applied with fluoro-2-deoxy glucose (FDG) marked with F-18 isotope, many malignant tumors might be visualized as noninvasive due to increased glucose metabolism. FDG PET decreases the glucose metabolism pathway of the EGFR signal

and lactate production of the EGFR-TKIs and glucose consumption in cells that have EGFR mutation (1,7-13). In this way, FDG involvement in PET/CT might be useful as a noninvasive marker in predicting EGFR mutation and ALK rearrangement⁸. The data in the literature that examine the relation between the presence of EGFR mutation and FDG involvement in lung cancer differ, and there are several studies examining the relation between glucose metabolism and ALK rearrangement (9,14,15).

In this study, the relation between FDG involvement changes, genetic mutation status and clinical parameters were evaluated retrospectively in lung cancer patients who had been studied in our clinic since 2014 and whose genetic mutation examinations were made in our clinic. These genetic tests are both expensive and tissue required. Therefore, we investigated whether the Suv (max) value in 18F-FDG could

help predict EGFR mutation or ALK positivity. We also investigated whether 18F-FDG PET is a valuable non-invasive method in estimating EGFR mutation and ALK positivity in NSCLC.

MATERIALS and METHODS

Patients and Inclusion Criteria

We retrospectively reviewed 232 NSCLC patients whose histopathological diagnosis and mutation results were reached between 2014 and 2018. Due to tissue insufficiency, both EGFR and ALK could not be measured in 14 cases. A total of 104 cases were excluded from the study due to the absence of prediagnosis PET/CT scan, or if the time interval between sampling and PET/CT exceeded 1 month. Therefore, a total of 114 patients with at least one of EGFR or ALK that could be tested with enough size of sampling were included in this study (Figure 1). Patient

Figure 1. Follow chart of the patients in the study.

clinical characteristics including age, sex, smoking history, histopathology, tumour size, nodal involvement, distant metastasis and tumour stage were recorded. The differences in several clinical characteristics and three parameters based on 18F-FDG PET/CT, [including the maximal standard uptake value (SUVmax) of the primary tumour (tSUVmax), the one with highest SUV uptake lymph node (nSUVmax) and distant metastasis (mSUVmax)] between EGFR and ALK subgroups were analysed. Also, when one of the ALK rearrangement or EGFR mutation analyses was not studied due to insufficient tissue, those cases were not included in the statistical analysis of that group.

18F-FDG PET/CT Acquisition and Analysis

All patients involved in the study underwent whole-body 18F-FDG PET/CT scanner (GEMINI TF 16 Slice, by Philips Healthcare, Koninklijke Philips Electronics N.V, Amsterdam). PET component is a high-resolution scanner with a spatial resolution of 4.7 mm and has no septa, thus allowing 3-dimensional-only acquisitions. CT portion of the scanner is 16-slices. After fasting for at least six hours before the integrated PET/CT examination, blood glucose level of the patient was obtained prior to tracer injection. In case blood glucose level for FDG injection was below 180 mg/dL, 3 MBq of 18F-FDG per kilogram of body weight was injected. After the injection, the patients rested for a period of about 60 ± 10 minutes in a comfortable room and chair. Tomography images were acquired for attenuation correction and anatomic localization, PET images were acquired in axial planes from the proximal femur to the vertex, 9-11 bed in 2 minutes per bed. Processed images were displayed in coronal, transverse, and sagittal planes and PET/CT images were also assessed quantitatively using the maximum standardized uptake value (SUVmax). All PET/CT data were reviewed by an experienced nuclear medicine physician. The lesions which were over SUVmax 2.5 were considered as pathological.

EGFR Mutation Analysis

EGFR mutation analysis was performed using tissue specimens from biopsy or surgical excision.

DNA isolation was carried out from the paraffin blocks of the patients (at least 3 sections of ca. 5 μ per patient) using the "QIAamp® DNA FFPE Tissue kit" (Qiagen, the USA) at 15-20 ng per reaction tube. For

mutation screening, "Easy® EGFR" (Diatech, Italy) kit was used. In the first stage of the study, 10 μ l Taq Premix 920, 4 μ l Water and 1 μ l EGFR ctrl mix were prepared, and pipettage and spin centrifuge were carried out. In the mutation detection step, 8 different mixtures were prepared and reproduced as EGFR G719x, EGFR T790M, EGFR S768I, EGFR ex20ins, EGFR L858R, EGFR L861Q, EGFR ex19del and EGFR ctrl. Distilled water was added for negative control and EGFR Pos. Ctrl II was added to the study for positive control. The RT-PCR stage was carried out with the Rotor gene system. Evaluation at the analysis stage was carried out by calculating the Δ Ct values according to the recommendations of the manufacturer, as written in the evaluation kit.

ALK Rearrangement Analysis

Genetic alterations were tested using tissue specimens obtained from biopsy or surgical excision. For ALK rearrangement, fluorescence in situ hybridization (FISH) was performed on tissue specimen. Approved DAKO ALK Break apart FISH Probe Kit was used for molecular testing. Paraffin sections from tumour block ranging between 4-6 μ m thickness were deparaffinized with special solutions in the Kit, unstained and hybridized overnight with the ALK probe, and were then evaluated by dual filtered microscopy. An ALK translocation was regarded as positive when separated red and green fluorophores or single red signals were observed in >15% of tumour cells in investigation of more than 50 tumour cells.

Statistical Analysis

SPSS for Windows® 20.0 was used for statistical analyses. Descriptive statistics were expressed as mean $\pm$ standard deviation or median (25%-75%) for continuous variables and as frequency (%) for categorical variables. Pearson's Chi-square test was used to determine the association between the categorical variables. Mann-Whitney U test were used to compare descriptive values of a continuous variable between two groups. $p < 0.05$ was assumed to be statistically significant. Receiver operating characteristics (ROC) curves were constructed to obtain the cut-off value of the primary tumour SUVmax (tSUVmax) for predicting the EGFR mutations status. Logistic regression analysis was performed to identify independent predictors of the EGFR or ALK status. Univariate analyses were performed before the regression model was formed. The variables that were statistically significant ($p < 0.05$) and those with p val-

ues of 0.25 and below were taken. Age (years), sex (male/female), smoking status (smoking/non-smoking), presence of cancer in the family (no/yes), primary tumour SUV value (tSUVmax), mediastinal lymph node SUV (nSUVmax) and metastasis (mSUVmax) were included. Statistical significance level was determined as $p < 0.05$ and removal $p < 0.10$. Multivariate logistic regression analysis was performed to determine the predictors of EGFR mutations and ALK positivity. The odds ratios and 95% confidence intervals of the predictors were obtained. The last step was presented in logistic regression analysis.

Ethics Statement

The present study protocol was reviewed and approved by the local committee of Health Sciences University İzmir Dr. Suat Seren Chest Diseases and Chest Surgery

Training and Research Hospital (approval no: 49109414-806.02.02). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

Patient Characteristics

In the EGFR group, there was no tissue insufficiency. However, in the ALK group, a total of 104 patients were analyzed due to tissue insufficiency in 10 patients. Out of a total of 114 NSCLC patients, 29 were females (25.50%) and 85 were males (74.50%) with a mean age of 58.51 ± 10.38 years. were included in the study. General characteristics of the patients are shown in Table 1. The most frequent mutations were exon 19 (53.33%) and L858R exon 21 (33.33%) mutations (Figure 2).

Table 1. The characteristics of 114 patients

Characteristics	n	%
Gender		
Female	29	25.5
Male	85	74.5
Nodal Involvement		
Absent	41	35.65
1	16	13.91
2	7	6.09
>2 and bulky	50	44.35
Smoking History	-	-
Ever-smoker	84	73.92
Never-smoker	30	26.09
Histopathology		
Adenocarcinoma	105	92.17
Squamous	7	6.09
Other	2	1.74
Stage		
Stage 1	9	7.83
Stage 2	6	5.22
Stage 3	31	26.98
Stage 4	68	60.00
Metastasis		
Absent	45	39.13
Present	69	60.87
Mutation		
Absent	80	70
Present	34	30
EGFR (114 patients)		
Negative	92	80.70
Positivity	22	19.30
ALK (*104 patients)		
Negative	92	80.7
Positivity	12	10.5
Insufficient tissue and/or failure to receive signal	10	8.7

EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase.

* Tissue insufficiency in 10 patients.

Figure 2. Frequency of EGFR mutations.

Table 2. Association between clinical characteristics, PET/CT parameters and EGFR, ALK, ROS status in NSCLC patients

	EGFR (114 patients)		p	ALK (*104 patients)		p
	Negative	Positive		Negative	Positive	
Age	57.56 ± 9.95	61.77 ± 11.96	0.09	59.30 ± 10.15	50.67 ± 10.63	0.019
Gender						
Female	16	13	0.00	25	2	0.435
Male	76	9		67	10	
Smoker	74	10	0.001	73	6	0.025
Non-smoker	18	14		19	6	
Pleural effusion at diagnosis			0.615			
Absent	71	16		75	6	0.014
present	21	6		17	6	
Mediastinal LAP						
0 -1	47	10	0.668	46	5	0.587
≥ 2. Bulky	45	12		46	7	
Cancer history in family						
Absent	57	18	0.073	61	7	0.585
present	35	4		31	5	
Stage						
Stage 1	7	2		8	1	
Stage 2	4	2	0.314	6	0	0.532
Stage 3	23	8		28	2	
Stage 4	58	10		50	9	
Tumour size	4.7 (3.7)	3.9 (1.4)	0.061	4.25 (3.3)	4.5 (3)	0.656
PET /BT						
tSUV max	11 (8.8)	8.7 (6.45)	0.032	10.9 (7.9)	9.9 (6.42)	0.467
nSUV max	10.1 (9.8)	7 (5)	0.059	8.4 (8.7)	8 (23.3)	0.499
mSUV max	8 (7.2)	6.8 (6.2)	0.201	7.2 (5.3)	6.4 (12.5)	0.799

EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, SUVmax: Maximal standard uptake value, TSUVmax: Primary tumour SUVmax, nSUVmax: Nodal metastasis SUVmax, mSUVmax: Distant metastasis SUVmax.

* Tissue insufficiency in 10 patients.

Figure 3. The relationship between EGFR mutation and smoking status and sex.

Association Between Clinical Characteristics, PET/CT Parameters and EGFR, ALK Status in NSCLC Patients

The clinical characteristics of NSCLC patients are summarized in Table 2 based on their EGFR and ALK status. EGFR mutations were found more frequently in females and non-smokers (p : 0.000, 0.001, respectively) (Figure 3). The patients with ALK-positive NSCLC were younger (59.30 ± 10.15 and 50.67 ± 10.63 , p = 0.019), and the rate of ALK positivity was higher in non-smokers (p = 0.025) (Table 2). tSUVmax was the only PET parameter that was lower in EGFR-positive patients than in EGFR-negative patients (8.7 vs. 11), with a p value (0.032). There were no differences between mSUVmax, nSUVmax results and EGFR mutation (Table 2). tSUVmax, nSUVmax and mSUVmax were not significantly different between ALK positive and ALK negative groups in NSCLC (Table 2). The presence of pleural fluid at the time of diagnosis was significantly associated with positive ALK expression (p = 0.014) (Table 2).

Association Between Clinical Characteristics, PET/CT Parameters and EGFR and Status in Lung Adenocarcinoma group

nSUVmax was significantly lower only in the adenocarcinoma subgroup (105 cases) in EGFR mutation positive patients than in EGFR mutation negative

patients (p = 0.042). Also, tSUVmax was lower in EGFR-positive patients than in EGFR negative patients (5.6 vs. 7.3), with a borderline p value (0.058). No statistically significant difference was found between ALK-positive and ALK-negative patients in terms of tSUVmax, nSUVmax and mSUVmax. In the adenocarcinoma group, as in the NSCLC group, there was a correlation between the presence of pleural fluid and ALK positivity at the time of diagnosis (p : 0.018) (Table 3).

Prediction of the EGFR Mutation Status

ROC curve analysis revealed that the cut-off point for the tSUVmax was ≤ 14.7 ; 95.4% sensitivity, 31.8% specificity, 25.3% positive predictive value (PPV), 96.7% negative predictive value (NPV) were achieved, and the area under curve (AUC) was 0.648 (95%CI, 0.553-0.736) with p = 0.001 (Figure 4).

In multivariate analysis, being female increased the risk of EGFR mutation 4.9 times. A one-unit increase in the primary tumor SUVmax value reduced the risk of genetic mutation at a rate of 14%. These risk changes were found to be statistically significant (p < 0.05) (Table 4).

DISCUSSION

In the present study, we evaluated the clinical significance of 18F-FDG uptake as a predictor of the pres-

Table 3. Association between clinical characteristics, PET/CT parameters and EGFR, ALK status in lung adenocarcinoma group

	*EGFR (n= 105)		p	**ALK (n= 95)		p
	Negative	Positive		Negative	Positive	
Age	57.35 ± 10.15	63.00 ± 10.74	0.026	59.68 ± 10.15	50.67 ± 10.63	0.005
Gender						
Female	16	13	0.000	23	2	0.345
Male	68	8		60	10	
Smoker	66	10	0.005	66	6	0.033
Non-smoker	18	11		17	6	
Pleural effusion at diagnosis						
Absent	63	15	0.607	68	6	0.018
Present	21	6		15	6	
Mediastinal LAP						
0 -1	42	10	0.884	41	5	0.589
≥ 2. Bulky	42	11		42	7	
Stage						
Stage 1	6	2		7	1	
Stage 2	4	2	0.314	5	0	0.532
Stage 3	21	8		25	2	
Stage 4	53	9		46	9	
Tumour size	2.8 (1.8)	2.7 (0.3)	0.053	2.72 (1.7)	2.5 (1)	0.793
In PET/BT						
tSUV max	7.3 (4.6)	5.6 (4.2)	0.058	7.1 (3.9)	6.4 (2.87)	0.618
nSUV max	5.55 (5.2)	4.07 (2.7)	0.042	4.6 (5.5)	7.1 (22.4)	0.445
mSUV max	6.2 (5)	4.25 (4.5)	0.161	5.4 (2.9)	4.25 (10.)	0.721

EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, SUVmax: Maximal standard uptake value, TSUVmax: Primary tumour SUVmax, nSUVmax: Nodal metastasis SUVmax, mSUVmax: Distant metastasis SUVmax.
 *EGFR (+) in 21 cases of 105 adeno carcinomas. 1 case squamous cell carcinoma with EGFR (+).
 ** Tissue insufficiency in 10 patients.

Figure 4. Receiver operating characteristic curves of primary tumour SUVmax for predicting EGFR mutation.

ence of the EGFR mutations and ALK rearrangement. Similar to previous studies, EGFR mutation was found more frequently in females, non-smokers, and in adenocarcinomas. And also, EGFR mutation was found to be associated with quantitative measurements of 18F-FDG uptakes (i.e., SUVs). We observed that patients with low SUVs in primary tumours (tSUVmax ≤14.7) harboured a higher incidence of EGFR mutation, when compared with those with high SUVs. Importantly, multivariate analysis confirmed that tSUVmax and female sex were predictive factors for the presence of EGFR mutation. The presence of pleural fluid at the time of diagnosis was significantly associated with positive ALK expression.

Our results agree with previous studies that show that EGFR mutations are found predominantly in female patients, in patients with adenocarcinoma histology, and in never-smokers (8,16,17). While in Europe, EGFR mutation incidences changes between 6% and 24 %; in Asia, this rate is 51.3% (14). In a study con-

Table 4. Multivariate regression analysis for factors associated with EGFR mutation in patients with NSCLC

	Beta	p	OR	%95 CI
Gender				
Male	1			
Female	1.596	0.006	4.93	1.60-15.33
Age	0.048	0.089	1.05	0.99-1.11
tSUVmax	-0.142	0.039	0.86	0.76-0.99

ducted with patients diagnosed with adenocarcinoma by Kanmaz et al. in Turkey, EGFR mutation rate has been reported as 28%; however, this rate has been found to be 13.5% in the patients diagnosed with NSCLC in a multicenter REDIGMA study conducted in Turkey. Na et al. have conducted a study in Korea and reported that EGFR mutation rate was 21% in patients with NSCLC. Cho et al. have reported a 50% rate in patients diagnosed with adenocarcinoma (14,16,17). In our study, on the other hand, most patients were diagnosed with lung adenocarcinoma, and EGFR mutation frequency was found to be 19.65% in the study group. Our results are similar to European data and were found to be lower than the results reported in Asian studies. This can be explained by ethnic differences.

The data from previous studies that have investigated the value of 18F-FDG PET for predicting EGFR status are conflicting. In a retrospective study conducted by Zhilei et al. (8), 849 Chinese NSCLC patients have been examined, and other studies conducted by Na et al. (16) and Cho et al. (17), Guan et al. (9) have reported that the presence of EGFR mutation in NSCLC was associated with low SUVmax (tSUVmax) in primary tumor; and that low tSUV max was an independent variable for the EGFR mutation. Mak et al. (11) have found that an SUVmax value higher than 5 was associated with cases having no EGFR mutation. In our study, we determined that low tSUV max value was associated with EGFR mutation according to the 18-FDG PET BT value in patients diagnosed with NSCLC. However, there are various studies with contrary findings reporting an association between high FDG uptake and an EGFR mutation. Huang et al. (13) have shown that patients with SUVmax ≥ 9.5 were more likely to have EGFR mutations than those with SUVmax < 9.5 , and Ko et al. (18) have found that a higher SUVmax (≥ 6) is associated with EGFR mutation. Similarly, Kanmaz et al. (14) have found a positive association between high SUVmax values and EGFR mutation. The reason of

having such different results may be related to the different histological types of tumours included in those studies. The ratio of bronchoalveolar carcinoma cases known to have a low SUV max involvement is high in the study conducted by Mac et al. (28/90; 25%) (11). In the study of Na et al. (16), 44% of the cases have been diagnosed with squamous cell carcinoma. Different tumour biology may have caused different FDG involvements. In our study, there were four bronchoalveolar carcinoma cases, seven squamous cell carcinomas and 2 different cell types including one neuroendocrine differentiated large cell and one malign epithelial tumour. Lee et al. (12) have revealed that tSUVmax was statistically significant only in the univariate regression analysis but not in the multivariate regression analysis. Our results showed that tSUVmax was statistically significant in the multivariate regression analysis. Moreover, SUVmax AUC value for EGFR positivity was found to be 0.648 by ROC analysis. Also, in our study, the cut-off point for the tSUVmax was ≤ 14.7 with 95.4% sensitivity, 31.8% specificity, 25.3% positive predictive value (PPV), and 96.7% negative predictive value. In another study in which, 731 patients with adenocarcinoma and 77 with non-adenocarcinoma were enrolled, conducted by Zhilei Lv et al., ROC curve analysis have revealed that the cut-off point for the tSUVmax was 7.0 with 72.8% sensitivity, 38.5% specificity, a 54.6% positive predictive value, a 58.2% negative predictive value, and 57.1% accuracy were achieved, and the area under curve (AUC) was 0.557 (8). Guan et al. have shown that SUVmax cut-off point was 8.1 and AUC was 0.65 [95% Confidence Interval (CI) 0.60-0.72].

In lung adenocarcinoma, primary tumor diameter tends to be smaller than other NSCLC subtypes. In our study, the average diameter of the primary tumor was determined as 2.7 in the adenocarcinoma group (n= 105). No correlation was detected between EGFR mutation and tumor diameter. In our study group, among the 114 patients who had NSCLC, 105

patients were diagnosed with adenocarcinoma. Only one of the patients who had squamous cell carcinoma had EGFR mutation. For this reason, our results might not have been found to be significant in terms of primary tumor diameter because of the homogeneity of the group. Guan et al. (9) have found a strong negative correlation between primary tumour size and EGFR mutations. Large primary tumour size (≥ 5 cm) was significantly associated with wild-type EGFR.

Recently, a new oncogene called “akinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion oncogene” has been defined in lung adenocarcinomas. It is not found frequently in lung adenocarcinomas (15-20). Dramatic response and a long progression-free survival might be achieved in patients with ALK rearrangement with the target-specific treatment (8,21).

Choi et al. have found a rate of 5.4% ALK rearrangement in 331 lung adenocarcinomas. Zhilei et al. (8) have investigated the metabolic features of 17 ALK positiveness in 223 NSCLC patients (7.6%) and 17 ALK positiveness in 190 adenocarcinoma subgroup patients (8.9%). ALK positiveness was found to be 11.5% in our study. Among the adenocarcinoma patients, nSUVmax was higher in the ALK-positive group than in the ALK-negative group. However, there was no difference in tSUVmax between the two groups. Jeong et al. (22) have reported that a higher tSUVmax was an independent predictor of ALK positivity. In our study, ALK rearrangement was statistically significant only in the young age and adenocarcinoma group and in the non-smokers ($p = 0.005$, $p = 0.033$, respectively). We also found that ALK positivity was present only in the adenocarcinoma group. No statistically significant differences were detected between ALK-positive patients and ALK-negative patients in the case of adenocarcinoma in terms of neither SUVmax nor nSUVmax and mSUVmax. The reason for this may be associated with the fact that 53 ALK positive patients who received pre-treatment were reported in Jeong's study; however, ALK positive patients were low in number in our study ($n = 12$). In another study, ALK-positive group demonstrated higher SUVmax, which suggests that ALK positivity is related with more malignant features with higher glucose metabolism. Additionally, higher tumour stage and more common metastases to lymph nodes have been observed in ALK positive group (15).

Higher FDG uptake of ALK positive group may have correlations with radiological phenotype and genetic interactions. In previous studies, ALK-rearranged lung cancer has exhibited solid pattern rather than ground-glass opacity (GGO) pattern on CT, whereas EGFR mutated tumours have been associated with high proportion of GGO (23,24). It has been reported that less aggressiveness of lung adenocarcinoma is related with lower FDG uptake and higher proportion of GGO (25). In our study, we found a correlation between ALK positivity and the presence of pleural fluid in adenocarcinoma group. However, we did not look at the relationship between ALK, EGFR mutation and other radiological findings (consolidation, GGO, nodule, etc.), which were detected in imaging methods.

This study has several limitations. Firstly, the design of this study was retrospective, and selection bias may have existed. Secondly, the patient population was not large enough for sufficient statistical significance and subgroup analysis.

CONCLUSION

This study presented the association of the presence of EGFR mutations with PET findings in patients with NSCLC. We showed that low tSUVmax was associated with mutant EGFR status and could be evaluated with other clinical factors to increase discrimination in EGFR mutation status in some NSCLC patients without EGFR testing. If a patient does not respond well to other treatments and cannot undergo gene testing, clinical factors (female, non-smokers) and low tSUVmax (≤ 14.7) might be helpful for assessing EGFR mutation status. This may determine whether to use EGFR-TKI or not. We also noted that ALK positivity might be only in the adenocarcinoma group and at a younger age. In addition, we found a correlation between ALK positivity and the presence of pleural fluid.

Ethical Committee Approval: This study approval was obtained from İzmir Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital Ethical Committee (Decision No: 49109414-806.02.02, Date: 19.01.2018).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MG, CA, NA

Analysis/Interpretation: MG, CA, AEE

Data acquisition: MG, NA, HK

Writing: CA, MG, AEE

Clinical Revision: CA, MG, AEE

Final Approval: All of authors

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