The relationship of PET/CT SUVmax with EGFR mutation status and ALK rearrangement in lung adenocarcinoma

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Abstract

Objective: Epidermal growth factor receptor mutations (EGFRm) and rearrangement of the anaplastic lymphoma kinase gene (ALKr) can be targeted for precision therapy in lung adenocarcinoma (LADC). As molecular profiling is not available for all, patient stratification can be achieved using non-invasive and economic tools, such as positron emission tomography/computed tomography (PET/CT). We aimed to evaluate the relationships between fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT maximum standardized uptake value (SUVmax) of primary tumors (pSUVmax) and lymph nodes (nSUVmax) and the EGFRm and ALKr status in a large series of Turkish LADC patients. **Materials and Methods:** In this retrospective study, medical records of histopathologically confirmed LADC patients were reviewed for demographic and clinical data. The ^{18}F-FDG PET/CT pSUVmax nSUVmax were calculated and analyzed for their relationships with EGFRm and ALKr using multiple regression analysis. **Results:** The study population consisted of 732 LADC patients with a mean age of 63±10 years. The frequencies of EGFRm and ALKr were 10.4% and 3.6%, respectively. Female gender, being a former- or never-smoker for EGFRm and age for ALKr were determined as independent risk factors (P<0.05). No significant differences in pSUVmax and nSUVmax were present between the patients with either EGFRm or ALKr compared to the wild-type genotype patients (P>0.05). **Conclusions:** We conclude that ^{18}F-FDG PET/CT semi-quantitative parameter SUVmax could not be validated for the prediction of the EGFRm or the ALKr in our large series of 732 Turkish patients with LADC.

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Introduction

Lung cancer, with approximately 2.2 million cases reported globally in 2020, ranks as the leading cause of mortality from malignant diseases [1]. Lung adenocarcinoma (LADC) is the most common histopathological type among non-small cell lung cancers (NSCLC) that is responsible for the majority of lung cancers [2]. The most common genetic alterations in LADC consist of the mutations in the epidermal growth factor receptor gene (EGFR) and the rearrangement of the anaplastic lymphoma kinase gene (ALK) [3]. Although the molecular profiling for genetic aberrations has been recommended as the gold standard in clinical practice, the medical and technical obstacles, such as the invasiveness of the procedure, insufficient amount of sample, poor quality of DNA, and economic burden, limit the use of this tool in the medical management of LADC patients [4-6]. Hence, there appears a need for cost-effective, non-invasive, and robust strategies for predicting the genetic alterations in LADC to stratify patients for molecular testing and plan for the most efficient treatment strategy accordingly [6-8].

One of the most widely used non-invasive approaches in the diagnosis and management of lung cancer is the fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) which applies the degree of glucose uptake by malignant cells to clinical aggressiveness [9]. The activation of the EGFR-signaling pathway due to EGFR mutations (EGFRm) favors oncogenicity both through prolifera-tive events, i.e. cell proliferation and angiogenesis, and inhibitive mechanisms i.e. apoptosis inhibition, as well as the promotion of metastasis [10]. Previously, the metabolic pathways, including glucose metabolism, have been shown to be influenced by EGFRm in LADC [11]. Moreover, the authors of a recent study speculated that the ^{18}F-FDG uptake alterations due to EGFRm might be through the NOX4/ROS/GLUT1 axis [8]. The demand for predictive diagnostic and prognostic markers for lung carcinoma generated research with conflicting results regarding the relationships between semi-quantitative ^{18}F-FDG PET/CT parameters, i.e. maximum standardized uptake value (SUVmax) and the genetic

aberrations, such as EGFRm, ALK rearrangement (ALKr) [12, 13]. In some studies, lower SUVmax in primary tumors (pSUVmax) has been associated with EGFRm in lung cancer patients [5, 8], while others correlated higher pSUVmax with EGFRm [14], as well as those that did not find any significant associations between SUVmax and EGFRm [15, 16]. Moreover, the literature on the relationship between ALKr and SUVmax in LADC is scarce, with inconsistent results [5, 13, 17, 18].

As emphasized in the literature, most of the studies that analyzed the relationship between SUVmax and EGFRm and ALKr have been conducted in small-sized groups. Therefore, in this study, we aimed to retrospectively evaluate the relationships among SUVmax and EGFRm and ALKr in a large series of Turkish patients with LADC using detailed demographic and clinical data.

Materials and Methods

Study design and patient population

The medical records of patients with LADC who were followed in the medical oncology outpatient clinics of Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Health Sciences University, Istanbul, Turkey, between January 2014 and December 2019, were retrospectively reviewed in the current study. The institutional ethics board approved the study, designed in line with the Declaration of Helsinki (116.2017.095, 06.20.2019). The committee waived the need for signed informed consent due to retrospective design. The confidentiality of patient data was maintained throughout the study.

The study inclusion criteria consisted.

The medical records were obtained from patient files and the hospital electronic database. The records reviewed for demographic (age, gender, smoking habit) and clinical (comorbidity, primary tumor site, nodal involvement, metastasis, stage, molecular results of EGFRm and ALKr, SUVmax of the primary tumor (pSUVmax) and lymph nodes (nSUVmax) calculated using PET/CT imaging) data.

The cancer stage was determined according to the 8th TNM classification for lung and pleural tumors [19]. The genetic alterations were tested using biopsy or surgical excision samples. The EGFRm in exons 18, 19, 20 and 21 were analyzed via the amplification-refractory mutation system (ARMS) method using the BIO-RAD CFX96 system and the Amoy Dx EGFR 29 Mutations Detection Kit (Amoy Diagnostics, Xiamen, China) according to the manufacturer's instructions. The ALKr was analyzed via fluorescence in situ hybridization (FISH) method using the Zytolight® SPEC ALK Dual Color Break Apart probe (2p23.1-p23.2) (ZytoVision, GmbH). The cut-off criteria for ALKr consisted of aberrant signal patterns in at least 15% out of the investigated minimum of 50 tumor cells. Representation of a positive signal for the ALKr was either the presence of split signals or 5'-deletions.

Positron emission tomography/CT imaging was performed on a 6-slice multidetector CT system integrated high-resolution PET scanner (Siemens Biograph True Point 16, Germany) using a 3D mode after a minimum of 4-hour fasting. The patients with a fasting blood glucose concentration below 180mg/dL were administered with intravenous 210-473MBq (5-13mCi) ^{18}F-FDG. The acquisition of low frequency and non-contrast images was conducted after 60-90 minutes to allow for ^{18}F-FDG biodistribution while the patients were in the supine position for 30 minutes, and followed by a PET scan from the proximal femur towards the vertex. The pSUVmax and nSUVmax were measured by placing a region of interest (ROI) over the lesions and calculated using the equation: SUVmax=maximum pixel activity (mCi/mL)/injected dose (mCi)/body mass (kg). The PET/CT equipment and scanning conditions were the same for all patients in the study, and the same nuclear medicine specialist evaluated all PET/CT datasets in the study.

Statistical analyses

Statistical analyses were performed using the NCSS system (Number Cruncher Statistical System, 2007, Kaysville, Utah, USA). The descriptive statistics with mean, median, standard deviation, frequency, minimum and maximum values were used to describe the categorical and numerical data. Quantitative data were assessed for normal distribution using the Shapiro-Wilk test, and comparisons between groups were performed using the Student's t-test, while the Mann-Whitney U test was used for variables without normal distribution. Pearson's chi-square, Fisher-Freeman-Halton and Fisher exact tests were used to analyze the categorical variables with normal distribution. Multiple logistic regression analysis was performed for independent predictors of the EGFRm and ALKr status. A P-value below 0.05 was considered statistically significant.

Results

Demographic and clinical data of 732 eligible patients were used. The rate of females (n:170, 23%) was less than the males (n:562, 77%). The mean age of patients was 63±10 years (min-max:26-93). The number of current-smokers (Sc) was 375 (51.2%), while 21.3% were never-smokers (Sn) (Table 1).

The family history of malignancy was present in 308 patients (42.1%). In almost half of the patients (n:353, 48.2%) there was comorbidity, such as hypertension (n:20, 58.6%), chronic obstructive pulmonary disease (n:137, 38.8%), coronary artery diseases (n:122, 34.6%), and diabetes (n:98, 27.8%). The follow-up was 11.4 months (min-max:0-72), and 38.8% of the study population were survivors during data collection.

The site of the primary tumor was mostly the right upper (n:282, 38.9%), followed by the left upper lobe (n:162, 22.4%). The right middle lobe was the least common site (n:69, 9.5%). Most patients (n:365, 49.9%) had stage IV disease, while stage II disease was found in 94 patients (12.8%). The PET/CT reports revealed that 512 (70%) had the involvement of lymph nodes. The most involved lymph nodes were group N2 (n:271, 37%), while group N1 was the least (n:56, 7.7%).

There was metastasis in almost half of the patients (n:365, 49.9%). The most common metastasis site was bone marrow in 54.1%, and the least common was the liver (n:54, 14.8%). The median pSUVmax was 11.4 (min-max:1.4-80) and nSUVmax was 8 (min-max:1.9-57.9) (Table 1).

Epidermal growth factor receptor gene mutuations were present in 10.4% of patients (n:76), and the majority of mutations were detected in exon 19 (n:46, 60.5%) and exon 21 (n:23, 30.3%). The exon 18 and exon 20 mutations were detected in 7 patients (9.2%). ALKr was present in 3.6% (n:26) of patients with a mean value of 35.5% (min-max:15-96) of all cancer cells tested.

The mean age of ALKr patients (55.62±14.88 years) was significantly less than that of the ALKr (-) patients (63.54± 9.79) (P:0.012). The rates of female EGFRm (25.9%) and ALKr (7.1%) patients were significantly more than the rates of male EGFRm (5.7%) and ALKr (2.5%) patients (P:0.001 and P: 0.005). The rates of Sn among patients with EGFRm (27.6%) and ALKr (7.7%) were significantly higher than those of Sc (4.3% and 8.2%) and former smokers (Sf) (8.5% and 3%). The presence of comorbidity or a family malignancy history did not significantly differ in patients, either positive or negative for EGFRm and ALKr (P>0.05) (Table 2).

Table 1. *Demographics and clinical characteristics of the patients.*

Characteristics	Value
Age (mean±SD) (years)	63±10
Gender (n) (%)	
Female	170 (23%)
Male	562 (77%)
Smoking (n) (%)	
Never	156 (21.3%)
Former	201 (27.5%)
Current	375 (51.2%)
Stage (n) (%)	
I	106 (14.4%)
II	94 (12.8%)
III	167 (22.8%)
IV	365 (94.9%)
Site of primary tumor (n) (%)	
Upper right	282 (38.9%)
Middle right	69 (9.5%)
Lower right	101 (13.9%)
Upper left	162 (22.4%)
Lower left	111 (15.3%)
Lymph node involvement (n) (%)	
N0	220 (30.1%)
N1	56 (7.7%)
N2	271 (37.0%)
N3	185 (25.3%)
T (%)	
T1	2 (0.3%)
T1a	53 (7.2%)
T1b	74 (10.1%)
T1c	29 (4.0%)
T2	2 (0.3%)
T2a	161 (22.0%)
T2b	75 (10.2%)
T3	172 (23.5%)
T4	164 (22.4%)
N (%)	
N0	220 (30.1%)
N1	62 (8.5%)
N2	258 (35.2%)
N3	192 (26.2%)
M (%)	
M0	367 (50.1%)
M1a	54 (7.4%)
M1b	137 (18.7%)
M1c	174 (23.8%)
SUVmax (median) (min-max)	
Primary tumor	11.4 (1.4-80)
Lymph nodes	8 (1.9-57.9)

T: Tumor, N: Lymph node, M: Metastasis, SUVmax: Maximum standardized uptake value

Table 2. *Demographic and clinical characteristics of the patients according to genetic aberrations.*

	EGFR (-) (n:656) (89.6%)	EGFR (+) (n=76) (10.4%)	P-value	ALK (-) (n=706) (96.4%)	ALK (+) (n=26) (3.6%)	P-value
Age (mean±SD) (years)	63.12±10.01	64.51±10.94	0.255	63.54±9.79	55.62±14.88	0.012
Gender (n) (%)						
Female	126 (74.1)	44 (25.9)	0.001	158 (92.9)	12 (7.1)	0.005
Male	530 (94.3)	32 (5.7)		548 (97.5)	14 (2.5)	
Smoking (n) (%)						
Never	113 (72.4)	43 (27.6)	0.001	144 (92.3)	12 (7.7)	0.006
Former	184 (91.5)	17 (8.5)		195 (97.0)	6 (3.0)	
Current	359 (95.7)	16 (4.3)		367 (97.9)	8 (2.1)	
Site of primary tumor (n) (%)						
Upper right	261 (92.6)	21 (7.4)	0.094	274 (97.2)	8 (2.8)	0.013
Middle right	57 (82.6)	12 (17.4)		65 (94.2)	4 (5.8)	
Lower right	89 (88.1)	12 (11.9)		101 (100)	0 (0)	
Upper left	142 (87.7)	20 (12.3)		157 (96.9)	5 (3.1)	
Lower left	102 (91.9)	9 (8.1)		102 (91.9)	9 (8.1)	
Stage (n) (%)						
I	97 (91.5)	9 (8.5)	0.171	103 (97.2)	3 (2.8)	0.721
II	84 (89.4)	10 (10.6)		91 (96.8)	3 (3.2)	
III	156 (93.4)	11 (6.6)		163 (97.6)	4 (2.4)	
IV	319 (87.4)	46 (12.6)		349 (95.6)	16 (4.4)	
Lymph node involvement (n) (%)						
(+)	460 (89.0)	57 (11)	0.377	499 (96.5)	18 (3.5)	0.873
(-)	196 (91.2)	19 (8.8)		207 (96.3%)	8 (3.7)	
Lymph node groups (n) (%)						
N0	201 (30.6)	19 (25.0)	0.055	212 (30.0)	8 (30.8)	0.554
N1	52 (7.9)	4 (5.3)		56 (7.9)	0 (0.0)	
N2	247 (37.7)	24 (31.6)		261 (37.0)	10 (38.5)	
N3	156 (23.8)	29 (38.2)		177 (25.1)	8 (30.8)	

(continued)

Metastasis (n) (%)						
(+)	319 (87.2)	47 (12.8)	0.029	350 (95.6)	16 (4.4)	0.231
(-)	337 (92.1)	29 (7.9)		356 (97.3)	10 (2.7)	
pSUVmax (median) (min-max)	11.5 (1.4-80)	10.4 (2.5-29.3)	0.130	11.4 (1.4-80)	10.6 (2.2-25.8)	0.680
nSUVmax (median) (min-max)	8 (1.9-57.9)	7.4 (2.5-23.9)	0.670	7.8 (1.9-57.9)	9.7 (3.1-27.7)	0.100

pSUVmax: Maximum standardized uptake value, primary tumor, nSUVmax: Maximum standardized uptake value, lymph node

Table 3. *Multiple logistic regression analysis of significant demographic characteristics dependent on genetic alterations.*

	EGFR		ALK	
	OR [95% CI]	**P-value**	**OR [95% CI]**	**P-value**
Age (years)	1.00 [0.97-1.02]	0.800	0.94 [0.90-0.98]	**0.003**
Gender (female)	3.60 [1.77-7.30]	**0.001**	2.66 [0.81-8.79]	0.108
Smoking (Current)		**0.001**		0.124
Smoking (Never)	4.87 [2.18-10.89]	**0.001**	3.47 [0.93-12.87]	0.063
Smoking (Former)	2.43 [1.04-5.66]	**0.040**	2.85 [0.77-10.53]	0.116
pSUVmax	0.96 [0.90-1.02]	0.150	0.97 [0.88-1.06]	0.447
nSUVmax	1.02 [0.96-1.08]	0.550	1.07 [1.00-1.15]	0.061

OR. Odds ratio, CI. Confidence interval

The ALKr was significantly related to a higher rate of left lower lobe site for primary tumors (8.1%) compared to the other sites (P:0.013). No significant differences in disease stage were observed considering the EGFRm and ALKr (P>0.05). The rate of nodal involvement had no significant differences regarding the mutational status. Additionally, no significant differences were present among the lymph node groups regarding the mutational status (for EGFRm P:0.055 and for ALKr P:0.554). The rate of metastasis was significantly less in the EGFRm group (12.8%) compared to the wild-type EGFR group (87.2%) (P:0.029).

No significant differences in pSUVmax and nSUVmax were present between the patients positive for either the EGFRm or the ALKr compared to the wild-type genotype patients (P>0.05) (Table 2).

Female gender (OR: 3.6, 95% CI: 1.77-7.3, P:0.001), being Sf (OR: 2.4, 95% CI: 1.04-5.66, P:0.04) or Sn (OR: 4.87, 95% CI: 2.18-10.89, P:0.001) were independent risk factors for EGFRm. Age was an independent risk factor for the ALKr (OR: 0.94, 95% CI: 0.9-0.98, P: 0.003) (Table 3).

Discussion

We retrospectively reviewed 732 patients with LADC in a Turkish population and presented their demographic and clinical features, and evaluated the relationships among ^{18}F-FDG PET/CT SUVmax, EGFRm, and ALKr. The EGFRm were present in 10.4% of our patients. According to the literature, the frequencies of EGFRm vary among different ethnicities, i.e.higher rates in Asian vs lower rates in white populations. For instance, the prevalence of EGFRm in LADC was 58% in an Asian population [20], while a prevalence of 23% was reported in a population of whites in a study that compared the rates of EGFRm in LADC patients with different ethnicities [15,20-24]. The authors of a recent Turkish study, in which a 14% rate of EGFRm in NSCLC patients was found, documented the results of similar Turkish studies, ranging between 14.39% and 28.9% [22]. Our results that showed the majority EGFRm were in exons 19 (60.5%) and 21 (30.3%) were consistent with the results of Musayeva et al. (2020), who reported 53.3% and 30.7% in exon 19 and 21, respectively [22]. The frequency of ALKr in the literature tended to be less than the EGFRm frequency in lung carcinoma patients. In a series of 221 patients with LADC, a frequency of 19% was found for ALKr [17]. Ruan et al. (2020) found that 11.7% of NSCLC patients had ALKr, while Liao et al. (2020) found a frequency of 9.5% ALKr in LADC patients [18, 25]. The frequency of ALKr in NSCLC and predominantly LADC patients was reported as 4% and 1.9% in two studies, both of which were close to the current finding of 3.6% frequency of ALKr in our LADS patients [23, 26].

There are many studies that investigated the demographic and clinical features of lung cancer patients for the relationships with EGFRm and ALKr. When the prognostic

demographic factors of EGFR-mutated metastatic LADC were evaluated, female gender and being an Sn were significantly associated with progression-free survival [27]. Although younger age has recently been significantly associated with the EGFRm in patients with lung carcinoma [20], no significant difference in the mean age of patients was present between the EGFR (+) and EGFR (-) groups in our study (P:0.255). In a study comparing the demographics and clinical characteristics of lung carcinoma patients with EGFRm vs ALKr, younger age was significantly associated with ALKr [12]. Recently, Ruan et al. (2020) also found that the patients with NSCLC and ALKr were significantly younger than those without ALKr [18]. The research studies that investigated the demographic features of LADC patients showed that younger age had a significant relationship with the ALKr [3]. Jeong et al. (2015) also determined the significant relationship between younger age and ALKr rearrangement in LADC patients [17]. In line with the previous reports, our results revealed that the age of patients with ALKr (mean:55.62 yrs) was significantly younger than that of the patients without the ALKr (mean: 63.54 yrs) (P:0.012).

Takamochi et al. (2017) found that the EGFRm were significantly more common in females patients [28]. Similarly, Yang et al. (2019) found more female patients (56.5%) with EGFRm compared to males (43.5%) with LADC [20]. Chang et al. (2021) also found a predominance of female gender for the presence of EGFRm in LADC [6]. On the contrary, Zhu et al. (2019) did not find any statistically significant relationship between the female gender and EGFRm in LADC patients [21]. In our study, we found that the rates of females compared to males were significantly more in patients with EGFRm (25.9% vs 5.7%) and ALKr (7.1% vs 2.5%) (P:0.001 and P:0.005). Although significant relationships between female gender and ALKr in LADC have not been reported as a common phenomenon in the literature, few studies showed female predominance among LADC patients with ALKr [13, 29, 30].

The smoking habits of LADC patients had been widely researched previously. While the significant relationship between being an Sn and EGFRm in LADC patients have been consistently reported [6, 20, 21], there are also some studies in which similar significance of being an Sm and ALKr was documented in LADC [13, 17]. The EGFR (+) patients who were Sn (27.6%) were significantly more than the Sc (4.3%) or Sf (8.5%) in our study (P:0.001).

The involvement of the right upper lobe (33.3%) was significantly more in LADC patients with EGFRm than the patients without (22.4%) (P:0.036) [20]. In our study, no significant difference in the site of the primary tumor was found between the patients with and without EGFRm (P>0.05). Similar to our results, Zhu et al. (2019) did not find any significant difference in the location of the LADC in patients with or without EGFRm [21]. Interestingly, we observed a significant relationship between the ALKr and the left lower lobe location of the primary tumor (P:0.013). In a recent study that characterized the clinicopathological features of ALK (+) lung tumors, the most common site of the primary tumor was reported as the right upper lobe in 37% of the study population, while the left lower lobe was only involved in 13% of the patients [31]. On the contrary, Mendosa et al. (2020) reported that the lower lobes were the most common sites for primary tumors in ALK (+) NSCLC patients [32].

The relationship between the stage of lung cancer and the genetic alterations has been previously researched. In some studies, early-stage LADC was significantly related to EGFRm [6, 33], yet in others, the advanced stage of lung carcinoma was significantly associated with EGFRm [20]. Our results that did not indicate any significant relationship between the disease stage and EGFRm status were in line with the findings of Zhu et al. (2019) that also indicated no significant difference in stage of the LADC in EGFR (+) or (-) patients [21]. Previously, Choi et al. (2013) reported a significant relationship between the presence of ALKr and nodal involvement and distal metastasis, suggesting the aggressiveness of LADC harboring ALKr [13]. Although we did not find a significant relationship between disease stage and EGFRm and ALKr per se, the presence of a trend for advanced disease can be speculated based on our observations on the trend of more involvement of N2 and N3 group of lymph nodes in EGFRm and ALKr patients, besides significantly more frequency of metastasis in EGFR (+) (12.8%) compared to EGFR (-) (7.9%) patients (p:0.029) as shown in Table 2.

In the current study, the median pSUVmax and nSUVmax were 11.4 (min-max:1.4-80) and 8 (min-max:1.9-57.9), respectively. Recently, Yang et al. (2019) reported that lower SUVmax (≤6.15) was significantly associated with EGFRm in LADC patients (P:0.01) [20]. The study results by Zhu et al. (2019) showed that the LADC patients with EGFRm had significantly lower SUVmax (7.70) than the patients without EGFRm (10.18) (P:0.004) [21]. On the contrary, higher SUVmax (≥6) was significantly associated with EGFRm in LADC patients [14]. The nSUVmax in LADC patients has not been widely studied, and limited literature indicated a significant association between low nSUVmax and EGFRm [5]. Takamochi et al. (2017) found that EGFR-mutated LADC had lower levels of glucose metabolism compared to wild-type tumors based on the observation of the presence of EGFRm more in tumors with lower SUVmax, which the authors speculated to be mostly due to exon 19 and 21 mutations. The researchers also found significant relationships between SUVmax and exon 21 L858R mutation and exon 19 deletions, while no significant relationships were found for minor EGFRm [28]. Although the results of a study indicated a relationship between lower SUVmax and EGFRm, no significant differences had been observed regarding the exon 21 and exon 19 mutations [5]. Neither the pSUVmax nor nSUVmax had not been significantly associated with the EGFRm in other studies [15,16]. Recently, the first example of a meta-analysis for assessing the value of ^{18}F-FDG PET/CT in predicting EGFRm in patients with NSCLC that reviewed data from 15 eligible studies indicated that ^{18}F-FDG PET/CT had low sensitivity and specificity in EGFRm prediction [34]. Our results did not indicate any relationships between SUVmax and neither the EGFRm in general nor in the spectrum of exon mutations.

In a study by Miao et al. (2017), the patients with pSUVmax>6.95 and nSUVmax>6.25 were significantly more common in ALKr compared to the EGFRm group [12]. Previously, higher SUVmax in LADC patients was reported to be significantly more common in patients with ALKr [13].

Ruan et al. (2020) detected a significantly higher pSUVmax (12.56±7.06) in LADC patients with ALKr compared to the ALK wild-type group. However, they did not find such significance in nSUVmax [18]. Moreover, Lv et al. (2018), who did not report a significant relationship between the pSUVmax and ALKr, stated that the nSUVmax was significantly higher in the ALKr group than the wild-type ALK group [5]. Previously, Jeong et al. (2015) found SUVmax (≥0.208) was significantly higher in the presence of ALKr in LADC patients [17]. Our study results indicated that the median pSUVmax and nSUVmax in EGFRm or ALKr patients were not significantly different from those with wild-type EGFR or ALK (P>0.05).

We suspect that the inconsistent results among studies, including ours, stem from several research content variations, such as the heterogeneity of the lung cancer types and subtypes, the small-sized study populations, and the technical differences that are inherent to the PET/CT procedure (e.g equipment used for image acquisition and reconstruction) or molecular testing techniques (e.g sequencing, immunohistochemistry, FISH) and/or tumor characteristics (e.g size, grade, histopathology). In our study with stage IV disease in half of the patients, the absence of significant relationships between SUVmax, and EGFRm and ALKr seems to support the conclusion of a recent study that assigned no predictive value to pSUVmax in stage IV patients due to heterogeneous metastasis [15]. Moreover, authors of a research study conducted on a more homogenous group of various cancer types suggested that higher SUVmax was significantly related to the total number of common oncogenic abnormalities, rather than individual mutations of genes, such as EGFR and ALK [35].

The first limitation needed to be addressed is the retrospective design which might have led to sampling bias. Second, data gathered from a single-centre might not reflect the larger population. Nevertheless, an important strength of our study is the large sample size which is superior to previous similar studies. Moreover, the current study has been conducted solely with data of LADC patients that enabled more reliable interpretations. Additionally, the inclusion criteria consisted of tumor size larger than one centimeter to minimize the ^{18}F-FDG PET interpretation regarding the volume averaging.

In conclusion, ^{18}F-FDG PET/CT semi-quantitative parameter SUVmax could not be validated to predict the EGFRm or the ALKr in our large series of 732 Turkish patients with LADC. We suggest that future studies with larger sample sizes that might allow subgroup analyses of patients with various genetic aberrations for LADC are warranted to clarify the value of ^{18}F-FDG PET/CT in predicting the mutational status of patients who would ultimately benefit from targeted molecular therapies.

The authors declare that they have no conflicts of interest.

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