Original Article

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Impacts of ^{18}F-FDG PET/CT Parameters on Differential Diagnosis and Outcome of Patients with Primary Invasive Mucinous and Lepidic Predominant Adenocarcinoma of the Lung

^{18}F-FDG PET/BT Parametrelerinin Primer İnvaziv Müsinöz ve Lepidik Baskın Akciğer Adenokarsinomlu Hastaların Ayırıcı Tanısı ve Sonuçları Üzerindeki Etkileri

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Abstract

Objectives: The purpose of this study was to investigate whether ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) parameters have a role in differentiating invasive mucinous lung adenocarcinoma (IMA) from lepidic predominant lung adenocarcinoma (LPA). Additionally, we compared the ^{18}F-FDG-PET/CT features between survivors and non-survivors.

Methods: Tumors were divided into 2 groups according to CT appearance: Group 1: nodular-type tumor; group 2: mass- or pneumonic-type tumor. Unilateral and bilateral multifocal diseases were detected. Clinicopathological characteristics and PET/CT findings were compared between IMAs and LPAs, as well as between survivors and non-survivors.

Results: We included 43 patients with IMA and 14 with LPA. Tumor size (p=0.003), incidence of mass/pneumonic type (p=0.011), and bilateral lung involvement (p=0.049) were higher in IMAs than in LPAs. IMAs had more advanced T, M, and Tumor, Node, and Metastasis stages than in LPAs (p=0.048, p=0.049, and p=0.022, respectively). There was no statistically significant difference in maximum standardized uptake value (SUV_{max}) between the IMA and LPA (p=0.078). The SUV was significantly lower in the nodular group than in the mass/pneumonic-type group (p=0.0001). A total of 11 patients died, of whom SUV_{max} values were significantly higher in these patients (p=0.031). Male gender (p=0.0001), rate of stage III-IV (p=0.0001), T3-T4 (p=0.021), M1 stages (p=0.0001), multifocality (p=0.0001), and bilateral lung involvement (p=0.0001) were higher in non-survivor.

Conclusions: Although CT images were useful for the differential diagnosis of LPAs and IMAs, SUV_{max} was not helpful for differentiation of these 2 groups. However, both ^{18}F-FDG uptake and CT findings may play an important role in predicting prognosis in these patients.

Keywords: ^{18}F-FDG PET/CT, primary invasive mucinous adenocarcinoma of the lung, lepidic predominant adenocarcinoma of the lung

Öz

Amaç: Bu çalışmanın amacı ^{18}F-florodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografinin (PET/BT) parametrelerinin invaziv müsinöz akciğer adenokarsinomunu (İMA) lepidik predominant akciğer adenokarsinomundan (LPA) ayırmada bir rolü olup olmadığını araştırmaktır. Ayrıca hayatta kalanlar ve hayatta kalmayanlar arasındaki ^{18}F-FDG PET/BT özelliklerini karşılaştırdık.

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Yöntem: Tümörler BT görünümlerine göre 2 gruba ayrıldı: Grup 1: Nodüler tip tümör; grup 2: Kitle veya pnömonik tip tümör. Tek taraflı ve iki taraflı multifokal hastalıklar tespit edildi. Klinikopatolojik özellikler ve PET/BT bulguları, İMA'lar ve LPA'ların yanı sıra hayatta kalanlar ve hayatta kalmayanlar arasında karşılaştırıldı.

Bulgular: Kırk üç İMA ve 14 LPA hastasını dahil ettik. Tümör boyutu (p=0,003), kitle/pnömonik tip insidansı (p=0,011), iki taraflı akciğer tutulumu (p=0,049) İMA'larda LPA'lara göre daha yüksekti. İMA'larda LPA'lara göre daha ileri T, M ve Tümör, Nod ve Metastaz evreleri vardı (sırasıyla p=0,048, p=0,049 ve p=0,022). İMA'lar ve LPA arasında maksimum standardize tutulum değeri (SUV_{maks}) açısından istatistiksel olarak anlamlı bir fark yoktu (p=0,078). SUV, nodüler grupta kitle/pnömonik tip gruba göre anlamlı derecede düşüktü (p=0,0001). Toplam 11 hasta öldü ve bu hastalarda SUV_{maks} değerleri anlamlı derecede yüksekti (p=0,031). Erkek cinsiyet (p=0,0001), evre III-IV (p=0,0001), T3-T4 (p=0,021), M1 evreleri (p=0,0001), multifokalite (p=0,0001) ve iki taraflı akciğer tutulumu oranı (p=0,0001) hayatta kalmayanlarda daha yüksekti.

Sonuç: BT görüntüleri LPA ve İMA'larda ayırıcı tanıda yararlı olsa da SUV_{maks} bu iki grubun ayrımında yardımcı olmadı. Ancak bu hastalarda hem ^{18}F-FDG tutulumu hem de BT bulguları prognozu öngörmede önemli rol oynayabilir.

Anahtar kelimeler: ^{18}F-FDG PET/BT, akciğerin primer invaziv müsinöz adenokarsinomu, lepidik predominant akciğer adenokarsinomu

Introduction

In 2011, a new classification of lung adenocarcinoma (ADC) was proposed in an international and multidisciplinary panel supported by the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS), and European Respiratory Society (ERS). The use of the terms "bronchioloalveolar carcinoma (BAC)" and "mixed subtype ADC" was discontinued based on the proposal of this panel. According to the extent of lepidic versus invasive growth patterns, BACs are reclassified into 5 subtypes: 1) Adenocarcinoma *in situ* (AIS), 2) minimally invasive adenocarcinoma (MIA), 3) lepidic predominant adenocarcinoma (LPA) 4) invasive mucinous adenocarcinoma (IMA), 5) ADC predominantly invasive with some nonmucinous lepidic components (1).

AIS and MIA have similar clinical and prognostic characteristics. The 5-year disease-free survival (DFS) rate is 100% for patients with AIS. Patients with MIA have nearly 100% DFS if the lesion is completely resected (2). LPA and IMA are more invasive than AIS and MIA. Additionally, IMAs exhibit different clinicopathological, radiological, and prognostic characteristics from those of non-mucinous ADCs (1,3). Although non-mucinous ADCs tend to be localized, IMAs are more likely to be multifocal, multilobar, and bilateral (1). The radiological appearance of these tumors is associated with prognosis. Localized ADC has a better prognosis after resection. As a radiolabeled glucose analog, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) reflects glucose metabolism in tumor tissue. ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) is an effective molecular imaging method for the diagnosis, staging, and monitoring of lung cancer. The standardized uptake value (SUV) is commonly used as a semiquantitative measure of ^{18}F-FDG uptake in tissues. In this retrospective study, we compared the ^{18}F-FDG PET/CT findings of LPAs with those of IMAs. Moreover, we investigated the differences between the ^{18}F-FDG PET/CT findings of survivors and non-survivor.

Materials and Methods

Patients

Patients with histologically confirmed LPA and MIA who underwent pretreatment with ^{18}F-FDG PET/CT between August 2008 and May 2019 were included in this retrospective study. The exclusion criteria were as follows: 1) Patients with another cancer; 2) prior chemoradiotherapy. Histological confirmation was performed via biopsy or surgical resection in all cases according to the 2011 IASLC/ATS/ERS and 2015 World Health Organization classification schemes. We collected data on age at diagnosis, sex, surgical approach, histopathological subtype, stage, treatment information, and ^{18}F-FDG PET/CT findings. Furthermore, follow-up data of patients were recorded. The 8th edition of the Tumor, Node, and Metastasis lung cancer staging system was used for the staging of all patients (4). Stages I and II were defined as early stages, while Stages III and IV were defined as advanced stages. This retrospective study was approved by University of Health Sciences Türkiye, Ankara Atatürk Pulmonary Diseases and Thoracic Surgery Training and Research Hospital Institutional Review Board (decision no.: 682, date: 16.07.2020).

^{18}F-FDG PET/CT Imaging

PET/CT scanning was performed from the vertex to the upper thigh using the Siemens Biograph 6 HI-REZ integrated PET/CT scanner (Siemens Medical Solutions, Knoxville, TN, USA). All patients fasted for at least 4-6 hours before PET/CT examination. After determining that the patients' blood glucose levels were <200 mg/dL, ^{18}F-FDG (5.18 MBq/kg) was injected intravenously. Approximately 45-60 minutes after ^{18}F-FDG injection, PET/CT scanning was performed. First, CT images were acquired with 130 kV, automatic, real-time dose modulation amperage. After CT, the PET scan was performed in 3D mode with 3 min per bed position for a total of 6-8 bed positions. CT was used for attenuation correction and anatomical localization of

the PET images. PET data were reconstructed using the ordered-subset expectation-maximization algorithm.

^{18}F-FDG PET/CT Analysis

Reconstructed transaxial, coronal, and sagittal PET, CT, fused PET/CT, and maximum-intensity projection images of all patients were reviewed using a dedicated Workstation. Tumors were divided into 2 groups according to CT appearance: Group 1: nodular-type tumor; group 2: mass- or pneumonic-type tumor. The nodular type was defined as a rounded or oval lesion 3 cm in diameter. The mass type was defined as a focal lesion >3 cm in diameter. The pneumonic type was defined as a lesion manifesting as pneumonia-like consolidation (5,6). Unilateral and bilateral multifocal disease was detected. Multifocal cases were classified as unilateral multifocal and bilateral multifocal. Maximal CT diameter, tumor site, characteristics of nodules [ground-glass opacity (GGO), solid or subsolid nodules], and accompanying radiolucencies (air bronchogram, air alveologram, pseudocavitation, true cavitation) within the tumor were noted. GGO was defined as increased hazy attenuation of the lung without obscuration of the underlying bronchial and vascular margins. A subsolid nodule was defined as a nodule with both ground glass and solid components. For semiquantitative analysis of ^{18}F-FDG uptake, a region of interest (ROI) was drawn over the tumors using PET images. The maximum SUV (SUV_{max}), which are the maximum pixel values within the defined ROIs, were calculated automatically on the workstation. The SUV_{max} values of the mediastinal and hilar lymph nodes were also recorded. ^{18}F-FDG uptake by lymph nodes was greater than that by the mediastinal blood pool and was interpreted as PET/CT positive.

Statistical Analysis

Survival time was defined as the period between the time of diagnosis and the time of death or last visit. Patients were divided into the following 2 groups: survivors and non-survivor. The associations between the categorical variables were evaluated by chi-square analysis. The Kruskal-Wallis H test was used to compare the three groups. The Mann-Whitney U test was used to compare the two groups. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences version 21.0.

Results

Clinicopathological Characteristics

A total of 57 patients were included in this study. Among the 57 patients, 43 (75.4%) were diagnosed with IMA and 14 (24.6%) with LPA. Curative surgery was performed in 48 patients (40 lobectomies, 3 bilobectomy, 1 pneumonectomy, 4 wedge resections). Percutaneous transthoracic needle aspiration biopsy was performed in 8 IMA cases and 1 LPA case. These 9 patients were not operated. Lymph node biopsy and/or dissection were performed in 44 (12 LPA, 32 IMA) cases.

Comparison of Clinicopathological Characteristics Between IMAs and LPAs

The clinicopathological characteristics of the patients are compared in Table 1. There were no significant differences in age (p=0.861) and sex (p=0.701) between the two groups. LPAs had lower T, M, and overall stage than in IMAs (p=0.048, p=0.0449 and p=0.022, respectively). The rate of receiving chemotherapy was higher among patients with IMA (p=0.011).

Comparison of ^{18}F-FDG PET/CT Findings in IMAs and LPAs

Among the 43 IMAs, 25 (58.2%) were mass (n=11) or pneumonic types (n=14) on CT images. Nodular IMAs presented as subsolid in 12 cases, solid in 3 cases, and cavitary in 3 cases. LPAs were of nodular type (1 solid, 10 subsolids, and 1 pure GGO) in 12 patients and pneumonic type in 2 patients. No mass-type tumor was observed in LPA. IMAs were more likely to occur as mass/pneumonic type tumors than LPAs (p=0.011) (Table 2).

The incidence of unilateral or bilateral multifocal disease was higher in IMAs than in LPAs, although there was no significant difference (p=0.478). However, bilateral involvement was significantly higher in IMAs than LPAs (p=0.049). No bilateral tumor involvement was observed in LPAs at the time of diagnosis. There was no significant difference in the presence of intralesional radiolucencies between LPAs and IMAs (p=1). Overt cavitation was obtained in 6 cases with IMAs.

The size of LPAs was significantly smaller than that of IMAs (p=0.003). There was no statistically significant difference in SUV_{max} between IMAs and LPAs (p=0.078). The SUV was significantly lower in the nodular group than in the mass/pneumonic-type group (mean ± standard deviation: 3.25±2.34 versus 5.28±2.78, respectively, p=0.0001). There was no distinctive ^{18}F-FDG uptake in patients with LPA and GGO. In all cases apart from this, there was ^{18}F-FDG uptake that could be distinguished from parenchymal activity. The SUV_{max} ranged from 0.79 to 14.7 in all 57 patients. The SUV_{max} was less than 2.5 in 10/47 (21.2%) patients with IMA. Otherwise, 6 of 14 patients (42.8%) with LPA had an SUV_{max} of less than 2.5. There was a significant correlation between the size of tumors and the SUV_{max} values (p=0.002).

The mediastinal and hilar lymph node stations were evaluated histopathologically (Table 1). There were 24 lymph node stations were ^{18}F-FDG-positive. The SUV_{max} values ranged from 2.6 to 5.2. Four of the 24 lymph node stations were positive on histopathological examination. Reactive lymphoid proliferation and/or anthracosis were detected in the remaining 20 ^{18}F-FDG-positive lymph node stations. A metastatic intrapulmonary lymph node was found on histopathological examination. However, this lymph node was not detected on PET/CT scan. The overall sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT in the detection of lymph node metastasis were 80%, 91.2%, and 90.9%, 16.6%, and 99.5%, respectively. All lymph node metastases were detected in 2 patients with IMA. PET/CT imaging revealed extrathoracic metastases in 2 cases with IMA**.** There were no pathological nodal involvement or extrathoracic metastases in LPAs.

Table 1. Clinicopathological characteristics between the groups

	Histopathological subtypes		p-value
	IMA (n=43)	LPA (n=14)	
Gender			
Males, n (%)	23 (53.5%)	6 (42.9%)	0.701
Female, n (%)	20 (46.5%)	8 (57.1%)	
Age, years (mean ± SD)	57.9±12.6	57.4±9.3	0.861
Chemotherapy present, n (%)	25 (41.9%)	2 (14.3%)	0.011
T classification, n (%)			
T1/T2	22 (51.2)	12 (85.7)	0.048
T3/T4	21 (48.8)	2 (14.3)	
Number of resected LNs stations	164	69	
Number of pathologically positive LNs	5	0	
N classification[±], n (%)			
N0	30 (93.7)	12 (100)	
N1	1 (3.1)	0 (0)	
N2	1 (3.1)	0 (0)	
N3	0 (0)	0 (0)	
M classification, n (%)			
M0	32 (74.4)	14 (100)	0.049
M1	11 (25.6)	0 (0)	
Stage, n (%)			
I/II	25 (58.1)	13 (92.9)	0.022
III/IV	18 (41.9)	1 (7.1)	

IMA: Invasive mucinous lung adenocarcinoma, LPA: Lepidic predominant lung adenocarcinoma, SD: Standard deviation, LNs: Lymph nodes
[±]Lymph node biopsy and/or dissection were performed in 44 (12 LPA, 32 IMA) cases. Lymph node metastases were found in only 2 patients

Analyses of Differences Between Survivors and Non-survivors

The mean follow-up duration was 40.9 months (range: 1-102). There was no significant difference in the mean survival time between IMA and LPA (46.2 versus 36 months, respectively, p=0.075). At the end of this study, a total of 11/57 (19.2%) patients died, including 9 IMA and 2 LPA patients (Table 3). One patient with LPA died 4 months after diagnosis. This patient had not undergone surgery. Another patient with LPA who underwent curative lower lobectomy died 15 months after the surgery. The causes of death in these patients were not available in the medical records.

No significant differences were found between groups regarding gender (p=0.0001), age (p=0.105), histopathological subtype of the tumor (0.714), size of the lesion (p=0.135), and the presence of intralesional radiolucencies (p=0.219). There were no significant differences in the incidence of nodular-type tumors versus mass/pneumonic-type tumors (p=0.386) between groups. Male gender (p=0.0001), rate of stages T3-T4 (p=0.021), M1 disease (p=0.0001), stages III-IV (p=0.0001), multifocality (p=0.0001), bilateral involvement (p=0.0001), and level of SUV_{max} (p=0.031) were higher in the dead group.

Table 2. Comparison of ^{18}F-FDG PET/CT characteristics between groups

	Histopathological subtypes		p-value
	IMA	LPA	
SUV_{max} of all cases (mean ± SD)	4.48±2.75	3.40±2.61	0.078
Diameter of lesion (cm), mean ± SD	4.8±3.3	2.5±1.2	0.003
CT appearances			
Mass/pneumonic type, n (%)	25 (58.1)	2 (14.3)	0.011[*]
Nodular type, n (%)	18 (41.9)	12 (85.7)	
Multifocality, n (%)	12 (27.9)	2 (14.3)	0.478
Bilateral multifocality, n (%)	11 (25.6)	0 (0)	0.049
Presence of intralesional radiolucency, n (%)	34 (79.1)	11 (78.6)	1

IMA: Invasive mucinous lung adenocarcinoma, LPA: Lepidic predominant lung adenocarcinoma, ^{18}F-FDG: F-18 fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value, SD: Standard deviation, [*]The mass/pneumonic-type was significantly more common in IMAs

Discussion

When we compared the CT features between LPAs and IMAs, we found that pneumonic/mass-type tumors were more associated with IMAs in our study. Patients with IMA had a higher incidence of multifocal involvement (Figure 1). These findings are consistent with those of previous studies (1,7). Tumor cells tend to spread through air spaces in IMAs. This pattern of invasion may lead to a pneumonia-like pattern and increased rates of intrapulmonary metastasis in these patients (8). LPAs are more likely to manifest as pure GGO or subsolid nodules (1). A majority of LPAs manifested as subsolid nodules in our study. We did not find any mass-type tumors in the LPAs. Two LPA cases were pneumonic. Only one LPA exhibited a pure GGO appearance with a diameter of 3 cm. There was no ^{18}F-FDG uptake in this lesion (Figure 2). The GGO component of lung ADCs generally corresponds with lepidic tumor growth. The spreading of malignant cells along the alveolar walls and septa without destruction in the parenchyma is referred to as a lepidic growth pattern. There is no invasion into the stroma, blood vessels, or pleura of this growth type (9). The solid component within GGO lesions is correlated with invasive tumor growth, fibrosis, and alveolar collapse (10). Pure GGO tumors are usually ^{18}F-FDG-negative, slow-growing, and well-differentiated tumors (11). In addition,

Table 3. Analyses of differences between survivors and non-survivors

	Survivors (n=46)	Non-survivors (n=11)	p-value
Gender			
Male, n (%)	18 (62.1)	11 (37.9)	0.0001
Female, n (%)	28 (100)	0 (0)	
Age (years), mean ± SD	56.6±11.3	62.7±13.1	0.105
Histopathological subtype			
LPA, n (%)	12 (85.7)	2 (14.3)	0.714
IMA, n (%)	34 (79.1)	9 (20.9)	
T classification			
I/II	31 (91.2)	3 (8.8)	0.021
II/IV	15 (65.2)	8 (34.8)	
M classification			
M0	43 (93.5)	3 (6.5)	0.0001
M1	3 (27.3)	8 (72.7)	
Overall stage			
I/II	36 (94.7)	2 (5.3)	0.0001
III/IV	10 (52.6)	9 (47.4)	
Tumor size (cm), mean ± SD	4.1±3.1	4.9±2.8	0.135
SUV_{max} of tumor, mean ± SD	3.66±2	6.52±4.08	0.031
Multiple lung involvement			
Present	6 (42.9)	8 (57.1)	0.0001
Absent	40 (93)	3 (7)	
Bilateral lung involvement			
Present	3 (27.3)	8 (72.7)	0.0001
Absent	43 (93.5)	3 (6.5)	
CT presentation			
Nodular type	26 (86.7)	4 (33.3)	0.386
Mass/pneumonic type	20 (74.1)	7 (25.9)	
Intralesional air			
Present	38 (84.4)	4 (19.3)	0.219
Absent	8 (66.7)	11 (33.3)	

SD: Standard deviation, IMA: Invasive mucinous lung adenocarcinoma, LPA: Lepidic predominant lung adenocarcinoma, SUV_{max}: Maximum standardized uptake value, CT: Computed tomography

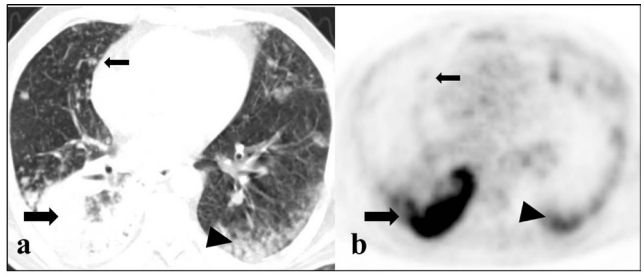

Figure 1. Axial ^{18}F-FDG PET/CT images of a 52-year-old male with bilateral IMA. a) CT image (lung window) showing pneumonic-type IMA on the right lower lobe (thick arrow), bilateral parenchymal infiltrates (arrowhead), and multiple small nodules (thin arrow). b) PET image demonstrating intense ^{18}F-FDG uptake in the pneumonic-type IMA. Mild-to-moderate ^{18}F-FDG uptake is observed in the bilateral parenchymal infiltrates and nodules (arrows)
^{18}F-FDG: F-18 fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, IMA: Invasive mucinous lung adenocarcinoma

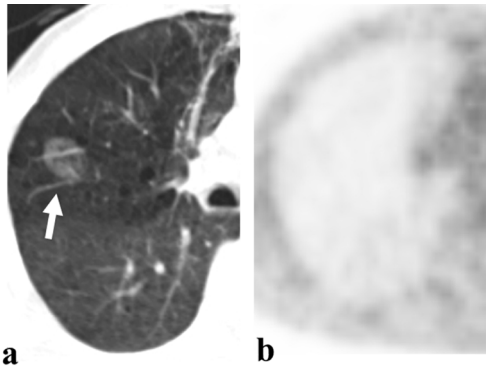

Figure 2. Axial ^{18}F-FDG PET/CT images of a 54-year-old male with LPA. a) CT image (lung window) showing a 30-mm-sized pure ground glass nodule in the right lung (arrow). b) There is no ^{18}F-FDG uptake in the nodule
^{18}F-FDG: F-18 fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, LPA: Lepidic predominant lung adenocarcinoma

the incidence of nodal and distant metastasis was low in these tumors. PET/CT imaging is not recommended for the diagnostic evaluation and staging of GGOs (12).

It has been reported that intralesional radiolucencies (air bronchogram, air alveologram, pseudocavitation, true cavitation) are characteristic findings of BACs (13). There was no significant difference in the presence of intralesional air between IMAs and LPAs in our study (Figure 3). It has been reported that cavity formation occurs in 5.6-13.9% of IMAs (14,15). We found overt cavitation in 6 of 47 patients with IMA (12.7%). Three of the cases were multifocal (Figure 4).

Variable ^{18}F-FDG uptake was observed in all 57 cases, ranging from 0.79 to 14.7. The predominant histologic subtype is associated with ^{18}F-FDG uptake. Several studies reported that AIS, MIA, LPA, and IMA had low SUV_{max} values, whereas acinar, papillary, micropapillary, and solid predominant ADCs had high SUV_{max} values (16). Consistent with these studies, the mean SUV_{max} was low in IMAs and LPAs in our study (mean SUV_{max}, 4.4 and 3.4, respectively). However, no statistically significant difference was found in SUV_{max} between IMAs and LPAs (p=0.078). LPAs refer to the proliferation of type II pneumocyte or Clara cells. IMAs typically comprise neoplastic goblet or tall columnar cells with abundant intracytoplasmic mucin (17,18). Tumors that were formerly called BAC have a small number of active malignant cells (9). The ^{18}F-FDG uptake intensity is associated with the number of malignant cells in the tumor.

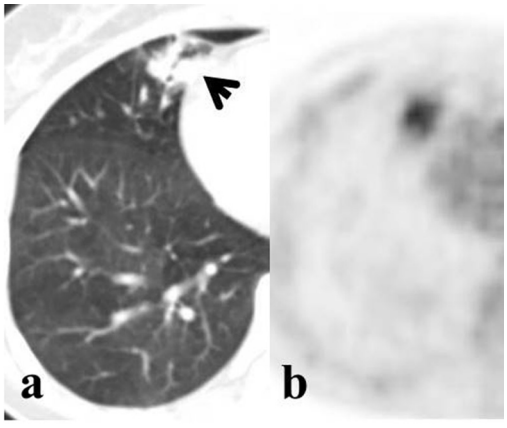

Figure 3. Axial ^{18}F-FDG PET/CT images of a 47-year-old female patient with a solitary LPA. a) CT image (lung window) showing a 25-mm-sized lobulated and spiculated nodule containing internal air densities in the right lung (arrow). b) PET image demonstrating ^{18}F-FDG uptake in the nodule with an SUV_{max} of 2.29
^{18}F-FDG: F-18 fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, LPA: Lepidic predominant lung adenocarcinoma, SUV_{max}: Maximum standardized uptake value

It is known that tumor size is correlated with ^{18}F-FDG uptake (19). Consistent with the literature, we found a positive and significant correlation between SUV_{max} and tumor size (p=0.002). The size of LPAs was significantly smaller than that of IMAs (p=0.003). Additionally, the SUV was significantly lower in the nodular group than in the mass/pneumonic-type group (p=0.0001). Lee et al. (20) found that consolidative patterns exhibited higher SUV_{max} than nodular patterns in IMAs.

The risk of lymph node involvement is associated with lung ADC subtypes. The incidence of regional nodal involvement was low for LPAs and IMAs (21,22). Yu et al. (21) investigated lymph node involvement in lung ADC with a tumor size ≤3 cm. They found that the percentages of lymph node involvement were: 47.6%, 47.2%, 24.0%, 18.9%, 18.1%, 0%, 0%, and 0% for solid predominant, micropapillary predominant, variants of invasive ADC, papillary predominant, acinar predominant, lepidic predominant, MIA, and AIS, respectively (21). The diameter of the tumor was 6 cm in a patient with LPA in our study. No lymph node was involved in this patient. The diameter of primary tumors was ≤3 cm in all other LPAs. In addition, we found lymph node involvement in 2 of 32 patients (6.25%) who underwent lymph node biopsy and/or dissection. Beck et al. (22) reported lymph node involvement in 7 of 46 patients (15.2%) with IMA. The overall sensitivity and specificity of PET/CT for the detection of lymph node involvement were 80% and 91.23%, respectively, in our study.

The prognosis of IMA is controversial. Several previous studies have demonstrated that mucinous ADCs are associated with poor survival (23,24). Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation is detected in 28-87% of IMAs. The frequency of epidermal growth factor

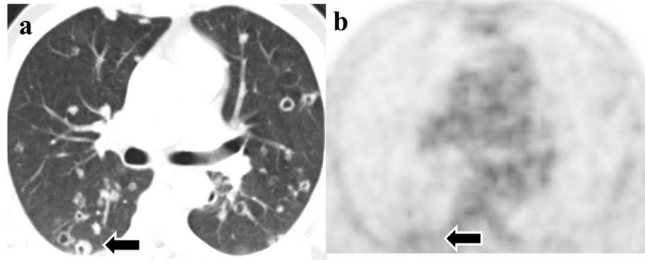

Figure 4. Axial ^{18}F-FDG PET/CT images of a 57-year-old female patient with IMA presenting as multiple cavitary lesions. a) CT image (lung window) showing multiple bilateral small cavitary nodules (arrow). b) PET image demonstrating mild ^{18}F-FDG uptake in the nodules (arrow)
^{18}F-FDG: F-18 fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, IMA: Invasive mucinous lung adenocarcinoma

receptor (EGFR) mutations in IMAs is 5% (25). LPAs, AIS, and MIAs are positively associated with EGFR mutations (26). Patients with EGFR mutation-positive tumors are sensitive to EGFR tyrosine kinase inhibitors. These agents are associated with significantly prolonged progression-free survival compared with standard chemotherapy (27). However, some recent studies have indicated that IMAs have a better prognosis than most ADCs (28,29). Cai et al. (29) indicated that there were no differences in overall survival (OS) between patients with IMAs and those with mucus-negative ADCs (OS: 49.5 months versus 63.5 months, p=0.524). Lee et al. (20) showed no significant difference in 5-year OS between IMAs, intermediate (acinar/papillary predominant) non-mucinous ADCs, and high-grade (micropapillary/solid predominant) non-mucinous ADCs. They found that patients with LPA (low-grade non-mucinous ADCs) had significantly better OS and DFS than those with other subtypes. Lee et al. (20) reported that the median survival of patients with IMAs was 47.8 months. Similarly, the median survival time was 46.2 months in patients with IMA. Although statistically insignificant, we found that the median survival time of patients with IMA was shorter than that of patients with LPA (69.3 months).

During follow-up, 11 (9 IMA and 2 LPA) patients died in our study. Male sex, rate of stage III-IV, T3-T4, M1 diseases, multifocality, and bilateral involvement were higher in the non-survivors group in our analyses. Previous studies reported that multifocal nodular tumors were associated with poor OS rates in IMAs (20). M1 disease was associated with multifocal lung involvement in our series. The incidence of extrathoracic metastases was low in both LPAs and IMAs (30,31). Consistent with previous reports, extrathoracic metastases were detected in only 2 patients with IMA in our study.

We found no significant difference between the nodular and mass/pneumonic forms in survivors and non-survivors. However, Lee et al. (20) demonstrated that IMAs with consolidative patterns had relatively poorer OS compared with nodular patterns. The differences were not statistically significant. Epstein (32) reported that the consolidative form has a poorer prognosis than the localized nodular form in patients with BAC. We found significantly higher T stages in IMAs than in LPAs (p=0.048). Tumors with a consolidative form tend to be large and occur in the advanced T stage.

There was no association between the presence of intralesional air and poor prognosis in our study. However, Yoshino et al. (33) demonstrated that air bronchogram was a good independent prognostic factor for stage I lung ADC. It has been reported that intralesional radiolucency corresponds to patent intratumoral bronchioles (14). However, contrary to these results, Zhang et al. (34) showed that the number of air bronchogram progressively increased from preinvasive atypical adenomatous hyperplasia (5.3%) and AIS (17.7%) to invasive MIA (30.5%) and IAC (54.1%). They also demonstrated the relationship between air bronchogram patterns and lung ADC invasiveness. As invasiveness increased, the dilated or tortuous bronchus lumen and obstructed bronchus were observed more frequently in their study. They suggested that tumor cell infiltration of bronchioles leads to airway tortuosity, ectasis, and obstruction.

The SUV_{max} was higher in the death group than in the survival group (p=0.031) in our study. Lee et al. (20) found that SUV_{max} was a significant independent poor prognostic predictor for DFS but not OS in patients with IMA. They reported that patients with SUV_{max} below 4.4 and those with an SUV_{max} of 4.4 or higher were associated with significantly different rates of DFS.

Study Limitations

Our analysis has some limitations. First, this is a single-institution study. In addition, IMAs are rare tumors, accounting for approximately 5% of all lung ADCs (35). First, the number of patients was low. Second, this was a retrospective study. Further larger prospective studies are needed to validate these results.

Conclusion

CT has an important role in the differential diagnosis of IMAs and LPAs. Multifocal lung involvement and mass/pneumonic type presentation are related to IMAs. However, SUV_{max} was not a determinative factor in the differential diagnosis between the two groups. SUV_{max} may be an important factor affecting the prognosis of IMAs and LPAs.

Ethics

Ethics Committee Approval: The study was approved by University of Health Sciences Türkiye, Ankara Atatürk Pulmonary Diseases and Thoracic Surgery Training and Research Hospital Institutional Review Board (decision no.: 682, date: 16.07.2020).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.T., F.D., D.K., S.B., Design: Ö.Ö., Data Collection or Processing: D.K., Analysis or Interpretation: E.T., Writing: E.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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