



Contribution of ¹⁸F-FDG PET/CT in the Differential Diagnosis of Pulmonary Hamartomas and Pulmonary Carcinoids

¹⁸F-FDG PET/CT'nin Pulmoner Hamartomların ve Pulmoner Karsinoidlerin Ayırıcı Tanısına Katkısı

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Abstract

Objectives: This study aimed to evaluate ¹⁸fluorine-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) findings in the differential diagnosis of pulmonary carcinoids and pulmonary hamartomas.

Methods: ¹⁸F-FDG PET/CT findings of 34 patients with pulmonary carcinoids (12 atypical, 22 typical) and 32 patients with pulmonary hamartomas were retrospectively evaluated. Both mean diameter and mean maximum standardized uptake value (SUV_{max}) of hamartomas and carcinoids were compared by Mann-Whitney U and Kruskal-Wallis H tests.

Results: The mean longest diameter of atypical carcinoids (3.5±1.7 cm) was higher than that of hamartomas (2.1±1 cm) (p=0.038). No significant difference was found between the mean diameter of typical carcinoids and mean diameter of hamartomas (p=0.128). The mean SUV_{max} of atypical carcinoids (5.97±3.7) and typical carcinoids (4.22±1.7) were higher than those of hamartomas (1.65±0.9) (p=0.002 and p=0.003, respectively). There were collapse/consolidation in 55.8%, bronchiectasis or mucoid impaction in 47%, and air trapping in 14.7% in the peripheral parenchyma of the 34 carcinoids. Collapse/consolidation was detected in a patient with endobronchial hamartoma, and other finding was not found in the parenchyma around hamartomas.

Conclusion: The ¹⁸F-FDG uptake of pulmonary carcinoids can vary from minimal to intense. ¹⁸F-FDG uptake can be seen in pulmonary hamartomas. However, the mean SUV_{max} of atypical carcinoids and typical carcinoids were higher compared to hamartomas. Pulmonary carcinoid must be suspected in cases with accompanying bronchial obstruction findings in the periphery of the mass.

Keywords: Pulmonary hamartoma, pulmonary carcinoid tumor, atypical pulmonary carcinoid tumor, ¹⁸F-FDG PET/CT

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Öz

Amaç: Bu çalışmanın amacı pulmoner karsinoid tümörlerin ve pulmoner hamartomların ayırıcı tanısında ^{18}F -flor-florodeoksiglukoz (^{18}F -FDG) pozitron emisyon tomografi/bilgisayarlı tomografinin (PET/BT) bulgularını değerlendirmektir.

Yöntem: Pulmoner karsinoidli 34 hastanın (12 atipik, 22 tipik) ve pulmoner hamartomlu 32 hastanın ^{18}F -FDG PET/BT bulguları geriye dönük olarak değerlendirildi. Hamartomların ve karsinoidlerin hem ortalama çapı hem de ortalama maksimum standardize uptake değeri (SUV_{maks}) değeri Mann-Whitney U ve Kruskal-Wallis H testleri ile karşılaştırıldı.

Bulgular: Atipik karsinoid tümörlerin ortalama en uzun çapı ($3,5\pm 1,7$ cm), hamartomlardan ($2,1\pm 1$ cm) daha fazlaydı ($p=0,038$). Tipik karsinoid tümörün ortalama çapı ($2,7\pm 1,7$ cm) ile hamartomların ortalama çapları arasında anlamlı bir fark yoktu ($p=0,128$). Atipik karsinoidlerin ($5,97\pm 3,7$) ve tipik karsinoidlerin ($4,22\pm 1,7$) ortalama SUV_{maks} değerleri hamartomlara ($1,65\pm 0,9$) göre daha yüksekti (sırasıyla; $p=0,002$ ve $p=0,003$). Otuz dört karsinoidin periferik parankiminde %55.8'inde kollaps konsolidasyon, %47'sinde bronşektazi veya mukoid impaksiyon ve %14.7'sinde hava hapsi vardı. Endobronşiyal hamartomlu bir hastada kollaps konsolidasyon tespit edildi. Bunun dışında hamartomların etrafındaki parankimde ek bulguya rastlanmadı.

Sonuç: Pulmoner karsinoidlerde ^{18}F -FDG tutulumu minimalden yoğunu kadar değişebilir. Ayrıca pulmoner hamartomlarda ^{18}F -FDG tutulumu görülebilir. Ancak, çalışmamıza göre atipik karsinoidlerin ve tipik karsinoidlerin ortalama SUV_{maks} 'i hamartomlara göre daha yüksekti. Ayrıca kitle çevresinde bronşiyal obstrüksiyon bulgularının eşlik etmesi durumunda pulmoner karsinoidden şüphelenilmelidir.

Anahtar kelimeler: Pulmoner hamartom, pulmoner karsinoid tümör, atipik pulmoner karsinoid tümör, ^{18}F -FDG PET/BT

Introduction

Hamartoma is a benign neoplasm consisting of an abnormal mixture of cells and tissues of the organ from which it originates and may contain cartilage, muscle, fat, connective tissue, and respiratory epithelium. Pulmonary hamartoma is the most common benign tumor of the lung in adults. They constitute 77% of benign lung lesions (1,2).

Pulmonary carcinoids are well-differentiated neuroendocrine carcinomas, originating from neuroendocrine cells called Kulchitzky, located in the bronchial or bronchiolar epithelium, comprising 1%-2% of all primary lung cancers (3,4). Pulmonary carcinoids and pulmonary hamartomas are often observed as well-circumscribed, lobulated, rounder oval lesions on computed tomography (CT) (1,5). ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/CT is a widely used method for the evaluation of suspected malignant lung nodules. It prevents unnecessary invasive procedures and enables detection of malignancy at an early stage (6). However, pulmonary carcinoids may not show significant ^{18}F -FDG uptake (7). In addition, false-positive ^{18}F -FDG uptake can be observed in infective and inflammatory processes (8). This retrospective study aimed to investigate the contribution of ^{18}F -FDG PET/CT findings in the differential diagnosis of pulmonary carcinoids and pulmonary hamartomas; thus, both CT and ^{18}F -FDG PET findings of these lesions were evaluated.

Materials and Methods

Medical records of patients who underwent ^{18}F -FDG PET/CT to evaluate pulmonary nodules, which were detected on CT between 2009 and 2019 at our hospital, were retrospectively reviewed. Patients with pulmonary

carcinoid or pulmonary hamartoma, which was pathologically confirmed by biopsy or surgical resection, were included in the study. The exclusion criteria of the patients were as follows: (1) Nodule with diameter <10 mm and (2) presence of significant respiratory motion artifacts that affected the assessment of lesion on PET/CT. Thus, a total of 34 patients with pulmonary carcinoids (12 atypical, 22 typical) and a total of 32 patients with pulmonary hamartomas were included in this study. Age, sex, lesion location within the lung parenchyma, type of operation, and PET/CT findings were recorded.

PET/CT (Biograph LSO HI-REZ PET/CT; Siemens, Medical Solutions, Knoxville, TN) was performed within 45-60 min after intravenous injection of 0.15 mCi/kg ^{18}F -FDG. Blood glucose was confirmed to be <200 mg/dL before the injection of ^{18}F -FDG. Patients fasted for at least 6 h prior to the ^{18}F -FDG injection. After taking CT images from the vertex of the skull to the proximal femur, PET was performed in 6-8 bed positions (3 min per bed). CT data were used for attenuation correction. After the reconstruction of raw data with ordered subset expectation maximization algorithms, images were evaluated in axial, coronal, and sagittal formats. The maximum standardized uptake value (SUV_{maks}), longest diameter values, and presence of intralesional calcification and fat were noted. In addition, accompanying findings in the peripheral parenchyma of the lesion, such as air trapping, bronchiectasis, mucoid impaction of the bronchi, and collapse/consolidation, were assessed. Density found similar to subcutaneous fatty tissue in the lesion was considered fat density. The SUV_{maks} of the lesions were calculated automatically by drawing the relevant area around the lesions.

This study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital (date: 16.07.2020, protocol number: 682).

Statistical Analysis

Data collected in this study were analyzed by the SPSS 21 statistical package software. As data were not normally distributed, the Mann-Whitney U test was used in two-group comparisons, and the Bonferroni-corrected Kruskal-Wallis H test was used in three-group comparisons. The Mann-Whitney U test was used for post-hoc comparisons. Significant difference was set at p value <0.05.

Results

A total of the 66 (42 male, 24 female) patients were included in the study. Of these patients, 34 had carcinoids and 32 had hamartomas. There were 12 atypical and 22 typical carcinoids. Clinicopathological features of the patients are given in Table 1.

The mean diameters of lesions and SUV_{max} value are shown in Table 2. The mean longest diameter of atypical carcinoids (3.5 ± 1.7 cm) was higher than that of hamartomas (2.1 ± 1 cm) ($p=0.038$). No significant difference was found between the mean diameter of typical carcinoids (2.7 ± 1.7 cm) and the mean diameter of atypical carcinoids ($p=0.325$). In addition, no significant difference was noted between the mean diameter of typical carcinoids and the mean diameter of hamartomas ($p=0.128$).

The mean SUV_{max} was 4.22 ± 1.7 (range, 1.2 ± 7.1) in typical carcinoids, 5.97 ± 3.7 (range, $2-13.25$) in atypical carcinoids, and 1.65 ± 0.9 (range, $0-3.3$) in hamartomas. The SUV_{max} of hamartomas was substantially low in comparison with

typical and atypical carcinoids ($p=0.003$ and $p=0.002$, respectively). No significant difference between SUV_{max} of typical and atypical carcinoids was determined ($p=0.325$).

The CT features of ^{18}F -FDG PET/CT images of lesions are shown in Table 3. Collapse/consolidation ($n=19$), bronchiectasis and/or mucoid impaction ($n=16$), and air trapping ($n=5$) were seen in the peripheral pulmonary parenchyma of 34 carcinoids (Figure 1). Pleural effusion on the side of the lesion was detected in two patients. Peripheral pulmonary collapse/consolidation was found in one patient with endobronchial hamartoma, and no other finding was found in the parenchyma around hamartomas.

Intralesional calcification was found in 52.9% of 34 carcinoids. Calcification was detected in 46.8% of 32 hamartomas (Figure 2). Intralesional fat density was observed in 4 of 32 (12.5%) patients with hamartoma (Figure 3).

Discussion

A meta-analysis revealed that ^{18}F -FDG PET/CT has high sensitivity (81.9%) but lower specificity (62.4%) in distinguishing benign from malignant pulmonary nodules. The presence of ^{18}F -FDG uptake in inflammatory or infective diseases, other than malignant diseases, reduces the specificity of PET/CT (8). Low ^{18}F -FDG uptake can be observed in pulmonary hamartomas (Figure 2) (9,10). Ergonul et al. (9) reported ^{18}F -FDG PET/CT findings of 106 patients with benign lung lesions. Of 106 patients, 19 had hamartomas. The SUV_{max} of 19 hamartomas ranged from 0 to 4.5 (9). Jiang et al. (10) reported the ^{18}F -FDG PET/CT findings of 14 pulmonary hamartomas with a mean diameter of 1.7 ± 0.8 cm (range, $0.7-3.1$ cm), and the mean SUV_{max} of lesions was 1.5 ± 0.6 (range, $0.7-2.6$)

Histopathologic diagnosis	Carcinoids	Hamartomas
n	34	32
Sex (male/female)	11/23	13/19
Age, y (mean \pm SD)	49 \pm 15.2	54.4 \pm 10.4
Location (central/peripheral) (n)	22/12	3/29
Location (right/lung) (n)	21/13	19/13
Type of biopsy or surgery		
Lobectomy or bilobectomy	24	1
Pneumonectomy	1	
Wedge resection or excision	8	18
TTNA or truncate biopsy		13
Bronchoscopic biopsy	1	
TTNA: Transthoracic needle aspiration SD: Standard deviation		

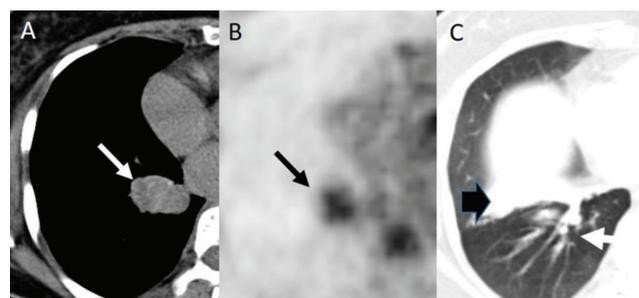


Figure 1. Atypical carcinoid. Axial CT (A) and PET (B) images of the PET/CT scan showing high ^{18}F -FDG uptake on a lobulated mass with eccentric calcifications (thin arrows). Adjacent atelectasis (black thick arrow) and air trapping (white thick arrow) are detected. The maximum standardized uptake value of carcinoid was 4.16

CT: Computed tomography, PET: Positron emission tomography, ^{18}F -FDG: ^{18}F -fluorodeoxyglucose

Diagnosis	AC	TC	Hamartoma	p value ^a	p value [*]	p value ^{**}	p value [‡]
n	12	22	32	-	-	-	-
Mean diameter ± SD range, (cm)	3.5±1.7 (1.2-7)	2.7±1.7 (0.7-8)	2.1±1 (0.7-5.5)	0.035	0.325	0.128	0.038
Mean SUV _{max} ± SD range	5.97±3.7 (2-13.2)	4.22±1.7 (1.2-7.1)	1.65±0.9 (0-3.3)	0.0001	0.325	0.003	0.002

^ap value for comparison among three groups (Kruskal-Wallis test), ^{*}p value for comparison between AC and TC, ^{**}p value for comparison between hamartoma and typical carcinoids, [‡]p value for comparison between hamartoma and AC. SUV_{max}: Maximum standardized uptake value, AC: Atypical carcinoid, TC: Typical carcinoid, SD: Standard deviation

Histopathologic diagnosis	Carcinoids	Hamartomas
n	34	32
Intralesional calcification (n)	18	15
Intralesional fat (n)	0	4
Bronchiectasis or mucoid impaction (n)	16	0
Collapse/consolidation (n)	19	1
Air trapping (n)	5	0
Pleural effusion (n)	2	0

PET/CT: Positron emission tomography/computed tomography, ¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose

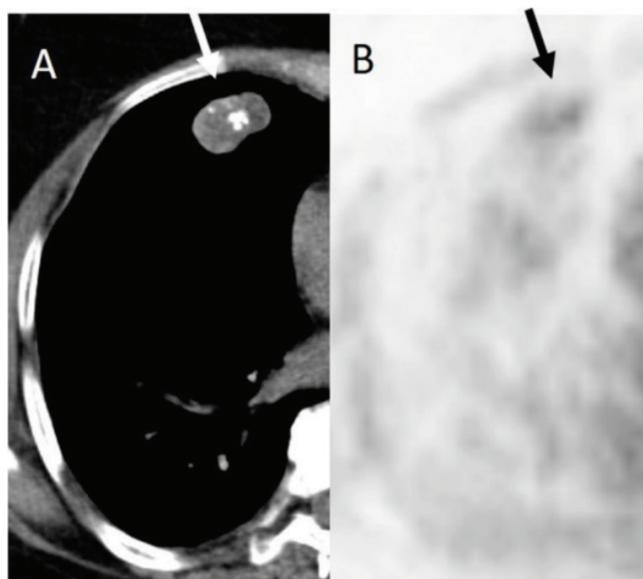


Figure 2. Pulmonary hamartoma. Axial CT (A) and PET (B) images of the PET/CT scan show low ¹⁸F-FDG uptake on a nodule with popcorn calcifications (arrows). The maximum standardized uptake value was 2.34

CT: Computed tomography, PET: Positron emission tomography, ¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose

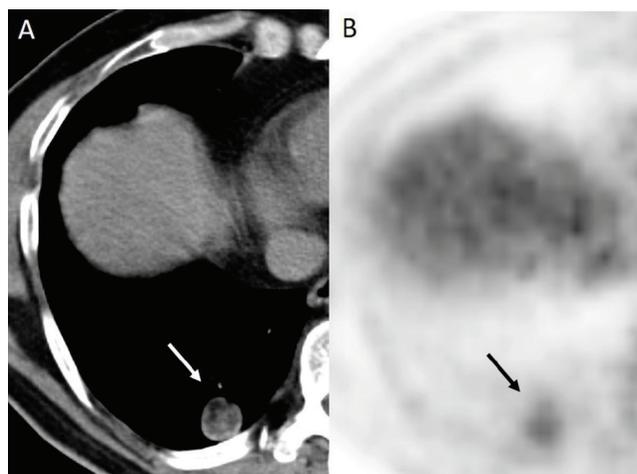


Figure 3. Pulmonary hamartoma. Axial CT (A) and PET (B) images of the PET/CT scan show low ¹⁸F-FDG uptake on the slightly lobulated, well-defined, fat-containing nodule (arrows). The maximum standardized uptake value of carcinoid was 2.33

CT: Computed tomography, PET: Positron emission tomography, ¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose

(10). Similarly, in the present study, the mean SUV_{max} was 1.65±0.9 (range, 0-3.38).

Although the sensitivity of ¹⁸F-FDG PET/CT is high, false-negative ¹⁸F-FDG results can occur in the determination of malignancy. In malignant tumors with low glucose metabolic activity such as carcinoid, solid adenocarcinoma, minimally invasive carcinoma, and atypical adenomatous hyperplasia, a lack of ¹⁸F-FDG uptake can be seen on PET images (8). ¹⁸F-FDG PET/CT is the first choice in the evaluation of indeterminate pulmonary nodules. However, at present, Gallium-68 (⁶⁸Ga)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-conjugated peptides that show affinity for somatostatin receptors are used in the imaging of carcinoids through PET/CT (11). While the sensitivity of ⁶⁸Ga-DOTA-conjugated peptides in detecting pulmonary carcinoids ranged from 79% to 100%, the sensitivity of ¹⁸F-FDG PET/CT in identifying pulmonary

carcinoids ranged from 52% to 100% (12). In our retrospective study in 2014, we evaluated ^{18}F -FDG PET/CT findings of 22 patients with pulmonary carcinoids (14 typical, 8 atypical). In that study, the sensitivity of ^{18}F -FDG PET/CT was 81.8% in detecting pulmonary carcinoids (13).

In the present study, the mean SUV_{max} was 4.22 for typical carcinoids and 5.97 for atypical carcinoids (Figure 1). No significant difference was found in the SUV_{max} between typical and atypical carcinoids ($p=0.325$). The mean SUV_{max} was significantly lower in hamartoma than in typical and atypical carcinoids ($p=0.003$ and $p=0.002$, respectively). Uhlén et al. (14) compared the ^{18}F -FDG PET/CT findings of 36 patients with pulmonary carcinoid and 51 patients with pulmonary hamartoma. They found that the SUV_{max} was lower in hamartomas (mean, 1.4) than in carcinoids (mean, 3.9) ($p\leq 0.00001$).

While approximately 80% of pulmonary carcinoids are located in central airways, 90% of pulmonary hamartomas are located peripherally (5,15). The central carcinoids may occur with associated pneumonia, atelectasis, air trapping, mucoid impaction, and bronchiectasis (5). In the present study, 64.7% of carcinoids were centrally located. Distal collapse/consolidation was detected in 55.8% of 34 carcinoids, mucoid impaction or bronchiectasis in 47%, and air trapping in 14.7%. Calcification was found in the 57.7% of 34 carcinoids. Moreover, 90.6% of the hamartomas were located peripherally. Accompanying collapse/consolidation was found in a patient with endobronchial located hamartoma, and no other finding was seen for hamartomas in the peripheral parenchyma.

Diffuse, punctate, or eccentric calcification can be observed in 30% of carcinoids on CT images (16). Moreover, 25%-30% of benign pulmonary hamartomas exhibit calcification/ossification. Especially, the presence of calcification in the form of popcorn or comma suggests hamartoma (1). We found intralesional calcification in 52.9% of the 34 carcinoids and also in 46.8% of 32 hamartomas. Pulmonary hamartoma and carcinoid may have similar morphologic features on CT. Especially, peripheral carcinoids are generally asymptomatic and found incidentally. Peripheral carcinoids are slow-growing tumors. It may be difficult to distinguish peripheral carcinoids from benign pulmonary nodules. Thin-slice CT images can show the relationship between small airways and carcinoid nodules (16).

Study Limitations

This study has some limitations. In a previous study, intralesional fat was seen in approximately 60% of hamartomas (1). Approximately -40 to -120 Hounsfield

units (HU) are compatible with intralesional fat density and are typical for hamartoma on thin-slice CT images (17). However, in the present study, fat density was found in 13.3% of 32 hamartomas. In addition, PET/CT images were taken while the patient was breathing freely. Respiratory motion during scanning causes artifacts in PET/CT images, particularly in cases of small nodules. Thus, we prefer to evaluate the presence of intranodular fat visually, instead of measuring the HU value. The rate of intrapulmonary fat content may be incorrectly low in our study. The contour, density, and size of pulmonary nodules, presence of intralesional calcification, and indirect findings of airway involvement, especially in peripheral and small nodules, can be evaluated more effectively by thin-slice CT (18).

Conclusion

The ^{18}F -FDG uptake in pulmonary carcinoids is higher than hamartomas. However, ^{18}F -FDG uptake can be seen in hamartomas. In the presence of calcifying central pulmonary lesions that are well circumscribed or lobulated, showing marked FDG uptake and bronchial obstruction findings in the peripheral parenchyma, carcinoids should be considered in the diagnosis. Differential diagnosis of peripheral carcinoids, particularly small ones, without a finding of bronchial obstruction in the adjacent parenchyma, is only possible by histopathological methods.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital (date: 16.07.2020, protocol number: 682).

Informed Consent: Informed consent was not required for such a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ö., Concept: E.T., Design: F.D., Data Collection or Processing: Ö.Ö., Literature Search: E.T., Writing: E.T.

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

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