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Original Article / Özgün Makale

Diagnostic performance of ^{18}F-FDG PET/CT in solitary pulmonary nodules of non-smokers

Sigara içmeyenlerde soliter pulmoner nodüllerde ^{18}F-FDG PET/BT görüntülemenin tanısal gücü

Sevda Sağlampınar Karyağar,[1] Zehra Pınar Koç,[2] Savaş Karyağar,[1] Yıldıray Bekar[3]

Institution where the research was done:
Trabzon Kanuni Training and Research Hospital, Trabzon, Turkey

Author Affiliations:
[1]Department of Nuclear Medicine, Okmeydanı Training and Research Hospital, İstanbul, Turkey
[2]Department of Nuclear Medicine, Medical Faculty of Fırat University, Elazığ, Turkey
[3]Department of Thoracic Surgery, Trabzon Kanuni Training and Research Hospital, Trabzon, Turkey

ABSTRACT

Background: This study aims to investigate the diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in patients with solitary pulmonary nodules without smoking history.

Methods: A total of 38 patients (25 females, 13 males; mean age 63±14 years; range 23 to 84 years) with solitary pulmonary nodules without smoking history who underwent ^{18}F-FDG PET/CT imaging between June 2009 and March 2013 were retrospectively analyzed. Medical history was obtained from each patient, and malignancy was initially made by computed tomography in all patients. The diagnosis was further confirmed by either histopathological analysis results or at least two-year follow-up results.

Results: The mean lesion diameter was 20±6 (range 8 to 28) mm. Eleven patients had a lung carcinoma, predominantly an adenocarcinoma (n=10), while 10 patients were found to have a FDG-avid tumor. The sensitivity, specificity, accuracy, and positive predictive and negative predictive values of ^{18}F-FDG PET/CT were 91%, 63%, 71%, 50%, and 94%, respectively. All patients diagnosed with malignancy were women with an advanced age. Only one of the male patients had a malignant nodule.

Conclusion: The sensitivity and negative predictive value of ^{18}F-FDG PET/CT were found to be high in non-smoker patients with solitary pulmonary nodules, although adenocarcinomas were predominant in our study.

Keywords: Computed tomography; fluorodeoxyglucose; non-smokers; positron emission tomography; solitary pulmonary nodule.

ÖZ

Amaç: Bu çalışmada, sigara içme öyküsü olmayan soliter pulmoner nodüllü hastalarda flor-18 florodeoksiglikoz pozitron emisyon tomografi/bilgisayarlı tomografinin (^{18}F-FDG PET/BT) tanısal gücü araştırıldı.

Çalışma planı: Haziran 2009 - Mart 2013 tarihleri arasında, sigara içme öyküsü olmayan, soliter pulmoner nodüllü olan, ^{18}F-FDG PET/BT görüntülemesi yapılan toplam 38 hasta (25 kadın, 13 erkek; ort. yaş 63±14 yıl; dağılım 23-84 yıl) retrospektif olarak incelendi. Her hastanın tıbbi öyküsü alındı ve malignite tanısı tüm hastalarda ilk olarak bilgisayarlı tomografi ile kondu. Tanı, daha sonra histopatolojik analiz sonuçları veya en az iki yıllık takip sonuçları ile doğrulandı.

Bulgular: Ortalama lezyon çapı 20±6 (dağılım 8-28) mm idi. On bir hastada, çoğunluğunda adenokarsinom olmak üzere (n=10) akciğer karsinomu var iken, 10 hastada FDG tutan tümör saptandı. ^{18}F-FDG PET/BT'nin duyarlılığı, özgüllüğü ve doğruluğu, pozitif öngörü ve negatif öngörü değerleri sırasıyla %91, %63, %71, %50 ve %94 idi. Malignite tanısı konan hastaların tümü kadın ve ileri yaşta idi. Erkek hastalardan yalnız birinde malign nodül vardı.

Sonuç: Çalışmamızda adenokarsinom baskın olmakla birlikte, sigara içmeyen soliter pulmoner nodüllü hastalarda ^{18}F-FDG PET/BT'nin duyarlılığı ve negatif öngörü değeri yüksek bulundu.

Anahtar sözcükler: Bilgisayarlı tomografi; florodeoksiglikoz; sigara içmeyenler; positron emisyon tomografi; soliter pulmoner nodül.

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Correspondence: Savaş Karyağar, MD. Okmeydanı Eğitim ve Araştırma Hastanesi, Nükleer Tıp Bölümü, 34384 Okmeydanı, İstanbul, Turkey.
Tel: +90 212 - 221 77 77 e-mail: skaryagar@yahoo.com

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A solitary pulmonary nodule (SPN) is defined as a lesion <3 cm in diameter surrounded by normal parenchymal tissues without atelectasis or adenopathy.[1-3] Since lung cancer has a poor prognosis, earlier identification of lung cancer as a solitary pulmonary nodule may improve prognosis. Previous studies have shown that the five-year survival of the patients subjected to thoracotomy for a SPN is highly associated with the histopathological subtype.[4] Therefore, early diagnosis and treatment of SPNs are of utmost importance for the public health.

In healthy population, the rate of SPNs is 7% on radiographs and 23 to 51% on computed tomography (CT).[5,6] Final decision is usually obtained by thoracotomy either mini-thoracotomy or video-assisted thoracoscopic surgery.[7] However, surgery is not indicated for all nodules, and as the capacity of CT to discriminate benign from malignant lesions is poor, there are an unacceptable number of indefinite results.[8]

Fluorine-18-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) 18F-has been introduced with high negative predictive values in differentiating malignant and benign SPNs.[9] As a result, the reduction in the number of unnecessary thoracotomies has been achieved by imaging of the SPNs with PET/CT.[10] However, false positive results are one of the major disadvantages of PET/CT imaging particularly in countries with a higher incidence of granulomatous diseases.[11] Another disadvantage of this imaging method is false negative results related to some specific histopathological subtypes, particularly to adenocarcinomas.

There is a new and growing aspect about the lung cancer patients without smoking history. Several studies including non-smokers demonstrated that the tumor characteristics included adenocarcinomas and CT characteristics included ground glass attenuation (GGA) with or without a solitary component.[12] To the best of our knowledge, however, no study has been carried out to investigate the ^{18}F-FDG PET/CT characteristics of the SPNs of non-smokers, yet. Therefore, in the present study, we aimed to investigate the diagnostic performance of ^{18}F-FDG PET/CT in patients with SPNs without smoking history.

PATIENTS AND METHODS

A total of 38 patients (25 females, 13 males; mean age 63±14 years; range 23 to 84 years) with SPNs without smoking history who underwent ^{18}F-FDG PET/CT imaging between June 2009 and March 2013 were retrospectively analyzed. Inclusion criteria were as follows: no history of cigarettes smoking or previous malignancy and having a SPN (8-30 mm in diameter) without benign calcification.

The study protocol was approved by the Ethics Committee of the Recep Tayyip Erdogan University Medical Faculty and an informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients underwent dynamic contrast-enhanced multi-detector row CT scans using the Siemens Somatom Sensation 16-Slice CT scanner (Siemens, Chicago, USA). Spiral scans were conducted with the collimator width of 1.5x16 mm, rotation time of 0.6 sec, spiral pitch of 1.5, 110 kVp and automatic 60 mAs. Enhanced CT scans were performed using a non-ionic contrast agent (80 mL) with a bolus injection rate (high-pressure injector) of 2.5 mL/sec and a scan delay time of 25 sec. The image data were reconstructed with a thickness of 1.5 mm using the standard algorithm (B31) for mediastinal window setting.

^{18}F-FDG PET/CT studies were carried out using an integrated PET/CT scanner, which consisted of a full-ring HI-REZ LSO PET and a 6-slice CT (Siemens Biograph 6; Siemens, Chicago, USA). All patients were instructed to fast for at least 6-h before the 18F-FDG injection. Blood glucose levels were measured before the study and the injection was given only, when the blood glucose levels were below 11.11 mmol/L. The patients were injected with 370 to 555 MBq 18F-FDG, according to the body weight. After 60 min of waiting on a semi-reclined relaxed chair, the patients were imaged using an integrated PET/CT scanner. The CT portion of the study was performed without injection an intravenous contrast medium to define anatomical landmarks and attenuate correction on PET images. Computed tomography was acquired first with the following parameters: 50 mAs, 140 kV, and 5 mm section thickness. Whole-body CT was performed in a craniocaudal direction. In addition, PET images were acquired in a three-dimensional mode, from the base of the skull to the mid-thigh, with five to eight bed positions of 3 min each, and PET data were collected in a caudocranial direction.

Two experienced nuclear medicine specialists who were blind to the confirmed diagnosis interpreted the ^{18}F-FDG PET/CT imaging. The images were displayed in rotating maximum intensity projections and in axial, coronal, and sagittal planes. Semi-quantitative examination of the PET images was performed.

The semi-quantitative analysis of FDG uptake was performed, creating a region of interest (ROI) over SPNs. The ROIs of the lesions which were invisible on PET images were located by the corresponding CT images. Maximum standardized uptake values (SUV_{max}) were automatically generated according to the following equation: SUV_{max} body weight (bw)=Ctis/Dinj/bw, where SUV_{max} bw is SUV_{max} normalized for body weight; Ctis, tissue concentration expressed as megabecquerels per milliliter; Dinj, injected dose expressed as megabecquerels; and bw, bw expressed in kilograms. Lesions with ≥2.5 SUV_{max} were considered malignant and those with <2.5 were considered benign.

The diagnosis of malignant lesions was established through histopathological examination. Malignant lesions were identified by either lobectomy (n=5; right lower lobe in 2, right upper lobe in 2, left upper lobe in 1) or transthoracic biopsy (n=6).

The diagnosis of benign lesions was established by transthoracic biopsy (n=10), based on radiological follow-up evaluations (n=9), and wedge resection (n=8; right upper lobe in 2, left lower lobe in 3 and left upper lobe in 3) or lobectomy (n=1, left lower lobe) was performed, if necessary. If nodule diameter remained unchanged after at least 24-month follow-up or disappeared on repeated CT, the nodule was considered benign.

Statistical analysis

Comparison of the numerical values were performed by Student's t test and $p<0.05$ was considered as statistically significant. The calculation of sensitivity, specificity, accuracy, negative and positive predictive values was performed additionally.

RESULTS

Eleven patients had a lung carcinoma (adenocarcinoma, n=10, squamous-cell carcinoma, n=1) (Figure 1). The mean SUV_{max} values of these lesions were 8±4.1 and mean diameter of the tumors was 24.2±4 mm. The PET/CT finding was positive in all patients, except one with malignancy. According to the CT scans, the mean nodule diameter was 20±6.7 (range 8 to 28) mm. The lesions were located in the right upper (n=13), right middle (n=2), right lower (n=9), left upper (n=5) and left lower (n=9) pulmonary lobes.

There were 27 patients with benign lesions which were confirmed to have different etiologies (the definition of etiology is based on the histopathology in 18 patients and no change in diameter during 24-month follow-up in 10 patients) including tuberculosis (n=4), round atelectasis, a bronchogenic cyst, chronic non-specific infection (n=3), an inflammatory pseudotumor (Figure 2), aspergillosis (n=2), granuloma (n=2), *Echinococcus granulosus*, pneumonia, hamartoma, and fibrosis (Table 1). The mean SUV_{max} of the benign lesions was 3.3±1.5 (range 0.2-7) mm and the mean diameter of these lesions was 18.2±6 (range: 10 to 29) mm. There were 10 false positive results including tuberculosis (n=2), chronic non-specific infection (n=3), granuloma (n=1), pneumonia (n=1), inflammatory pseudotumor (n=1), and missing follow-up data (n=2).

The difference between the SUV_{max} values of the lesions, size of the lesions, and ages of the patients with and without malignancy were statistically significant ($p=0.004$, $p=0.001$, and $p=0.29$, respectively). Additionally, all of the patients with malignant tumors were female in this group and only one of the male patients had malignant lesions.

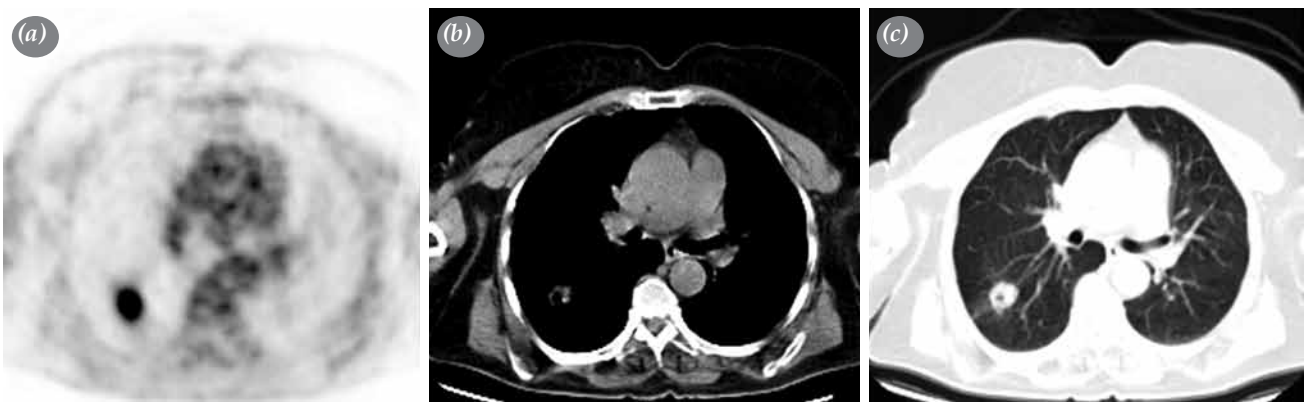

Figure 1. (Patient 12; 63 years old, female) Axial slice positron emission tomography **(a)**, CT in soft tissue window **(b)** and in lung window **(c)** images showing a hypermetabolic lesion in the lower lobe of the right lung in 22 mm diameter (SUV_{max}: 5.60). After lobectomy, the diagnosis was reported as an adenocarcinoma.

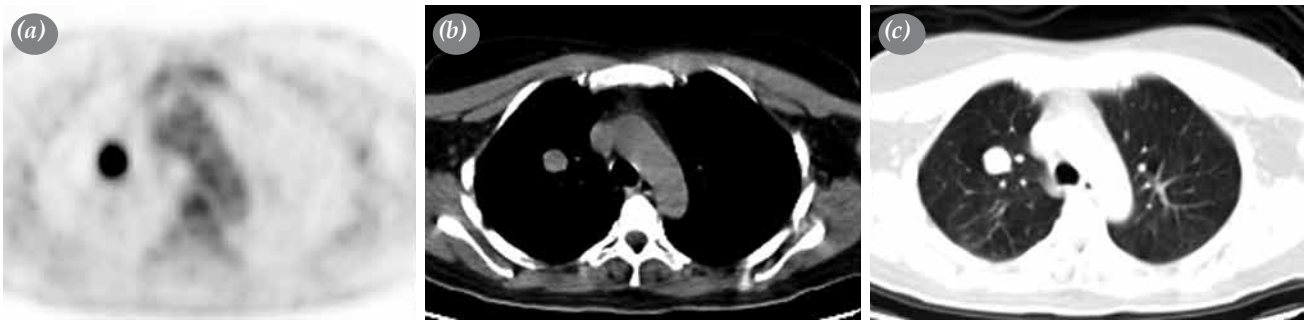

Figure 2. (Patient 13; 45 years old, female) Axial slice positron emission tomography **(a)**, CT in soft tissue window **(b)** and in lung window **(c)** images showing an increased FDG accumulation in the lesion in right upper lobe in 24 mm diameter (SUV_{max}: 6.17). After wedge resection, the diagnosis was reported as an inflammatory pseudotumor.

Using a cut-off value for SUV_{max} of 2.5, the sensitivity, specificity, accuracy, and positive and negative predictive values of the ^{18}F-FDG PET/CT were 91%, 63%, 71%, 50% and 94%, respectively.

DISCUSSION

The most of the histopathological results of SPNs were adenocarcinomas in our study group consisting of non-smoker and female patients. This result was particularly anticipated, since one of the previous studies showed that non-smoker patients with SPNs ended up to be adenocarcinomas in the histopathological analysis.[11] In the present study, ^{18}F-FDG accumulation was observed in most of the patients with malignant pulmonary nodules, which was not expected, as most of the nodules were adenocarcinomas and particularly some subtypes of adenocarcinomas were not FDG-avid.[4] In our study, the sensitivity and negative predictive value of PET/CT in non-smoker SPNs were extremely high. The specificity and positive predictive value of the test were low, which probably was a consequence of the high prevalence of granulomatous diseases in Turkey. In a study, Huang et al.[12] introduced dynamic PET imaging to improve specificity of the test and concluded that, although SUV_{max} values of the granulomatous lesions were similar with malignant tumors, different scores might be achieved to differentiate them with malignant ones using this imaging technique.

In our study, there were 10 false positive results including tuberculosis (n=2), chronic non-specific infection (n=3), granuloma (n=1), pneumonia (n=1), inflammatory pseudotumor (n=1), and there were two patients without data. In a previous study, nearly half of the false positives results were disclosed as tuberculosis.[13] Although some of the lesions with an increased tracer accumulation would not be necessarily malignant, every FDG positive nodule requires further analysis by biopsy.[14] Of note, all patients in this study were referred for PET/CT examination due to positive findings in the initial CT imaging. Therefore, the number of false positivity may have increased, due to this protocol.

According to the previous reports, the prevalence of malignancy increases with increasing diameters which may be seen in 64 to 82% of the cases with nodules up to 2 cm in diameter.[8] In a recent study, it has been suggested that, in lesions smaller than 1 cm, PET/CT results may be unsatisfactory.[15] In our study, there were only three patients with small nodules (≤10 cm) who did not undergo operation and follow-up. However, in our study group, although the patients with malignant nodules had an advanced age and SUV_{max} values were higher than the benign ones, the diameters of the malignant and benign nodules were not statistically significantly different. This may be a characteristic of our selected patient population of non-smokers. According to the guidelines, if the probability of malignancy is not high (5 to 60%) and the nodule is indeterminate and larger than 8 to 10 mm in diameter, ^{18}F-FDG PET/CT scan is recommended.[16] The diagnostic accuracy of PET/CT is also close to invasive procedures such as CT-guided needle biopsy.[17] Additionally, diagnostic performance of PET/CT is higher than those of CT or PET alone.[10] Although there are limited number of comparative studies on the diagnostic performance of CT versus PET/CT in SPNs, one of the studies has shown that ^{18}F-FDG PET/CT is superior to CT alone in nodules smaller than 1.5 cm, proving that it is the most optimal diagnostic method in characterization of small nodules.[10] In our study, there were seven patients with SPNs smaller than 1.5 cm which had a SUV_{max} value above 2.5 in three (who had negative follow-up results in one, tuberculosis in one, and adenocarcinoma in one) and below 2.5 in four

Table 1. The characteristics of the lesions

Patients	Age/Gender	Location	Diameter (mm)	$SUV_{max.}$	Diagnosis criteria	Histopatological diagnosis
1	65/F	Right middle lobe	15	1.13	Follow-up	No
2	40/F	Right upper lobe	14	1.88	Wedge resection	Tuberculosis
3	67/F	Right middle lobe	10	2.74	Follow-up	No
4	63/F	Right lower lobe	20	2.39	Transthoracic biopsy	Round atelectasis
5	54/F	Left lower lobe	15	2.01	Follow-up	No
6	57/F	Left lower lobe	28	2.26	Wedge resection	Bronchogenic cyst
7	68/F	Right lower lobe	20	4.21	Transthoracic biopsy	Granuloma
8	48/F	Left lower lobe	15	5.09	Lobectomy	Chronic nonspecific infection
9	71/F	Left lower lobe	27	6.48	Transthoracic biopsy	Adenocarcinoma
10	82/F	Right upper lobe	23	6.13	Lobectomy	Adenocarcinoma
11	81/F	Left upper lobe	21	7.95	Lobectomy	Adenocarcinoma
12	63/F	Right lower lobe	22	5.60	Lobectomy	Adenocarcinoma
13	45/F	Right upper lobe	24	6.17	Wedge resection	Inflammatory pseudotumor
14	81/F	Left lower lobe	28	12.21	Transthoracic biopsy	Squamous cell cancer
15	84/F	Right upper lobe	27	2.68	Lobectomy	Adenocarcinoma
16	79/F	Right lower lobe	26	10.39	Transthoracic biopsy	Adenocarcinoma
17	66/F	Left lower lobe	28	15.07	Transthoracic biopsy	Adenocarcinoma
18	83/F	Right upper lobe	28	2.24	Transthoracic biopsy	Adenocarcinoma
19	66/F	Left upper lobe	12	3.78	Wedge resection	Tuberculosis
20	60/F	Left upper lobe	27	4.02	Wedge resection	Tuberculosis
21	65/F	Right upper lobe	28	3.65	Transthoracic biopsy	Chronic nonspecific infection
22	58/F	Left upper lobe	8	0.24	Follow-up	No
23	46/M	Left lower lobe	18	1.53	Wedge resection	Aspergillosis
24	70/M	Right lower lobe	23	0.49	Follow-up	No
25	82/M	Right upper lobe	18	1.16	Follow-up	No
26	56/M	Right upper lobe	21	6.89	Follow-up	No
27	68/M	Right lower lobe	17	2.76	Transthoracic biopsy	Chronic nonspecific infection
28	62/M	Right upper lobe	20	1.75	Transthoracic biopsy	Granuloma
29	23/M	Left lower lobe	27	2.46	Wedge resection	Echinococcus granulosus
30	54/M	Left upper lobe	12	2.09	Wedge resection	Hamartoma
31	40/M	Right upper lobe	24	0.97	Transthoracic biopsy	Fibrosis
32	62/M	Right upper lobe	16	0.99	Transthoracic biopsy	Aspergillosis
33	48/M	Right lower lobe	18	2.39	Follow-up	No
34	41/M	Left lower lobe	29	2.30	Transthoracic biopsy	Tuberculosis
35	59/F	Right lower lobe	25	2.80	Follow-up	No
36	84/M	Right upper lobe	22	12.10	Transthoracic biopsy	Adenocarcinoma
37	61/F	Right lower lobe	10	0.48	Follow-up	No
38	73/F	Right lower lobe	14	6.75	Lobectomy	Adenocarcinoma

SUV_{max}: Standardized uptake value maximum.

patients (which confirmed to be tuberculosis in one and who had negative results in three). In another study, the diagnostic efficacy of FDG PET/CT and quantitative first-pass 320 detector row perfusion CT were compared in discrimination of malignant and benign pulmonary nodules and concluded that CT had potential to be more specific and accurate.[12] In our study, the specificity of PET/CT was low; however, if the PET/CT imaging had not been performed, most of the patients had been undergone unnecessary surgery due to pulmonary nodules.

To date, additional methods to improve the diagnostic utility of PET/CT in determining malignancy have been introduced, such as late-phase or dual-time imaging or additional evaluation of non-attenuation corrected images, which have been shown to be helpful in certain circumstances.[18,19] Another recent approach is the additional inspiration CT application which becomes a preferable method in routine practice of many centers.[20] Visual comparison with mediastinal blood pool activity with activity of the lesion is a standard approach[21,22] and SUV_{max} values above 2.5 are accepted as a malignancy, that is the reason why we used this cut-off value. Respiratory gated imaging has also improved the detectability of the SPNs particularly in small lesions.[23] However, as only three of our patients had small nodules, we did not perform an additional imaging method in these patients. Additional late-phase imaging may have provided data regarding granulomatous diseases and increased false positive results in our study.

The CT characteristics of all our patients included solid lesions without calcification. However, there was a classical CT appearance of the patients without smoking history and adenocarcinoma as the histopathological type showing the pattern. In our patients, we did not observe this CT pattern, possibly due to the larger diameter of the tumors. Previous studies showed that localized GGA was not present in patients with advanced lung cancer.[11] Although all of our patients presented with only SPNs, the nodule diameters were not small (mean: 20±6 mm). A previous case report documented that an adenocarcinoma might present in any CT character, which was a cystic lesion in a young non-smoker patient.[24]

Nonetheless, the major limitation of the present study is its retrospective design. Also, additional interventions such as late-phase imaging during the PET/CT examination were unable to be performed, which are shown to improve the specificity of the test. In addition, lack of the previous contrast-enhanced CT scans hampers the correlation of the results. The number of the male patients was also low; however, as women are more subjected to passive smoking by their husbands in our population, the majority of our patients with SPNs were women. Non-smoker patients warrant further prospective studies to understand the characteristics of the tumors related to passive smoking. This group of patients are often neglected to inform about the risks of passive smoking and their number has been increasing, leading to an important public health problem. In their study, Barkley and Green[25] demonstrated that bronchioloalveolar carcinomas (a subtype of adenocarcinoma) were associated with being non-smoker and female gender. Grover et al.[26] also reported that bronchoalveolar carcinomas were related to non-smoking, although female sex was not found to be associated. In another study, Kosaka et al.[27] showed that epidermal growth receptor mutations were associated with bronchioloalveolar carcinomas in non-smoker male patients. The accuracy of PET, PET/CT, and high-resolution CT in bronchioloalveolar carcinomas was found to be 36.6%, 93.3%, and 93.3%, respectively.[28] In the present study, we performed PET/CT to all patients. However, we found no significant correlation between the female sex, non-smoking status, and adenocarcinomas. In general, no further evaluation is considered necessary in non-smokers with pulmonary nodules, as previously reported. Additionally, as there is no evidence regarding pulmonary nodules of non-smokers, we are unable to compare our findings with previous data. Therefore, further large-scale, prospective studies are warranted on this subject.

In conclusion, the histopathology of the solitary pulmonary nodules is generally adenocarcinomas in non-smoker patients and ^{18}F-FDG PET/CT is highly sensitive method in the identification of malignancy in these lesions. Based on our study results, negative predictive value of the test is extremely high, although most of the pathologies are adenocarcinomas. However, false positive results can be anticipated due to the presence of granulomatous lesions.

Declaration of conflicting interests

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