The role of FDG-PET in the evaluation of solitary pulmonary nodules

Soliter pulmoner nodüllerin değerlendirilmesinde flor-18-deoksiglukoz pozitron emisyon tomografisinin rolü

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Background: We investigated the clinical role of fluorine-18-deoxyglucose positron emission tomography (FDG-PET) in the initial management of patients with an indeterminate solitary pulmonary nodule (SPN).

Methods: A total of 158 patients (83 males, 75 females; mean age 64 years; range 32 to 91 years) underwent FDG-PET to reveal the metabolic activity of an SPN, <3 cm in size, incidentally detected on a chest X-ray or computed tomography. The findings were correlated with those of *(i)* histology after lobectomy in 43 patients (27.2%) and transthoracic or open biopsy in 97 patients (61.4%), *(ii)* bronchial washing in two patients (1.3%), or *(iii)* clinical follow-up for a period of time not less than six months in 16 patients (10.1%).

Results: Malignancy was documented in 119 nodules (75.3%), being primary lung cancer in 115, and metastatic lesions in four patients. FDG-PET revealed malignant disease successfully in 115 patients. PET scanning was false positive in four patients whose definitive diagnoses were histoplasmosis, granuloma, tuberculosis, and histiocytosis with organizing pneumonia, respectively. FDG-PET was also concluded to be false positive in two patients because no malignancy was noted histologically after performing transthoracic needle-aspiration biopsy. FDG-PET yielded a true negative result in 33 patients. It was false negative in four patients with bronchoalveolar carcinoma (n=2) and adenocarcinoma (n=2). The sensitivity, specificity, negative-positive predictive value, and accuracy of FDG-PET were 96.6%, 84.6%, 89.2%-95.0% and 93.7%, respectively.

Conclusion: In the evaluation of an indeterminate SPN, FDG-PET can be used as a noninvasive diagnostic alternative with no risk or complications, that may otherwise necessitate more invasive surgical interventions.

Key words: Diagnosis, differential; fluorodeoxyglucose F18/diagnostic use; lung neoplasms/diagnosis/imaging; tomography, emission-computed.

Amaç: Bu çalışmada niteliği belirsiz tek akciğer nodülü olan hastaların ilk müdahalelerinde fluorine-18-deoksiglukoz pozitron emisyon tomografisinin (FDG-PET) klinik rolü araştırıldı.

Çalışma planı: Çalışmaya alınan 158 hastaya (83 erkek, 75 kadın; ort. yaş 64; dağılım 32-91) akciğer grafisi veya bilgisayarlı tomografide tesadüfen saptanan tek akciğer nodülünün (büyüklük <3 cm) metabolik aktivitesinin belirlenmesi amacıyla FDG-PET yapıldı. Bulgular, 43 hastada (%27.2) lobektomi, 97 hastada (%61.4) transtorasik veya açık biyopsi sonrası histopatolojik inceleme; iki hastada (%1.3) bronşiyal yıkama; 16 hastada (%10.1) da altı aydan az olmamak kaydıyla takip sonrası elde edilen klinik bulgular ile karşılaştırıldı.

Bulgular: Hastaların 119'unda (%75.3) malignite saptandı (115 hastada primer akciğer kanseri, birer hastada kolon kanseri, non-Hodgkin lenfoma, larinks karsinomu ve timoma metastazı). FDG-PET görüntülerinde 121 hastada aktif bir odak izlendi, bunların 115'i gerçek pozitif idi. Altı hastada sonuç yanlış pozitif idi. Bunların dördünde tanı histoplasmosis, tüberküloz, granüloma ve organize pnömonili histiositosis iken, iki hastada uygulanan transtorasik iğne biyopsisinde maligniteye rastlanmadı. Otuz üç hastada FDG-PET ile gerçek negatif sonuç alındı. Bronkoalveoler karsinom ve adenokarsinom tanılı ikişer hastada yanlış negatif sonuç alındı. Bu sonuçlara göre FDG-PET'nin duyarlılık, özgüllük, pozitif-negatif öngördürücü ve doğruluk oranları sırasıyla %96.6, %84.6, %89.2-%95.0 ve %93.7 olarak hesaplandı.

Sonuç: Tek akciğer nodülünün değerlendirilmesinde FDG-PET, malignitenin öngörülmesi ve gereksiz cerrahi girişimlerden kaçınılmasında yararlı, invaziv olmayan, herhangi bir risk ya da komplikasyon taşımayan bir işlemdir.

Anahtar sözcükler: Tanı, ayırıcı; florodeoksiglukoz F18/tanısal kullanım; akciğer neoplazileri/tanı/radyonüklid görüntüleme; bilgisayarlı tomografi, emisyon.

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A solitary pulmonary nodule (SPN) is defined as a single, well-circumscribed, round or oval radiographic opacity of less than 3 cm in size. The lesion is surrounded by normal aerated lung and there is no hilar enlargement, pleural effusion, or atelectasis.[1] Most nodules are detected incidentally in 1/500 of chest radiographs or computed tomograms, and 15% to 75% of such nodules have been found malignant depending on the population investigated.[2,3] The most common underlying etiology is primary lung carcinoma and benign granuloma which accounts for over 80% of all pulmonary nodules.[4] Computed tomography (CT) findings suggestive of malignancy are thickness of the cavity wall and the presence of speculated or nodular edge, whereas central, laminated, or diffuse calcifications are more likely to be related to a benign etiology.[5] Radiological findings are not helpful enough to avoid invasive diagnostic procedures in the evaluation of an SPN as calcifications are rarely seen in such lesions. Thus, a noninvasive and accurate diagnostic test in the initial evaluation of an SPN would contribute to defining diagnostic strategies that would avoid unnecessary morbidity and reduce costs.

In 1930s, it was shown that malignant cells exhibited increased glucose metabolism.[6] Fluorine-18-deoxyglucose (FDG) can neither proceed to the upper metabolic pathways of glucose nor exit the cell after phosphorylation to FDG-6-PO4. It remains trapped within the tumor cell and comparable enhancements of FDG accumulation in malignant cells may predict malignancy.[7] It was reported that positron emission tomography (PET) using FDG (FDG-PET) might prove to be an accurate procedure in differentiating benign from malignant lesions detected in the lung.[8,9] In this study, we evaluated the clinical role of FDG-PET in the evaluation of patients with an indeterminate solitary lesion in the lung of less than 3 cm in size.

PATIENTS AND METHODS

Patients. The study included 158 patients (83 males, 75 females; mean age 64 years; range 32 to 91 years), in whom an SPN was detected in Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, USA, between 1994 and 1998. The nodules were incidentally detected on chest radiograms obtained for other reasons (dyspnea, chest pain, cough, preoperative X-ray, etc.) and on computed tomograms obtained for further evaluation of patients with pulmonary or extrapulmonary cancer.

Inclusion criteria for the nodules were as follows: a single lesion greater than 7 mm and smaller than 3 cm with normally aerated peripheral lung parenchyma, round or oval shape, no sign of benign or malignant disease, and absence of any hilar/mediastinal lymph node enlargement. All medical records were reviewed to obtain data about age, gender, history of malignancy, pathology, and the last date of radiological and clinical follow-up.

FDG-PET imaging. FDG-PET was performed using a dedicated system (ECAT EXACT; Siemens-CTI, Knoxville, TN, USA) in two-dimensional mode, 5 to 7 min per bed position, 45 to 60 minutes after intravenous injection of approximately 370 MBq of FDG. The patients fasted for at least four hours and a blood check was made prior to each FDG-PET. Diabetics and patients with a blood glucose concentration ≥140 ng/ml were excluded. The patients were placed in the supine position in the gantry with their arms above their heads and a 2-minute transmission scan was performed with a rotating Ge-68/Ga-68 rod source for attenuation correction immediately after a series of three to five overlapping emission images. Prior to FDG-PET, approximately 1,500 ml normal saline was slowly infused intravenously -if not contraindicated otherwise- to ensure adequate clearance of radioactivity and minimize pelvic stasis in the kidney that might obscure image quality in the upper abdomen.

FDG-PET images were reconstructed with filtered back-projection using a Hanning filter (frequency cut-off 0.6 x Nyquist value). Emission images were recorrected for measured attenuation using a local threshold for segmented attenuation. Images were displayed in three orthogonal projections and whole-body maximum pixel re-projection images for visual analysis. Images were reviewed by two qualified nuclear medicine physicians without any clinical or histological knowledge of the patients. The lesion in the lung was interpreted as benign or malignant depending on the intensity of the FDG uptake. If no focal FDG uptake was noted in the area known to have the SPN the interpretation was in favor of benign etiology. It was classified as malignant if FDG accumulation in the lesion was greater than that of the surrounding lung parenchyma and mediastinum. Final decision was based on the findings obtained from histopathology and clinical follow-up. The solitary nodule in the lung was classified as benign if no change in size was noted after a follow-up period of not less than six months on repeated CT scans.

RESULTS

Malignancy was documented in 119 nodules (75.3%), being primary lung cancer in 115, and metastatic lesions from colon carcinoma, non-Hodgkin lympho-

Table 1. FDG-PET results and final diagnoses of the SPNs according to the operation notes, histopathology and clinical follow-up

Final diagnosis	True positive	False positive	True negative	False negative
Adenocarcinoma	46			2
Non-small cell lung cancer	22			
Squamous cell carcinoma	26			
Bronchoalveolar carcinoma	12			2
Small cell carcinoma	3			
Large cell carcinoma	2			
Colon carcinoma	1			
Non-Hodgkin lymphoma	1			
Larynx carcinoma	1			
Thymoma	1			
Histoplasmosis		1	1	
Granuloma		1	5	
Hystiocytosis and pneumonia		1	1	
Biopsy (–)		2	8	
Follow-up			16	
Tuberculosis		1	1	
Fibrous tissue			1	
Total	115	6	33	4

ma, larynx carcinoma, and thymoma in four patients, respectively (Table 1). The lesion size differed 0.8 cm to 3 cm as that measured on CT images. A definitive diagnosis was achieved by surgical intervention, including lobectomy in 43 (27.2%), transthoracic aspiration (TTNA) in 97 (61.4%), bronchial washing in two (1.3%), and follow-up in 16 (10.1%) patients. FDG-PET imaging revealed malignant disease successfully in 115 patients. PET scanning was false positive in four patients whose definitive diagnoses were histoplasmosis, granuloma, tuberculosis, and histiocytosis with organizing pneumonia, respectively. FDG-PET was also assumed to be false positive in two other patients because no malignancy was noted histologically after performing transthoracic needle-aspiration biopsy (TTNAB). FDG-PET yielded true negative results in 33 patients confirmed by histological diagnosis and radiological follow-up. It was false negative in four patients whose definitive diagnoses were bronchoalveolar carcinoma (n=2) and adenocarcinoma (n=2). The sensitivity, specificity, negative-positive predictive value, and accuracy of FDG-PET were 96.6%, 84.6%, 89.2%-95.0% and 93.7%, respectively.

DISCUSSION

Determining the nature of an SPN is a challenge as up to 75% of the lesions might be malignant (Fig. 1). Nodule evaluation usually begins with a careful review of the patient characteristics including age, history of any previous malignancy, smoking, size and the edge of the lesion as well as the presence of any calcification inside the nodule. It has been reported that advanced age, history of smoking, and the presence of a prior malignancy are the most common additional factors associated with an increased likelihood of malignancy. Radiographic findings such as thickness of the cavity wall, lesion size >3 cm, and the speculated nodule edge are suggestive of malignancy, while a benign etiology is likely if a central, laminated, or diffuse pattern of calcification is evident in the lesion.[10] The observation with repeated radiographs is also useful as the doubling time for a malignant nodule rarely exceeds two years and the stability of the lesion for a certain period of time strongly suggests a benign etiology. It should be noted that, in some cases, doubling time might exceed two years and the underlying etiology in the lesion cannot be predicted with chest radiographs or CT as in bronchoalveolar carcinoma presenting as ground-glass opacity on CT images.[11] In our study the minimum time period for surveillance was six months. Since chest radiographs or CT fail to reveal the underlying etiology, an accurate and noninvasive test is needed for the evaluation of SPNs.

Invasive procedures in the management of SPNs include fiberoptic bronchoscopy, TTNAB, video-assisted thoracoscopy, and thoracotomy with their respective risks and benefits. The sensitivity of bronchoscopy including bronchial washing and brushing is approximately 65% in detecting malignancy and its sensitivity increases up to 79% with transbronchial biopsy especially for centrally located lesions.[12] CT-guided TTNAB is the preferred procedure for peripheral lesions

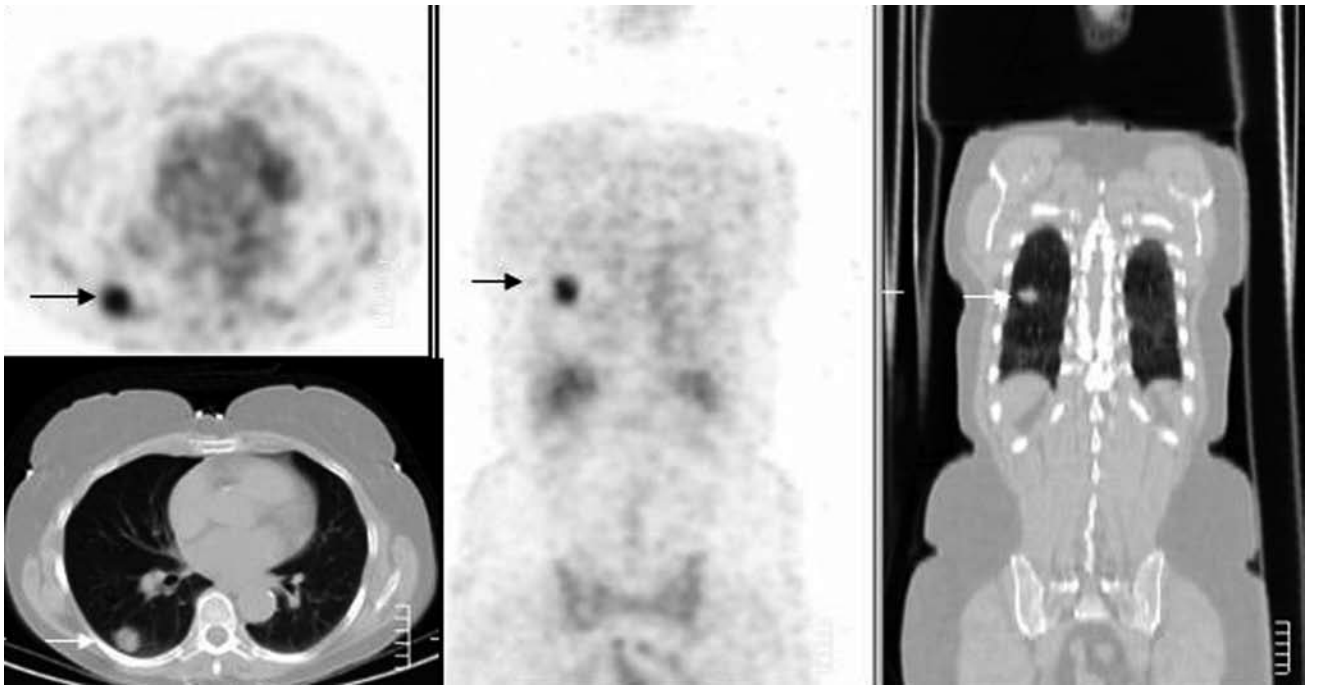

Fig. 1. A solitary pulmonary nodule was detected incidentally by CT in the right lung (white arrow) in a 56-year-old female. The lesion was FDG-avid (black arrow) and the final diagnosis was made as adenocarcinoma after transthoracic lung biopsy. There was no hilar enlargement or metastasis elsewhere and FDG-PET was useful for initial staging of the patient.

with sensitivity and specificity rates ranging from 85% to 90% and 91% to 96%, respectively. However, both methods are invasive presenting a relatively high risk of pneumothorax (24.5%) and bleeding following transbronchial and transthoracic procedures. Moreover, it has been emphasized that the likelihood of malignancy cannot be ruled out with a negative cytology.[13,14] Thoracotomy and open lung resection are more invasive procedures increasing morbidity and cost in the work-up of an SPN.

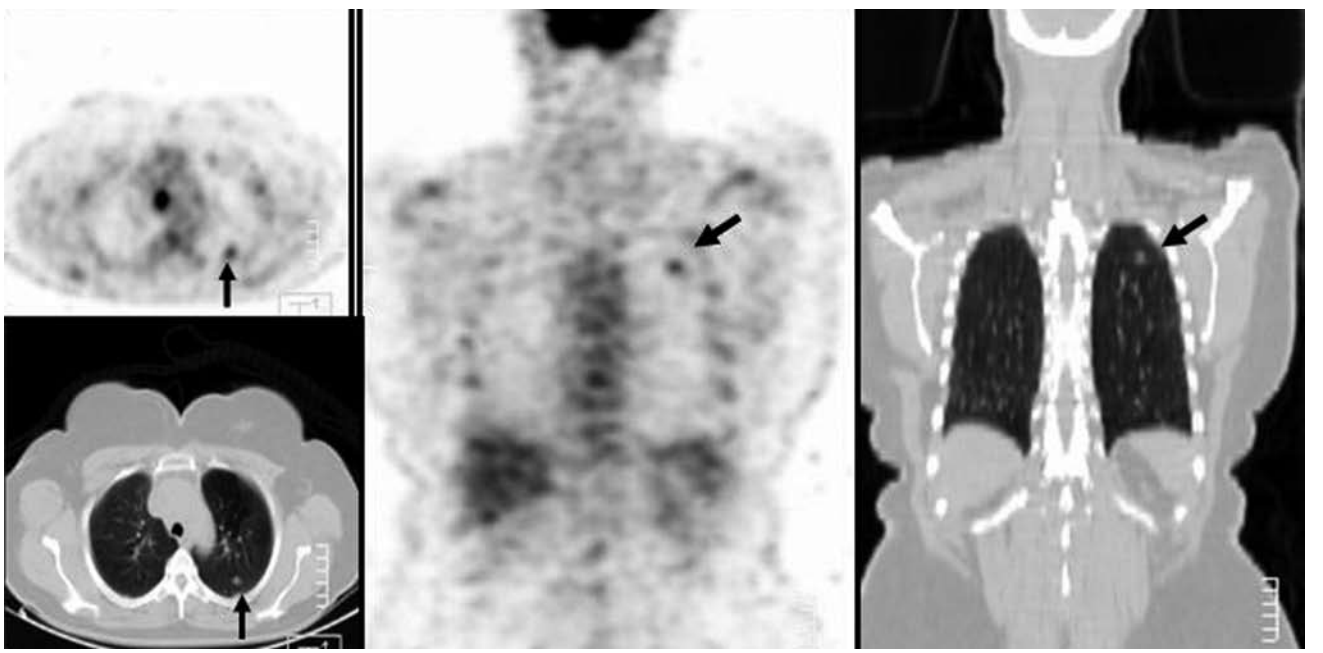

Fig. 2. In a 38-year-old female patient with left breast cancer, a solitary pulmonary nodule was detected on FDG-PET and CT images in posterior upper localization of the left lung (black-arrow). Initially, the patient was thought to have developed metastasis as she had already a primary cancer; however, the final diagnosis was tuberculoma following partial lung resection.

In this study, we investigated the value of FDG-PET in the evaluation of patients with an SPN. Sensitivity and specificity rates of this procedure were reported to be 83% to 97% and 69% to 100%, respectively. An abnormal FDG-PET in the group of patients represented an increased likelihood ratio (LR) for malignancy, while a negative scan had a very low LR suggesting that the nodule was benign.[8,11,15] In our study, the sensitivity and specificity of FDG-PET were 96.6% and 84.6%, respectively. Malignancy rate was 75.3% in our group, which was relatively higher than that reported in some other studies.[2,3] This might be related to selection bias as we excluded the patients with a nodule size of less than 8 mm, considering the limited resolution of the procedure. In a study by Lowe et al.[7] the sensitivity of FDG-PET decreased as the lesion size decreased and the detection rate of malignancy was only 44% in the subgroup of patients with a SPN <15 mm, while the overall rate of detection was 67%.

Fluorine-18-deoxyglucose uptake is not solely specific for malignancy, which is one major disadvantage of the technique.[16] Granulomatous lesions such as tuberculosis or sarcoidosis and infectious/inflammatory lesions may cause false positive results in FDG-PET. In our study, there were six false positive cases, in four of which the diagnoses were histoplasmosis, granuloma, tuberculosis, and histiocytosis with organizing pneumonia, respectively (Fig. 2). In two other patients with a positive FDG-PET, the underlying etiology was assumed as benign as no malignancy was demonstrated with cytology after TTNAB. Potential errors resulting from biopsy sampling were likely to be small, because multiple cuts through the nodule were attempted.

It was reported that dual-time point FDG-PET, first described for head and neck malignancies, might be useful in differentiating benign from malignant lung nodules.[17,18] The authors reported that malignant tumor cells exhibited an average increase up to 12% in the standardized uptake value (SUV) between the first and second scans, while the uptake by inflammatory lesions remained relatively stable over time.[17] The SUV changes in tumors were greater when the time interval between the first and second studies exceeded 30 minutes.

FDG-PET failed to show malignancy in four patients (bronchoalveolar carcinoma in two, well-differentiated adenocarcinoma, and papillary adenocarcinoma). It was reported that the sensitivity of FDG-PET in detecting malignancy decreased as cellu-

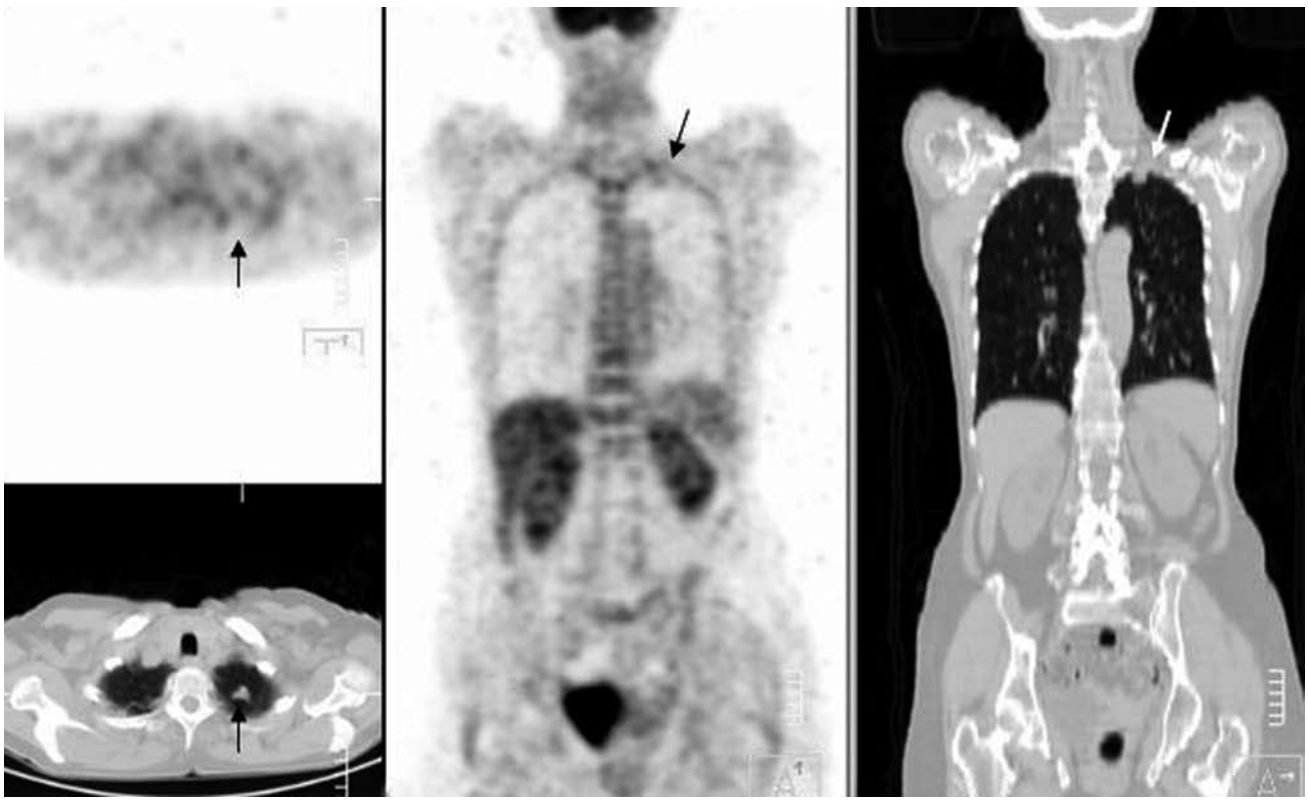

Fig. 3. A non-FGD avid solitary nodule in the upper left lung (long arrow) in a 28-year-old male patient. No difference was noted in size in repetitive CT scans with an interval of more than a year. Invasive procedures such as transthoracic biopsy and wedge-resection are not justified in such lesions as the negative predictive value of PET is high and the etiology is almost always benign.

lar FDG uptake and glucose metabolism of the lesion decreased. For example, the sensitivity of PET was only 33% for pure bronchoalveolar lesions, as reported by Yap et al.[19] Similarly FDG-PET might yield a false negative result in well-differentiated adenocarcinoma, particularly for the nodules of ground-glass opacity seen on CT.[20] FDG-PET was true negative in 33 patients (Fig. 3). Considering a negative predictive value of 89.2% with FDG-PET in our study, we recommend a conservative management strategy for the benefit of the patients.

Fluorine-18-deoxyglucose uptake by the lesions can be evaluated in several ways such as SUV assessment, visual assessment, and relative uptake compared to a normal organ. It has been reported that SUV assessment depends on a variety of factors including the body size, blood glucose concentration, acquisition time after FDG injection, lesion size, methodology of image reconstruction, level of noise, resolution, and selection the area of region of interest. Visual assessment comparing the FDG uptake in the lesion to that of normal mediastinal activity is the simplest way for image interpretation and it has been reported that semi-quantitative image interpretation contributes less to the accuracy of the study.[21-25] In our study, we performed visual analysis in the evaluation of FDG-PET.

In conclusion, an abnormal FDG uptake in an SPN predicts an increased likelihood of malignancy, while a negative scan strongly suggests a lesion of benign etiology. In the evaluation of an indeterminate SPN, FDG-PET can be used as a noninvasive diagnostic alternative with no risk or complications, that may otherwise necessitate more invasive surgical interventions.

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