Original Article

18F-fluorodeoxyglucose positron emission tomography/computed tomography in the diagnosis of benign pulmonary lesions in sarcoidosis

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Background: Many benign pulmonary lesions, especially sarcoidosis, are metabolically active and are indistinguishable from lung cancer using 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) imaging. This study sought to analyze the 18F-FDG PET/CT imaging features of benign pulmonary lesions and to improve the differential diagnosis of benign pulmonary lesions by 18F-FDG PET/CT imaging.

Methods: One hundred and thirteen patients with benign pulmonary lesions were studied retrospectively. Each patient underwent an 18F-FDG PET/CT scan. All cases were identified by pathology, diagnostic therapy or follow-up. The maximum standardized uptake value (SUVmax) was calculated for each pulmonary lesion.

Results: According to the final results, the benign pulmonary lesions were classified as inflammatory lesions (n=77) and granulomas (n=36) by histopathological diagnoses. The SUVmax of inflammatory lesions and granulomas were both high (4.55±2.77 and 6.81±3.96, respectively; $P<0.05$). When the benign pulmonary lesions were classified by clinical diagnoses, the SUVmax of sarcoidosis was significantly different from other diseases (15.12±5.67; $P<0.01$)

Conclusions: Inflammatory lesions and granulomas show moderate or high FDG uptake on 18F-FDG PET/CT, but granulomas have higher values. 18F-FDG PET/CT appeared to have a higher SUVmax for the differential diagnosis of sarcoidosis and benign pulmonary lesions.

Keywords: 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET); standardized uptake value (SUV); pulmonary

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Introduction

18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) has been shown to be an accurate, noninvasive imaging modality for differentiating benign from malignant pulmonary lesions. Compared with classical methods of imaging, a PET/CT scan shows not only the morphology but also the metabolism of the suspicious lesions.

However, increased uptake of 18F-FDG may also represent nonneoplastic infectious lesions, which is connected with excessive activity of macrophages and neutrophils in the tissues (1). Some of the benign lung lesions may appear as false positives, because 18F-FDG

is nonspecific tumor imaging agent. If the morphological appearance of the lesion is not typical, it can be difficult to diagnose, and there may be the possibility of the misdiagnosis of lung cancer.

The objective of this study was to analyze the uptake characteristics of benign pulmonary lesions on 18F-FDG PET/CT imaging and to assess the usefulness of PET/CT in the evaluation of benign pulmonary lesions to improve the diagnosis and differential diagnosis of benign pulmonary lesions.

Methods

Patients

This study was approved by the Institutional Ethics Board of Jinling Hospital (No. DBNJ005), and the requirement for patient informed consent was waived.

Patients with pulmonary nodules or masses referred to Jinling Hospital for 18F-FDG PET/CT imaging from January 2010 to May 2017 were retrospectively evaluated.

The study group included 113 patients (75 men and 38 women). All cases were proven to be benign pulmonary lesions by pathology or diagnostic therapy. Histological or cytological examination of the biopsy specimens obtained from bronchoscopy and percutaneous lung puncture was performed.

18F-FDG PET/CT imaging acquisition

18F-FDG PET/CT images were obtained using a Discovery ST PET/CT scanner (General Electric, USA) equipped with high-resolution bismuth germinate detectors and a 16-slice CT scanner. All patients fasted for at least 6 h before 18F-FDG PET/CT examinations, and their blood glucose was documented as below 8 mmol/L before receiving the 18F-FDG injection. According to weight, the patients received intravenous injections of the imaging agent 18F-FDG 3.70–4.44 MBq/kg. A low-dose unenhanced CT scan was performed before PET imaging to provide attenuation correction by a standard protocol using 120 kV, 150 mAs, a tube-rotation time of 0.8 s per rotation, and a pitch of 3.75 mm. The cross-sectional sinogram data were corrected for dead time, decay, random coincidences, and attenuation.

Image analysis

The uptake of 18F-FDG in lesions was based on semiquantitative analysis and the visual comparison method to make a comprehensive judgment. Semiquantitative analysis was performed by using the maximum standardized uptake value (SUVmax) corrected by lean body mass (LBM).

The specific method was to set the region of interest (ROI) at the location of the lung lesions. The system automatically measured the SUVmax of the lesions. The size of the lesion was expressed by maximum diameter (2).

Statistical analysis

SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA) was used for all analyses. The data of the continuous variables were expressed as mean ± SD. ANOVA single factor variance analysis and the Kruskal-Wallis test were used to compare the uptake of different pathological lesions. Pairwise comparison of the areas under receiver operating characteristic (ROC) curves (AUC) for the parameters used to diagnose sarcoidosis lesions was made to determine significant differences. The determination of cut-off values was based on an acceptable value of sensitivity (>80%) and the Youden index in ROC analysis, which is the sum of sensitivity and specificity minus 1 (3). A P value less than 0.05 was considered to indicate a statistically significant difference.

Results

One hundred and thirteen patients (75 men and 38 women) with benign pulmonary lesions, whose mean age was 58.57±12.85 years, were evaluated. The average diameter of the 113 pulmonary lesions was 3.49±1.84 cm (range, 0.14–10.8 cm), and they were measured along their greatest diameter for the CT images. According to its pathological type, pulmonary lesions can be divided into two broad categories: inflammatory lesions and granulomatous lesions. There were 77 cases of inflammatory lesions and 36 cases of granulomatous lesions. The values of SUVmax were significantly higher in granulomatous lesions compared with inflammatory pulmonary lesions, while age, gender, size, average diameter and smoking history did not reflect such differences (*Table 1*).

The histopathologic diagnoses subcategories of the 113 lesions are shown in *Table 2*. Neutrophil-based inflammation was the most common inflammatory lesion (38/77, 49%), and tuberculosis was the most common granulomatous lesion (25/36, 69%). There were 24 lymphocytic-based lesions, accounting for 21% of the total. In the

Table 1 The age, gender, size and SUVmax by 18F-FDG PET/CT imaging of the inflammatory and granulomatous pulmonary lesions

Clinical features	Inflammation and infection	Granuloma	P value
Age, years	60.03±11.18	56.81±15.24	0.263
Gender			0.636
Male [%]	50 [44]	25 [22]	
Female [%]	27 [24]	11 [10]	
Smoking history			0.887
Never [%]	34 [30]	17 [15]	
Ex or current [%]	43 [38]	19 [17]	
Size (cm)	3.47±1.78	3.84±1.88	0.294
18F-FDG PET SUVmax	4.55±2.77	6.81±3.96	0.001

SUVmax, the maximum standardized uptake value; 18F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography.

Table 2 The histopathological diagnoses of the 113 benign pulmonary lesions and values of SUVmax

Classification	Number of patients [%]	SUVmax*	The mean rank SUVmax
Inflammation and infection			
Neutrophil predominant	38 [34]	5.81±2.37	62.92
Lymphocyte predominant	24 [21]	2.03±1.57	20.15
Inflammatory pseudotumor	8 [7]	6.54±2.72	64.63
Interstitial pneumonia	7 [6]	4.51±1.97	49.64
Total	77 [68]		
Granuloma			
Tuberculosis	25 [22]	6.93±4.29	67.90
Fungus	2 [2]	5.30±1.56	59.50
Unclassified granuloma	9 [8]	6.82±3.58	70.10
Total	36 [32]		

*, P=0.001. SUVmax, the maximum standardized uptake value.

inflammatory lesions, the values for SUVmax of the lesions with neutrophil-based inflammation were significantly higher than that of the lesions with lymphocytic-based inflammation (5.81±2.37 *vs.* 2.03±1.57).

We conducted further investigation and follow-up of the cases. Each patient had been given a clinical diagnosis. The clinical diagnosis classifications of the 113 lesions are shown in *Table 3*. Pneumonia was the most common inflammatory lesion (52/113, 46%), and tuberculosis was the most common granulomatous lesion (31/113, 27%). Patients with cryptococcosis and cryptococcosis were the least common, both with only 1 case (1%). The average age of the patients with interstitial pneumonia was the oldest (70±11.53 years).

The values of uptake of 18F-FDG of the clinical diagnoses subcategories are shown in *Table 4*. In the clinical diseases, the SUVmax of sarcoidosis was significantly higher than that other types of diseases (15.12±5.67). The second highest values were for tuberculosis and cryptococcosis (6.79±3.96; 6.3), respectively. However, cryptococcosis had only one case and could not reflect the general trend.

Table 3 The age, gender, size and smoking history of the clinical diagnosis of pulmonary lesions

Clinical features	COP	Pneumonia	Interstitial pneumonia	Tuberculosis	Sarcoidosis	Aspergillus	Inflammatory pseudotumor	Cryptococcosis
Age, years	60.14±6.47	59.56±12.21	70±11.53	58.77±13.54	50±14.2	39.5±1.41	57.6±9.66	63
Gender								
Male [%]	5 [4]	35 [31]	3 [3]	23 [20]	4 [4]	1 [1]	6 [5]	1 [1]
Female [%]	2 [2]	17 [15]	0	8 [7]	3 [3]	1 [1]	4 [4]	0
Smoking history								
Never [%]	5 [4]	22 [19]	3 [3]	11 [10]	3 [3]	2 [2]	5 [4]	0
Ex or current [%]	2 [2]	30 [27]	0	20 [18]	4 [4]	0	5 [4]	1 [1]
Size (cm)	2.25±2.53	3.47±1.52	3.56±1.73	4.03±2.26	1.71±0.63	4.4±1.41	3.36±1.22	6

COP, cryptogenic organizing pneumonia.

Table 4 The values of SUVmax of the clinical diagnoses subcategories

Classification	Number of patients [%]	SUVmax*	The mean rank SUVmax
COP	7 [6]	3.78±2.14	39.71
Pneumonia	52 [46]	4.33±2.96	45.01
Interstitial pneumonia	3 [3]	5.23±1.81	58.33
Tuberculosis	31 [27]	6.79±3.96	67.44
Sarcoidosis	7 [6]	15.12±5.67	104.93
Aspergillus	2 [2]	5.3±1.56	58.5
Inflammatory pseudotumor	10 [9]	5.89±3.29	63.3
Cryptococcosis	1 [1]	6.3	72.5
Total	113		

*, P=0.000. SUVmax, the maximum standardized uptake value; COP, cryptogenic organizing pneumonia.

Discussion

Previous studies have demonstrated the value of 18F-FDG PET/CT in characterization of lung lesions (4,5), and in the study by Fletcher *et al.*, the diagnostic sensitivity and specificity of 18F-FDG PET for lung cancer could reach 91.7% and 82.3%, respectively, in a cohort of 344 patients (5). However, some studies suggested that the value of 18F-FDG PET/CT in evaluating lung lesions had been overestimated (6), especially in the solitary pulmonary nodules (SPNs), and its diagnostic sensitivity did not exceed 70% in characterizing SPNs (6,7). Nonsolid cancerous nodules, which typically exhibit slow-growth characteristics, are liable to be mistakenly diagnosed as benign lesions by 18F-FDG PET (8-12). The SUVmax threshold of 2.5, when used for diagnosing malignant solitary pulmonary lesions in some previous studies, was found to retain a high sensitivity (97%); however, the specificity was low (38%) (13,14). The 18F-FDG uptake in inflammatory nodules, tuberculosis and other granulomatous lesions can also be very high. Rogers *et al.* (15) found the metabolism of inflammatory cells, such as macrophages, lymphocytes and granulocytes, sharply increased demand for glucose and the expression of glucose transporters, resulting in more 18F-FDG uptake. The characteristics of 18F-FDG uptake on 18F-FDG PET/CT are important to diagnose benign pulmonary lesions, so we can avoid misdiagnosis and give patients better treatment.

This study assessed the values of 18F-FDG uptake in benign pulmonary lesions with histopathologic diagnoses and clinical diagnoses. According to its pathological type,

pulmonary lesions can be divided into two broad categories: inflammatory lesions and granulomatous lesions. We found the values of 18F-FDG uptake were significantly higher in granulomatous pulmonary lesions compared with inflammatory pulmonary lesions in our study. Davis *et al.* (16) found that the degree of aggregation of 18F-FDG was related to the degree of inflammatory activity; active pulmonary tuberculosis was characterized by high intake, but after treatment or resolution of pulmonary tuberculosis, there was no apparent uptake or moderate uptake. The 18F-FDG uptake in tuberculosis was high, especially for studies performed in tuberculosis-endemic regions (17). This is consistent with our findings. In our subgroup analysis of histopathological groups, tuberculosis was in the majority, and tuberculosis and fungus had higher values of 18F-FDG uptake. However, the SUVmax of the lesions with neutrophil-based inflammation was significantly higher than that of lymphocytic-based inflammation. According to these studies (and also based on our data), we inferred that the metabolism of neutrophil-based inflammation was more active than the metabolism of lymphocytic-based inflammation.

Is the size of benign pulmonary lesions related to the uptake of 18F-FDG? Hara *et al.* (18) reported that SUVmax was positively correlated with the size of tuberculosis lesions. Lee *et al.* (19) analyzed ten cases of pulmonary sclerosing hemangioma (PSH), and they concluded there was a positive correlation between the uptake of the lesions (SUVmax) and lesion size. In our study, we found no statistically significant correlation between lesion size and SUVmax. We concluded it probably was because most of the patients in our group had large lesions, as the mean maximum diameter of the lesions was 3.49±1.84. Large lesions probably contain more active cells than small lesions, and their uptake is also higher.

We conducted further investigation and follow-up of the cases and evaluated SUVmax in the clinical diagnostic groups. We found the SUVmax of sarcoidosis was highest in all the types of diseases (15.12±5.67). The second highest values were in tuberculosis and cryptococcosis (6.79±3.96; 6.3), respectively. The data analysis showed that the SUVmax of sarcoidosis was useful for discriminating between other pulmonary benign lesions. Sarcoidosis is characterized by the formation of noncaseating granulomas in multiple organ systems and is associated with symptoms such as dyspnea, low-grade fever, weight loss, skin rashes, and vision changes (20). In the study by Treglia *et al.*, 18F-FDG-PET/CT appeared to be useful for staging, evaluating disease activity, and monitoring treatment responses in patients with sarcoidosis (21). Our study found that 18F-FDG-PET/CT plays a differential role in the diagnosis of sarcoidosis. Furthermore, the SUVmax of 2.5 (delayed SUVmax of more than 2.5) was used as the traditional threshold for diagnosing malignant pulmonary lesions (13,22). In our study, all the lesions were benign, but the SUVmax was generally higher than the threshold of 2.5. According to those studies (and also based on our data), we inferred that a SUVmax threshold of 2.5 seemed inadequate for determining the nature of pulmonary lesions due to its low specificity; therefore, a higher cut-off value was needed.

Our study had several limitations including its small sample size and selection bias, since this was a retrospective study and enrolled only patients with pathologically proven pulmonary lesions. In addition, we did not use the delayed scan to compare early and delayed SUVs, although Cheng found that delayed 18F-FDG PET imaging may lead to easier detection of either malignant or benign lesions (23). Future studies are required to evaluate the efficacy of 18F-FDG PET/CT imaging in delineating the subgroups of pulmonary lesions.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Ethics Board of Jinling Hospital (No. DBNJ005), and the requirement for patient informed consent was waived.

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