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*Review Article*

# Sensitivity of $^{18}$F-FDG PET in evaluation of solitary pulmonary nodules

Farise Yilmaz[1], Gungor Tastekin[2]

[1]*Department of Nuclear Medicina, Meram Education Hospital, Konya, Turkey;* [2]*Department of Nuclear Medicina, NE University Medical School, Konya, Turkey*

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**Abstract:** Introduction: The solitary pulmonary nodule (SPN) may be an early sign of lung cancer. Due to the difficulties of radiological imaging techniques in differentiation of benign/malignant nodules, functional imaging techniques like PET-CT are required in patients diagnosed with SPN. The aim of this study was the evaluation of the role of PET-CT in differentiation of malignant/benign SPN by some characteristic findings in PET-CT. Moreover, among the nodules with histopathologically diagnosed as benign, malignant or metastatic, the SUVmax and Hounsfield Units (HU) of PET-CT imaging were also aimed to be compared to assess the role of PET-CT in discrimination of malignant/benign SPN. Material and method: Among the patients evaluated with PET-CT with the pre-diagnosis of pulmonary nodule or non-pulmonary malignancies, between July 2010 and January 2012, in Konya University Meram Medical School Nuclear Medicine Department, 241 patients (167 male, 74 female) diagnosed with pulmonary nodule were enrolled in the study. In visual evaluation of PET-CT of all patients, there was only one nodule in lung parenchyma. The diameter in cm, location as central or peripheral, regularity of borders, presence of calcification and HU and Maximum standardized uptake values (SUVmax) values with quantitative analysis of all nodules was recorded. The histopathological evaluation of nodules was available in 91 of those 241 patients and they were also recorded. Results: In comparison of mean SUVmax values in regards to the characteristic findings of nodules in PET-CT, the mean SUVmax value of patients was statistically significantly higher in patients with the nodule diameter ≥1 cm, centrally located nodules, or nodules with irregular borders. Conclusion: In malignant/benign differentiation of solitary pulmonary nodules with the diameter of higher than 1 cm, PET-CT plays an essential role; however, for the nodules smaller than 1 cm in diameter, in small, single metastatic nodules and some benign nodules with high SUVmax values, PET-CT may be unsatisfactory. However, it is clear that, in especially undetermined nodules, PET-CT is an important complementary tool in diagnosis.

**Keywords:** Solitary pulmonary nodule, PET-CT, malignant, benign

## Introduction

The solitary pulmonary nodule (SPN), named as 'coin lesion' in past, is defined as the single, circular opacity smaller than 3 cm in diameter, that is clearly differentiated from normal lung parenchyma without the presence of any associated lymphadenopathy or atelectasis [1]. The incidence of SPN in posterior-anterior lung graphics (PALG) is reported as 0.09-0.2% [2]. By the evolution of spiral CT on last decades, their prevalence is increasing day by day in clinical practice. Those nodules may be the sign in about 40-60% of patients with lung cancer [3]. Since the early diagnosis is very important in treatment of lung cancer, by allowing surgical resection and increasing 5 year survival rates, the diagnosis and follow up of SPN gains more importance.

The patients with SPN are divided as low, undetermined and high risk groups in terms of their risk factors and radiological appearance [4]. Unfortunately, it has been shown that, the radiological signs of benign nodules like regular borders, calcifications or stability in 2 year follow up are not always valid for the differentiation of a benign SPN from a malignant one because both benign and malignant ones may carry similar characteristics [5]. On the other hand, among patients in undetermined group, sometimes neither trans-thoracic, nor transbronchial biopsies give the exact results and more than half of the patients are forced to

experience a severe surgery as thoracotomy [6]. Due to the difficulties of radiological imaging techniques in differentiation of benign/malignant nodules, functional imaging techniques like PET-CT are required in patients diagnosed with SPN.

It is clearly known that, among malignant nodules, in parallel to the increase in glucose metabolism, F18-FDG absorption increases. However, among nodules without FDG absorption, the risk of malignancy is extremely low. In many studies, the differentiation of malignant/benign SPN could be exactly completed with FDG-PET [7-9]. However, at the same time, all these investigations have shown that, FDG-PET may give false positive results (10-25%) in many infectious and inflammatory diseases containing active macrophages, especially granulomatous diseases. Moreover, carsinoid, bronchoalveolar and mucinous tumors may give false negative results with normal or moderate FDG absorptions due to their lower sizes and decreased metabolic activities. Especially in nodules smaller than 1 cm in diameter, for PET-CT, low sensitivity and specificity values are reported [10]. The characteristic findings of PET-CT on malignant and benign nodules should be known clearly for an exact differential diagnosis.

The aim of this study was the evaluation of the role of PET-CT in differentiation of malignant/benign SPN by estimating nodule size, border regularity, and localization, presence of calcifications and determination of nodule standardized uptake values (SUVmax) and Hounsfield units (HU) values with quantitative analysis. Moreover, among the nodules with histopathologically diagnosed as benign, malignant or metastatic, the SUVmax and HU values of PET-CT imaging were also aimed to be compared to assess the role of PET-CT in discrimination of malignant/benign SPN.

## Material and method

### *Patient groups*

Among the patients evaluated with PET-CT with the pre-diagnosis of pulmonary nodule or non-pulmonary malignancies, between July 2010 and January 2012, in Konya University Meram Medical School Nuclear Medicine Department, 241 patients diagnosed with pulmonary nodule were enrolled in the study. One hundred and sixty seven of patients were male, while 74 were female and their ages were ranging in between 20-86 years.

In visual evaluation of PET-CT of all patients, there was only one nodule in lung parenchyma. The diameter in cm, location as central or peripheral, regularity of borders, presence of calcification and HU and SUVmax values with quantitative analysis of all nodules was recorded.

The histopathological evaluation of nodules was available in 91 of those 241 patients and they were also recorded.

### *PET-CT Imaging protocol*

In PET-CT imaging of patients, "Siemens Biography 6 HI-RES PET-CT" device in our Nuclear Medicine department was applied. PET/CT studies were carried out using an integrated PET/CT scanner, which consisted of a full-ring HI-REZ LSO PET and a six-slice Computerized Tomography (CT) (Siemens Biography 6; Siemens, Chicago, USA). Patients were instructed to fast for at least 6 hours and avoid heavy physical activity in last day before the $^{18}$F-FDG injection. Blood glucose levels were measured before study (GlucoDr Super sensor) and $^{18}$F-FDG injections were given only when the blood glucose levels were below 150 mg/dL mmol/l. The patients were rested on home temperature after the administration of 5 mg Alprazolam and 30 minutes before the imaging patients were given to drink 100 ml Osmolac solution in 1000 ml water. The patients were injected with 10-15 mCi $^{18}$F-FDG. After injection, the patients were rested on a calm and relaxed setting for 45-60 minutes in order to show enough biodistribution of pharmaceutics and existence of tissue absorptions. Whole-body CT was performed in a craniocaudal direction without an intravenous contrast medium from the skull base to the 1/3 proximal of the thigh region followed by PET images acquired in a three-dimensional mode. In average, 7-8 bed positions of all patients were collected with 2 mm slices in about 20-25 minutes.

### *Image evaluation*

All images were evaluated visually on a computer display with the knowledge of the clinical data by consensus of two experienced nuclear

**Table 1.** Characteristic features of nodules in PET-CT

| | Number of nodules | Mean SUVmax ± S.D. | P |
|---|---|---|---|
| Gender | | | >0.05 |
| Male | 167 | 3.94 ± 4.00 | |
| Female | 74 | 2.85 ± 2.71 | |
| Nodule diameter | | | |
| ≤1 cm | 190 | 4.26 ± 3.89 | <0.05 |
| >1 cm | 51 | 1.17 ± 0.46 | |
| Location | | | <0.05 |
| Central | 88 | 4.36 ± 4.36 | |
| Peripheral | 153 | 3.17 ± 3.15 | |
| Border Regularity | | | <0.05 |
| Irregular | 103 | 5.56 ± 4.29 | |
| Regular | 138 | 2.15 ± 2.25 | |
| Calcification | | | <0.05 |
| Calcification (+) | 29 | 1.82 ± 2.00 | |
| Calcification (-) | 212 | 3.85 ± 3.79 | |

S.D.: Standard deviation.

**Table 2.** Hounsfield Units of nodules

| | Number of nodules | Mean HU ± S.D. | P |
|---|---|---|---|
| SUVmax 2.5> | 101 | 29.83 ± 63.551 | <0.05 |
| SUVmax 2.5≤ | 140 | 86.06 ± 300.522 | |

**Table 3.** SUVmax values of nodules with histopathological diagnosis

| Histopathological evaluation | Number of nodules | Mean SUVmax ± S.D. |
|---|---|---|
| Benign | 32 | 3.49 ± 3.03 |
| Malignant | 37 | 7.69 ± 4.08 |
| Metastatic | 22 | 3.19 ± 3.13 |

S.D.: Standard deviation.

medicine physicians. FDG-PET CT images were interpreted in the axial, coronal, and sagittal planes along with maximum intensity projection images of 2 mm slice. The interpretation of anatomical localization of FDG-PET images was performed with CT images. By visual evaluation, nodule localization, border regularity and presence of calcifications were determined. The nodule diameter was measured with quantitative analysis in cm. Maximum standardized uptake values and HU were obtained by drawing three-dimensional regions of interest (ROIs) around each lesion and calculated with the program on workstation (Siemens Multimodality Workplace TrueD).

*Histopathological evaluation*

Retrospectively, we have reached the histopathological diagnosis of 91 patients in those 241 patients in our archive analysis. Along with those, 32 were benign, 37 were malignant and 22 were metastatic nodules. All histopathological evaluations were performed in Meram Medical School Pathology Department, Konya.

*Statistical analysis*

All analyses were performed with the Statistical Package for Social Sciences (SPSS) for Windows 17.0 program. Independent Sample t Test (t test) was used in determination of differences between groups. In evaluation of patients with histopathological diagnosis, oneway-anova test was used. Results were expressed as mean ± S.D. The $P<0.05$ was considered as statistically significant.

## Results

Among the 241 patients included in the study, 167 (69.2%) were male and 74 (30.7%) were female. The ages of patients were ranging from 20 to 86 years while the mean age was 61.7 years. Characteristic features of nodules are summarized in **Table 1**. Although the mean SUVmax value was higher in male patients, the difference was not statistically significant between genders. Similarly although with the increase in age, mean SUVmax value was increasing but the difference was not statistically significant between age groups.

On visual and quantitative evaluation of PET-CT images, in 51 (21.1%) patients the nodule diameter was smaller than 1 cm, while it was equal to or larger than 1 cm in 190 (78.8%) patients. In comparison of mean SUVmax values in regards to the nodule diameter, the mean SUVmax value of patients was statistically significantly higher in patients with the nodule diameter ≥1 cm (**Table 1**). Among all those nodules, 88 (36.5%) were centrally located, while 153 (63.5%) were located peripherally. SUVmax value of centrally located nodules was significantly higher than that of peripheral ones (**Table 1**). In evaluation of border regularity of nodules, 138 (57.2%) were regular, while

103 (42.8%) were irregular. SUVmax value of nodules with irregular borders was significantly higher than that of nodules with regular borders (**Table 1**).

Calcification was present in only 29 (12.0%) nodules. The SUVmax value of nodules with calcification was statistically significantly lower than that of nodules without calcification.

Moreover the nodules were divided into 2 groups according to their SUVmax values as <2.5 and ≥2.5. In that analysis, 140 (58.0%) nodules were having a SUVmax value of lower than 2.5 and in that group HU value was statistically significantly higher than the other group (**Table 2**).

In retrospective estimation of those 241 patients, histopathological diagnosis was present in 91 patients. Within those 91 patients, 37 (40.6%) were malignant, 32 (35.1%) were benign and 22 (24.2%) nodules were metastatic (**Table 3**). In evaluation of those 37 malignant nodules, 14 (37.8%) were squamous cell ca, while 16 (43.2%) were adenocancer, 5 (13.5%) were small cell lung cancer, 1 (2.7%) were bronchoalveolar cell cancer and 1 (2.7%) were adenosquamous cancer. The mean diameter of those nodules, with the histopathological diagnosis, was 21.54 mm, 17.93 mm and 11.68 mm, in malignant, benign and metastatic nodules retrospectively. Among malignant nodules, only 1 (2.7%) was smaller than 1 cm in diameter. The mean SUVmax value of nodules was 3.49 ± 3.03, 7.69 ± 4.08 and 3.19 ± 3.13 in benign, malignant and metastatic groups respectively. The mean SUVmax value of malignant nodules was statistically significantly higher than other two groups but there was no statistically significant difference between the SUVmax values of benign and metastatic nodules. Interestingly in 5 (13.5%) nodules of malignant group SUVmax value was lower than 2.5; while in 18 (46.3%) nodules of benign group SUVmax value was higher than 2.5.

## Discussion

We have determined that; in malignant/benign differentiation of solitary pulmonary nodules with the diameter of higher than 1 cm, PET-CT plays an essential role; however, for the nodules smaller than 1 cm in diameter, in small, single metastatic nodules and some benign nodules with high SUVmax values, PET-CT may be unsatisfactory. Because of this reason, all patients should be evaluated carefully and all physical examination, clinical features, laboratory findings and radiological results should be evaluated together in order to determine the early and correct diagnosis in patients with SPN. In that point, it is clear that, in especially undetermined nodules, PET-CT is an important complementary tool in diagnosis.

Nowadays, the mostly diagnosed and the most common cause of cancer deaths is the lung cancer [11]. In all over the world, 12.4% of the total cancer cases and 17.6% of cancer deaths belong to the lung cancer [12]. Lung cancer first starts with the SPN or focal non-specific opacities in lung graphics. Due to the consequences and mortality rates of lung cancer, early diagnosis and identification of those nodules gains more importance.

The etiology of pulmonary nodules ranges from benign granulomas to malignant lesions. The first and most essential point after the diagnosis of a nodule in radiography is the differentiation of malignant ones from the benign ones [13]. Although some criteria like presence of calcification, regular borders and stability in 2 years follow-up give the idea of a benign nodule; it has been clearly determined that it is not always possible to make benign/malignant identification exactly by radiological criteria [14]. Spicular borders, heterogeneity in appearance, presence of central necrosis support the malignancy in CT. However, it has been reported that, 25-39% of malignant nodules are classified as benign in radiological evaluation [15]. By this reason, alternative radiological methods like PET-CT are necessary in evaluation of SPN for early and correct diagnosis [16]. In lung cancer diagnosis, lung radiography, CT and PET-CT are shown to be complementary to each other [13].

In identification of characteristics of solitary pulmonary nodule, PET and PET-CT were found to be superior to clinical and morphological criteria [17]. In a retrospective study, the sensitivities of CT, PET and PET-CT were 93%, 69% and 97% while specifities were 31%, 85% and 85% respectively; showing the essential role of PET-CT in classification of SPN [18]. On the other hand, the diagnostic value of bronchoscopy was 64% in malignant nodules and 35% in benign nodules [19].

In the light of these data, we have compared the characteristic PET-CT findings of our patients diagnosed with SPN in order to determine the criteria that can help us to differentiate the malignant ones from the benign ones.

The diameter of nodule was one of the most important characteristics in differentiation of malignant nodules from benign ones. In a study of Lowe et al, the sensitivity of PET in identification of malignant nodules was 90% in nodules larger than 1.5 cm but it was 80% in nodules smaller than 1.5 cm and they concluded that, different criteria are necessary for the exact diagnosis of malignancies in nodules smaller than 1.5 cm [20]. Moreover in other studies, the sensitivity of PET was 69% for nodules with a diameter of 5-10 mm while it was 95% for nodules larger than 10 mm [10, 21]. In different studies evaluating nodules smaller than 1 cm without calcification, the benign SPN ratios were ranging from 64-92% [22, 23]. Similar to all these results, in our study we have determined that, the nodules larger than 1 cm in diameter had significantly higher SUVmax values than smaller nodules indicating a positive correlation of nodule diameter with malignancy. Moreover, in histopathologically evaluated nodules, the mean nodule diameter was larger in malignant nodules, supporting the data of increased nodule diameter increases the malignancy risk.

The border regularity was one of the other considered criteria in PET-CT evaluation of SPN. Radiating irregularities in lesion borders, in other words 'corona radiata' appearance, was reported with the presence of cancer in 88-94% of patients [24]. Although regular borders without lobulation and speculations were commonly reported with benign nodules, 22.2% of histopathologically malignant nodules were also reported with these border characteristics [25]. In our study we have determined a higher mean SUVmax value in nodules with irregular borders compared to that of nodules with regular borders supporting the data of irregularity in borders increases the risk of malignancy in SPN evaluation.

The presence and pattern of calcification in SPN is another important criterion in discrimination of malignant and benign SPN. In a study of Toomes et al with a large population of 955 patients, 92% of calcified SPN were benign [26]. Similar to this data we have determined that the mean SUVmax value was lower in calcified SPN compared to uncalcified ones.

Another very important data, we have determined in this study was about the association of location with malignancy. Among 37 patients, histopathologically diagnosed with malignant nodules, 22 were central while 15 were peripheral. Moreover, in centrally located SPN, the mean SUVmax value was significantly higher than that of peripherally located ones. This higher SUVmax value may be associated with higher blood flow in central regions or higher ground activities of lung hilus and mediastinal organs.

In a study of Cardillo et al on resected 429 SPN cases, 309 (86.3%) were benign while 59 (13.7%) were malignant [27]. In a study of Tasci et al on 202 malignant nodules, the ratio of metastatic nodules was 44% [28]. On the other hand, in an interesting study, the ratio of metastatic nodules was 87% in patients already diagnosed with a cancer other than lung [29]. In our study, in 91 patients with histopathological diagnosis, 32 (35.2%) were benign, 37 (40.6%) were malignant and 22 (24.2%) were metastatic nodules.

The nodules diagnosed as malignant histopathologically had a mean SUVmax value statitistically significantly higher than that of benign or metastatic nodules. However, there was no statistically significant difference between the SUVmax values of benign and metastatic nodules moreover, the mean SUVmax value of these 2 groups were also higher than 2.5. The mean SUVmax value of higher than 2.5 in benign nodules may be associated with the presence of inflammation in these nodules. The lower SUVmax values in metastatic group may be associated with the lower diameter of nodules in metatstatic group.

If PET-CT is used in diagnosis of SPN, false positive and false negative results should be evaluated carefully. Muscle tissue, brown adipose tissue, inflammation or infections are some of the benign conditions that may result in false negative outcomes [30]. In a study of Zhuang et al, it has been determined that, in malignant lesions SUVmax value increases progressively by the time while it decreases generally in benign lesions in follow-up [31]. On the other

hand, small nodules, malignancies with low metabolic or mitotic activities, like bronchoalveolar carcinoma or carsinoid tumor may give false negative results [32, 33].

In the light of these findings, we can conclude that, high nodule diameter, border irregularity, absence of calcification, central location may be the sign of malignancy in a SPN evaluated with PET-CT and the clinicians must be aware of all these findings. Moreover, since there was no difference significantly between the SUVmax values of metastatic and benign nodules; the possibility of metastasis should be kept in mind in nodules although they are single and having low SUVmax values particularly in patients with a diagnosis of cancer in any organs other than lung. In conclusion, PET-CT is a complementary tool in differentiation of malignant nodules from benign ones especially in undetermined cases.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Farise Yilmaz, Department of Nuclear Medicina, Meram Education Hospital, Konya, Turkey. E-mail: hyilmazmd@hotmail.com

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