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ORIGINAL ARTICLE

Diagnostic value of PET/CT in differentiating benign from malignant solitary pulmonary nodules

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Summary

Purpose: *Solitary pulmonary nodules (SPNs) are round or oval lesions with a clear border with the surrounding parenchymal tissue and a radiologic diameter smaller than 3 cm which are not associated with atelectasis, pneumonia, lymphadenopathy, or chest wall pathologies. The purpose of the present study was to evaluate the efficacy of positron emission tomography (PET) / computerized tomography (CT) in differentiating benign from malignant SPNs.*

Methods: *In this retrospective study, 209 patients, who were diagnosed with SPN by thoracic CT and demonstrated positive or negative results for malignancy in the PET/CT examination between January 2007 and June 2010, were enrolled. Among the 91 patients who gave consent for interventional procedures, performed were bronchoscopic endobronchial biopsy in 10, transbronchial biopsy in 15, bronchoscopic brushing in 4, transthoracic needle biopsy in 11, video-assisted thoracoscopy (VATS) in 4, lobectomy in 22, pneumonectomy in 2, and wedge resection in 23. The materials were histopathologically examined.*

Results: *129 (61.72%) of the SPN cases were benign and 80 (38.27%) malignant. The mean SUVmax value for the benign SPNs was 2.06 ± 3.29 and 7.39±5.69 for the malignant SPNs (p=0.000). Positive correlation was found between the nodule diameter and risk for malignancy. A SUVmax value of 4 was found to have the best sensitivity and specificity.*

Conclusion: *PET/CT was shown to be an accurate method in the differential diagnosis of benign from malignant solitary pulmonary nodules.*

Key words: *malignant tumor, positron emission tomography, solitary pulmonary nodules, SUVmax*

Introduction

SPN are round or oval lesions with a clear border with the surrounding parenchymal tissue and a radiologic diameter smaller than 3 cm, which are not associated with atelectasis, pneumonia, lymphadenopathy, or chest wall pathologies [1-3]. They have a prevalence of 0.09-0.2% in posteroanterior lung X-rays [2] and their significance is connected with their nature (benign or malignant). In the general population, although approximately 5% of all SPNs shown by radiology are reported to be carcinomas, more than 50% of the SPNs detected in patients older than 50 years are carcinomas [4]. In the USA, the prevalence of new SPN cases per year is 52/100,000. PET with fluorodeoxyglucose (FDG) has become one of the common modalities used for oncologic purposes in the recent 10-15 years. The most frequently applied agent is FDG marked with Fluor-18 (18F) [6]. FDG is a glucose analog which is used in oncology based on the assumption that tumor cells consume higher levels of glucose than normal cells. Patient series show considerable variation in the sensitivity and specificity of PET for the evaluation of the SPN, mainly as a consequence of the different methodologies used in each study. The results of a meta-analysis published in 2001 are therefore important. That meta-analysis, which included 40 studies with a to-

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tal of 1474 focal pulmonary lesions of any size, established a sensitivity of 96.8% and specificity of 77.8%, based on analysis of the maximum area under the diagnostic efficacy curve [7]. Differentiation of benign from malignant lesions is often possible with 18F-FDG-PET . In a study including 61 SPNs with a diameter range between 6-30 mm, the sensitivity and specificity of 18F-FDG-PET for differentiation of benign and malignant lesions was 93% and 88%, respectively [8]. However, PET imaging may produce false negative results in bronchoalveolar carcinoma and carcinoid tumors [9]. Infectious conditions such as active tuberculosis and sarcoidosis may demonstrate false positivity in PET imaging. PET has high efficacy in differentiating of benign from malignant lesions in SPN [7,10-12]. A meta-analysis found the sensitivity and specificity of PET for malignant nodules as 96.8 and 77.8%, respectively, while reporting a sensitivity of 96% and a specificity of 88% for benign nodules [7].

In the present study we aimed to evaluate the efficacy of PET/CT in SPN diagnosis and differentiation of benign and malignant nodules.

Methods

Study group

In this retrospective study, 209 patients diagnosed with SPN by thoracic CT and found to be positive or negative for malignancy by PET/CT examination between January 2007 and June 2010, were enrolled. These were patients who had visited the Chest Diseases Clinic and/or the Chest Surgery Clinic, School of Medicine, Dicle University. Our study was approved by the local ethics committee. Routine patient examinations, such as history, physical examination, CBC, bleeding-coagulation profile etc were evaluated in a retrospective fashion.

The diameter of the nodules shown by thoracic CT was ≤ 3 cm in all patients and there were no cases with signs of pneumonia, atelectasis, lymphadenopathy or chest wall pathology, and no patient had a history of diabetes mellitus. Radiologic follow-up assessments or histopathology were utilized for benign-malignant distinction of the lesions. Patients with a lymph node sized >1 cm shown by thoracic CT, poor overall health, history of lung cancer, and age over 85 years, as well as those who did not give consent to biopsy/operation despite the need for an interventional procedure, and those who did not visit us for their prearranged serial CT follow-up assessments, were excluded from the study.

We used standard criteria for the definition of a benign lesion: histologically confirmed excisional biopsy, serial CT images showing the stability of the lesion size for at least 24 months or spontaneous reduction in the lesion size. In this study, the following definitions were applied: sensitivity: probability of accurately diagnosing a malignant lesion; specificity: probability of negative results in the absence of malignancy; accuracy: probability of all lesions to be benign or malignant; positive predictive value: probability of malignancy in the presence of positive test results; negative predictive value: probability of malignancy in the presence of negative test results.

FDG/PET imaging

The patients were examined with whole-body PET/CT scan (Siemens Biograph 6 LSO). Following the measurement of blood pressure and glucose levels after a 10-min fasting period, the F18-FDG dose, arranged according to the body weight (0.15 mCi/kg), was intravenously injected. After 1-h rest, whole body scans (5-mm sections) were performed from the base of the skull to the proximal femur in 7 bed positions with 3-5 min duration of emission and transmission.

Image analysis

The images were taken in different planes such as transaxial, coronal, and sagittal, and were evaluated separately. The size, type, and localization of the lesion detected by thoracic CT were confirmed by PET/CT imaging. Each image was analyzed separately by 2 experienced radiologist and nuclear medicine specialist. Maximum standard uptake value (SUVmax) that has been standardized based on the formula shown below, was calculated automatically by a computer:

$$SUV = \frac{\text{Mean ROI} * \text{activity (MBq/g)}}{\text{Injected dose(MBq) / body weight (g)}}$$

(ROI: Regions of interest)

Lesions with a diameter > 2 cm and a SUVmax value ≥2.5 were characterized to be at high risk for malignancy.

Histo-cytological diagnosis

All of the patients, whether with FDG uptake on PET/CT images or not, were advised to undergo diagnostic interventional procedures. Among them, 118 did not give consent to interventional procedures. The remaining 91 patients were evaluated by the following interventional procedures and histo-cytological diagnosis was carried out by the pathology laboratory of our university: bronchoscopic endobronchial biopsy in 10, transbronchial biopsy in 15, bronchoscopic brushing in 4, transthoracic needle biopsy in 11, video-assisted thoracoscopy (VATS) in 4, lobectomy in 22, pneumonectomy in 2, and wedge resection in 23.

Statistics

In this study, the SPSS (Statistical Package for Social Sciences) 15.0 for Windows was employed for

Table 1. Demographic characteristics of patients

Characteristics	*All patients (N=209) N (%)*	*Malignant SPNs (N=80) N (%)*	*Benign SPNs (N=129) N (%)*	*p-value*
Age (years), mean±SD	54.4±14.8	56.66±15.69	53.14±14.26	0.06
Gender				0.074
Male	125 (59.8)	54 (43.2)	71 (56.8)	
Female	84 (40.2)	26 (30.9)	58 (69.1)	
Cigarette				0.06
Smoker	103 (49.2)	46 (44.6)	57 (55.3)	
Nonsmoker	106 (50.7)	34 (32.0)	72 (68.0)	
Average cigarette consumption (pack-years)		25.60±29.46	14.00±21.67	0.003
Chest pain				0.001
Yes	113 (54.0)	56 (70.0)	57 (44.1)	
No	96 (45.9)	24 (30.0)	72 (55.8)	
Dyspnea				0.257
Yes	150 (71.7)	61 (76.2)	89 (68.9)	
No	59 (28.2)	19 (23.7)	40 (31.0)	
Weight loss				0.01
Yes	55 (26.3)	29 (36.2)	26 (20.1)	
No	154 (73.6)	51 (63.7)	103 (79.8)	
Hemoptysis				0.009
Yes	26 (12.4)	16 (20.0)	10 (7.7)	
No	183 (87.5)	64 (80.0)	119 (92.2)	

SPN: solitary pulmonary nodule, SD: standard deviation

the statistical analyses. Student's t-test was used for the parametric analysis of quantitative data, whereas Mann-Whitney U test was used for the non-parametric quantitative data. Qualitative data were compared by Chi-square test. The data were analyzed for sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rates. The results were evaluated with 95% confidence interval and $p<0.05$ was accepted as statistically significant.

Results

Eighty-four (40.2%) of the patients were female and 125 (59.8%) male. The mean age was 54.4±14.8 with a range of 18-85 years. There was no statistically significant difference in the age of patients with benign or malignant nodules (p=0.06; Table 1).

Of the patients with diagnostic and follow-up procedures, 129 (61.72%) had benign and 80 (38.27%) had malignant nodules. Of the 129 patients with benign SPN, 105 (81.3%) were characterized as benign SPN cases due to showing no change in the nodule size during the 2-year radiologic follow-up period.

Twenty-four (18.60%) of the 129 benign SPN patients had histopathologic examination. Among those, 8 had nonspecific infection, 1 rheumatoid granuloma, 10 tuberculous granuloma, and 2 aspergilloma and 3 undefined benign cytology. The mean SUVmax value for the 129 benign SPN patients was 2.06 ± 3.29. Sixty-seven (83.7%) of the 80 malignant SPN patients had histopathologic confirmation. Among those patients, the diagnosis of SPN malignancy was achieved with endobronchial biopsy in 6, transbronchial biopsy in 12, brushing in 1, transthoracic needle biopsy in 6, VATS in 2, lobectomy in 22, pneumonectomy in 2, and wedge resection in 16. The remaining 13 malignant SPN patients had been diagnosed by at least 2 experienced radiologists based solely on PET/CT images due to lack of their consent for any interventional diagnostic procedures. The SUVmax value for the 80 malignant patients was 7.39 ± 5.69.

The mean SUVmax value was statistically significantly higher in patients with malignancies compared to patients with benign SPN (p=0.000). The SUVmax values of the entire study population varied between 0.0 and 27.00, with a mean value of 4.10 ± 5.07. Among the 80 malignant SPN patients, cytologic-histopathologic examinations revealed that 41 (51%) were non small cell lung cancer (NSCLC), 3 (4%) small cell lung cancer, and 36 (45%) were metastatic cases (Table 2). The diameter of the lesions varied between 4 and 30 mm (mean 18.8 ± 7.5). All the benign lesions had a diameter < 20 mm (mean 16.9 ± 7.5), while all the malignant lesions had a diameter > 20 mm (mean 21.9±6.6). The difference between the benign and malignant cases relative to lesion

Table 2. Cytopathological results of patients diagnosed with malignant solitary pulmonary nodule

Cytopathological type	*N*	*%*
NSCLC	41	51
Adenocarcinoma	10	24
Bronchoalveolar carcinoma	1	2.5
Squamous cell	5	12
Large-cell	1	2.5
Undefined subtype	24	59
SCLC	3	4
Metastasis from		
Breast carcinoma	36	45
Lymphoma / leukemia	10	28
GIS (colon cancer, rectal cancer)	4	11
GUS (renal cell carcinoma, ovarian carcinoma)	10	28
Prostate carcinoma	9	23
Bone (osteosarcoma)	3	10

GIS: gastrointestinal system, GUS: genitourinary system, SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer

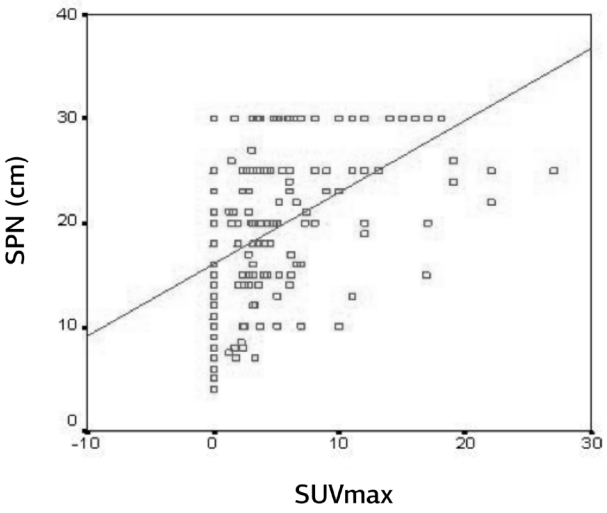

Figure 1. SUVmax correlated with the size of the SPN.

diameter was highly significant (p=0.000). SPNs were right-sided in 55.5% (N=116) and left-sided in 44.5% (N=93) of the cases. Benign lesions were right-sided in 58.1% and left-sided in 41.9% of the cases, whereas malignant lesions were right-sided in 51.2% and left-sided in 48.8% of the patients. There was no statistically significant difference between malignant and benign SPNs with regard to left- or right-sided localization (p=0.330). In addition, no statistically significant difference was determined between benign and malignant cases in terms of localization in superior, middle, or inferior lobes (p=0.900).

A positive correlation between lesion diameter and SUVmax value (i.e. FDG uptake) in malignant nodules was found in this study . This correlation was statistically significant (r=0.463, p<0.05) (Figure 1).

Regarding the laboratory parameters, platelet count was lower and LDH levels were higher in malignant SPNs compared to benign ones. This relationship was statistically significant (p=0.016 for platelets and p=0.030 for LDH; Table 3). In our study, SUVmax 4 showed the highest sensitivity and specificity in demonstrating malignancy in SPNs by PET/CT imaging (Table 4).

Discussion

Lung cancer is an important health issue worldwide, and one of the foremost causes of mortality in the USA. It is the most common cancer type across the world [13], accounting for 12.3% of all cancer diagnoses per year. Most of the patients seek help during locally advanced stage (stage III) or metastatic stage. Patients with NSCLC bear poor prognosis and the average life expectancy is low with 5-year survival rate less than 9% [14]. All stages included, 5-year survival rate is 14%. Survival and response to therapy are associated with many factors such as disease stage, patient performance status, and genetic factors [15,16]. Patients with the same stage vary in terms of survival, response to therapy, and recurrence rates. Therefore, some clinical and laboratory parameters are needed in order to be able to determine treatment strategies and evaluate prognosis and response to treatment in newly diagnosed lung cancer cases [17].

SPNs may indicate a primary lung cancer in patients with advanced age. In the general population, while 5% of the SPNs detected by routine radiologic examinations are reported as carcinomas, in patients aged ≥ 50 years, more than 50% of the detected SPNs are carcinomas [4]. In the present study, 80 (38.2%) of the 209 SPN patients had carcinoma and 70% of the patients with malignancy were aged above 50 years (p= 0.05), a result consistent with the literature. FDG uptake is observed to be higher in fast-growing and metabolically active lesions with large diameter. On the contrary, FDG uptake is not present or is very low in slow-growing, well-differentiated, or small lesions [18]. Meta-analyses have shown that when the threshold value for SUVmax is 2.5, the sensitivity and specificity of FDG-PET for differentiation of malignant from benign lesions are 90-100% and 69-95%, respectively [7,8,15,19,20]. In the present study, when the threshold value of SU-

Table 3. Laboratory results (mean ± SD)

Laboratory results	*Normal range*	*Benign group N=129*	*Malignant group N=80*	*p-value*
Leukocytes (K/UL)	4.6 - 10.2	7.60 ± 3.27	6.88 ± 3.14	0.119
Hemoglobin (g /dL)	12.2 - 18.1	12.71 ± 1.41	12.56 ± 1.82	0.526
Hematocrit (%)	37.7 - 53.7	38.45 ± 4.89	37.50 ± 5.38	0.192
Platelets (K/UL)	142 - 424	234.83 ± 82.69	205.29 ± 88.93	0.016
ESR (mm/h)	1.7	20.96 ± 20.96	23.98 ± 18.04	0.288
C-reactive protein (mg/dL)	0 - 0.8	3.91 ± 18.20	2.72 ± 4.72	0.567
Calcium (mg/dL)	8.4 - 10.2	8.86 ± 0.61	9.66 ± 9.23	0.325
Alkaline phosphatase (U/L)	4 - 150	78.08 ± 31.50	82.01 ± 29.36	0.370
Lactate dehydrogenase (U/L)	125 - 243	223.93 ± 83.57	267.90 ± 166.12	0.030

ESR: erythrocyte sedimentation rate

Table 4. Sensitivity and specificity in different SUVmax cut-off values for demonstrating malignancy

SUVmax cut-off value	*Sensitivity (%)*	*Specificity (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*	*Accuracy (%)*
SUVmax = 2.5	67.4	86.2	88.7	62.1	74.6
SUVmax = 3.0	7.8	81.2	86.2	65.0	76.0
SUVmax = 4.0	84.0	70.0	81.8	73.0	78.4
SUVmax = 5.0	89.1	56.2	76.6	76.2	76.5
SUVmax = 10	96.1	23.7	67.0	79.1	68.4

SUVmax: maximum standard uptake value

Vmax was set at 2.5, the sensitivity and specificity were found to be 67.4% and 86.2%, respectively; our results were consistent with the literature.

The sensitivity of bronchoscopy and transbronchial biopsy in the diagnosis of malignant pulmonary nodules are 65 and 79%, respectively [21]. The sensitivity and specificity of transthoracic needle biopsy varies between 94-98% and 91-96%, respectively, whereas the rate of pneumothorax development is about 19-26% [22]. The most common invasive method applied in our patient group was wedge resection (11%). Compared with the clinical and morphological criteria, PET scan alone can provide better data about the characteristics of the SPNs and the probability of malignancy [8,16]. In a retrospective study, the sensitivity of CT, PET, and PET/CT was found 93, 69, and 97%, respectively, whereas the specificity was 31, 85, and 85%, respectively. PET/CT was reported as an important modality in the classification of SPNs [23].

In a study, a SUVmax value of 0-2.5 was associated with 25% probability of malignancy, a SUVmax value of 2.5-4.0 was associated with 80% probability of malignancy, and SUVmax values greater than 4.1 were correlated with a 96% probability of malignancy [24]. In the present study, the mean SUVmax value shown by PET was 7.39 ±5.69 for the malignant nodules and 2.06 ±3.29 for the benign nodules which were consistent with the results in the literature. The most important risk factors relative to malignancy in the clinical assessment of patients with SPN are age, history of smoking, and history of cancer concerning the lung or other organs [25-28]. Lillington et al. noted that malignancy risk increased after 48 years of age [24]. In the present study, the mean age among patients with malignancy was 56.66 ±15.69, which was a result consistent with the literature. Smoking is known as another important risk factor and risk of malignancy increases 2% per each pack year of cigarette smoking [29]. In our study, when evaluated as pack year, the mean cigarette consumption was 14.00±21.67 in patients with benign lesions and 25.61±29.47 in those with malignant lesions (p=0.003). Quint et al. evaluated SPNs in patients with head/neck cancer and found that 76% were primary lung cancer, 9% were solitary metastases, and 15% were benign lesions. In the same study, the rate of SPNs diagnosed as primary lung cancer was 24-58% in the presence of cancers concerning other organs [30]. In our study, among the 80 patients with malignant SPNs 36 (45%) were metastases and 44 (55%) were primary lung cancer. In addition, 58 (28%) of the 209 patients with SPNs had a history of another malignancy. Thirty-six (62%) of these 58 patients had metastases, which was also consistent with literature data.

The most common causes of false positive results are granulomatous diseases such as tuberculosis, sarcoidosis, and aspergillosis [8]. When a threshold value of 4 was used for SUVmax, 21 (16%) of the 129 SPNs benign patients demonstrated a SUVmax value of ≥4. Furthermore, when a threshold value of 4 was used for SUVmax, 24 patients (30%) exhibited a SUVmax value below 4 and false negativity was determined.

In three separate studies evaluating single nodules having no calcification and with a diameter < 1 cm, benign SPN rates were found to be 64, 57, and 92%, respectively [27,31,32]. In our study, the mean diameter was 21.99±6.68 mm for malignant nodules and 16.90±7.50 mm for benign nodules (p=0.000). In the literature, 70 % of malignant SPNs have been observed to localize in the superior lobes, whereas benign SPNs have been reported to show an even distribution [30]. In the present study, 34 (42.5%) of the 80 malignant nodules were localized in the superior lobes, a finding inconsistent with the literature. We believe that this may be associated with the fact that 36 of the 80 malignant nodules were metastatic nodules.

Hickeson et al. conducted a study on 47 patients with a SPN and reported the sensitivity, specificity and accuracy rates of FDG-PET/CT as 82-100%, 60-100%, and 79-100%, respectively [33]. In the same study, when the threshold value of SUVmax was set at 2.5 for nodules with a diameter up to 2 cm, the sensitivity, specificity, and accuracy rates were 47, 80, and 59%, respectively; when the threshold value of SUVmax set at 3, the sensitivity, specificity and accuracy rates were 35, 100, and 59%, respectively.

Our study has some limitations. Firstly, it was a retrospectively designed study which did not allow us to access some of the patient data. Furthermore, the study design did not allow us to compare the sensitivity and specificity of various imaging methods and invasive diagnostic procedures for differentiation of benign and malignant SPNs, since there was no standard in applying these imaging modalities and procedures. We believe that further prospective case-control studies enabling such analyses should provide additional and detailed data in this regard.

Generally, lesions with high FDG uptake are of malignant character. However, there may be cases with false positivity. We found that patients with other organ malignancies presenting with a SPN had small lesion sizes, while nodules with low or no FDG uptake were highly likely to be of malignant nature. There was a positive correlation between the nodule diameter and risk of malignancy. In similar studies, when SUVmax threshold value was 2.5, the sensitivity and specificity for malignancy were reported be 83-97% and 69-100%, respectively. However, our study differed from others with a SUVmax value of 4 which provided the best sensitivity and specificity for malignancy. Analyses in the present study showed better sensitivity and specificity rates with a SUVmax value of 4, compared to those in the literature obtained with lower SUVmax values. Contrary to the low sensitivity rates at various SUVmax values reported in previous studies, we showed that sensitivity can be as high as 83% with a SUVmax value of 4, in other words, the probability of accurately diagnosing a malignant lesion may be even higher.

Conclusion

In the present study FDG-PET/CT was found to be a highly accurate method in differentiating benign from malignant SPNs. Lesions with high FDG uptake are generally of malignant nature. However, false positivity should always be considered. In patients with another known organ malignancy along with a SPN, small nodular lesions with low or absent FDG uptake showed a high risk of being malignant as well. There was a positive correlation between the nodule diameter and malignancy risk. Similar studies have shown that when a threshold value of 2.5 is taken as SUVmax, the sensitivity and specificity for malignancy are 83-97% and 69-100%, respectively. In the present study, the SUVmax value providing the best sensitivity and specificity was 4.

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