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The role of F-18 FDG PET/CT in differentiating benign from malignant pulmonary masses and accompanying lymph nodes

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SUMMARY

The role of F-18 FDG PET/CT in differentiating benign from malignant pulmonary masses and accompanying lymph nodes

Introduction: The aim of this study was to evaluate the usefulness of SUV_{max} and lesion size to differentiate benign and malignant lesions of the lung and accompanying mediastinal lymph node on F-18 FDG PET/CT imaging.

Materials and Methods: A retrospective analysis was carried out on 100 patients with suspected lung cancer who were recommended for PET/CT scans for diagnosis and staging. The results of the SUV_{max} , lesion size and patient's age were compared with histopathology which was considered to be the 'gold standard' and sensitivity and specificity were calculated respectively. Lymph nodes greater than 1 cm in patients with benign pathology were evaluated and the SUV_{max} values were recorded.

Results: Of the 100 patients, 38 were found to have benign, whereas 62 had malignant on histopathology. The SUV_{max} was signifi-

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cantly more elevated in malign masses (13.1 ± 6.4) than in benign masses (8 ± 5.7) ($p < 0.05$). The dimensions of malignant masses (4.5 ± 2.5 cm) were larger than benign ones (3 ± 1.6 cm) ($p < 0.05$). SUV_{max} of 7.6 was determined as the cut-off value, while the sensitivity and specificity were 82% and 55% respectively. The sensitivity was 87% and specificity was 45% for the lesion sizes in differentiation of the malignant and benign lesions.

Conclusion: There are significant overlaps between benign and malignant lesions and specialists must be aware of the various pathological conditions that can give false positives and negatives.

Key words: F-18 FDG, positron emission tomography/computed tomography (PET/CT), lung cancer

ÖZET

Akciğer kitleleri ve eşlik eden lenf nodlarının benign/malign ayırımında F-18 FDG PET/BT'nin rolü

Giriş: Bu çalışmada, akciğerde kitle ve eşlik eden mediastinal lenf nodu saptanan hastalarda F-18 FDG pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) görüntülemesinde elde edilen SUV_{max} değerinin ve lezyon çapının benign ve malign kitleleri ayırt etmedeki rolünü belirlemek amaçlanmıştır.

Materyal ve Metod: Akciğerde kitle nedeniyle tanı ve evreleme amaçlı PET/BT yapılan ve biyopsi veya kitle rezeksiyonu ile histopatolojik sonuçlarına ulaşılan 100 hasta çalışmaya dahil edildi.

SUV_{max} değerleri, lezyon boyutu ve hasta yaşı, altın standart kabul edilen histopatolojik sonuçlar ile karşılaştırılarak duyarlılık ve özgüllük değerleri hesaplandı. Benign patolojilere eşlik eden 1 cm'den büyük lenf nodları değerlendirilerek SUV_{max} ölçümleri kaydedildi.

Bulgular: Histopatolojik olarak 62 lezyon malign, 38 lezyon benign olarak saptandı. Malign kitlelerdeki SUV_{max} değerleri (13.1 ± 6.4) benign kitlelerin SUV_{max} değerinden (8 ± 5.7) istatistiksel anlamlı olarak yüksek idi ($p < 0.05$). Malign kitlelerde boyut (4.5 ± 2.5 cm), benign kitlelerden (3 ± 1.6 cm) istatistiksel anlamlı olarak artmış saptandı ($p < 0.05$). Malign ve benign kitleleri ayırt etmede lezyon SUV_{max} değeri için sensitivite %82, spesifisite %55, lezyon boyutu için sensitivite %87, spesifisite %45 olarak saptandı.

Sonuç: Malign ve benign akciğer kitlelerinin değerlendirilmesinde önemli düzeyde birbiri ile çakışan değerler olabilmektedir. Uzmanlar değerlendirmelerinde yanlış pozitif ve yanlış negatif sonuçları göz önünde bulundurulmalıdır.

Anahtar kelimeler: F-18 FDG; pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT); akciğer kanseri

INTRODUCTION

Imaging plays an important role in the diagnosis and staging of lung cancer as well as in assessing treatment response and indetermining tumor recurrence. F-18 fluorodeoxyglucose (FDG) positron emission tomography and computed tomography (PET/CT) is a functional and anatomical imaging method for management of patients with pulmonary masses. FDG uptake is a good indicator of glycolysis which is markedly greater in malignant lesions. Maximum standardized uptake value (SUV_{max}) is used as a semi-quantitative measurement of FDG uptake which quantifies the glucose avidity of the tumor (1,2). Generally, an SUV_{max} threshold of 2.5 is applied to distinguish between benign and malignant lesions.

Mediastinal lymph node enlargements are caused by various inflammatory and infectious lesions as well as malignant diseases. CT and magnetic resonance imaging (MRI) take account of lymph nodes greater than 1 cm to be pathological. The SUV_{max} threshold is taken as 2.5 and PET/CT can differentiate between benign and malignant lymph nodes with high

sensitivity. But its specificity is lower especially due to granulomatous diseases (3).

The aim of the our study is to determine the value of SUV_{max} in differentiating malignant and benign pulmonary lesions and accompanying lymph nodes.

MATERIALS and METHODS

Between December 2010 and January 2013, all patients who were suspected of having lung cancer and undergone PET/CT for diagnosis and staging were evaluated retrospectively. Only patients with pathological confirmation with biopsy or surgical resection of the mass were selected. Patients with history of malignancy, previous therapy or surgical staging for lung cancer before PET and a recent history of pneumonia were excluded. One hundred patients (age range 36-85 years, mean 63.62 ± 11.5) were enrolled and analyzed. All patients who had blood glucose level less than 180 mg/dL were administered 270-370 MBq FDG intravenously. At 60 minutes after the injection, images were obtained from the vertex to the upper thigh using a PET/CT scanner (Biograph True point, Siemens, Germany). PET was performed with 2

minutes acquisition per bed position. CT scanning was performed using 120 kV, 50 mA, and a 3 mm section thickness immediately before PET imaging and intravenous contrast enhancement was used. PET/CT images in transaxial, sagittal and coronal planes were analyzed by two nuclear medicine physicians and the SUV_{max} of the lesions was obtained from transaxial images. For semi-quantitative analysis of FDG uptake, irregular regions of interest (ROIs) were placed over the most intense area of FDG accumulation. FDG uptake in these ROIs was quantified by calculating the SUV in each pixel according to the following formula: $SUV_{max} = \text{activity concentration} / (\text{injected dose} / \text{body weight})$. A SUV_{max} over 2.5 was considered as positive for malignancy. In mediastinum, lymph nodes greater than 1 cm were considered pathological and SUV_{max} values of these nodes were recorded. In the event only larger than 1 cm lymph nodes in patients with benign pathology were evaluated.

Our Institutional Review Board does not require approval for informed consent form patients for retrospective studies such as ours.

Statistical Analysis

Results are reported as the mean \pm SD and statistical analysis of clinical data between two groups consisted of unpaired t-tests for parametric data and Mann-Whitney U test analysis for nonparametric data. A Receiver Operating Characteristics (ROC) analysis was calculated on the SUV_{max} score change using the dichotomous pathological findings ("Benign" and "Malignant") as the external criteria. Using the ROC curve, the responsiveness is described in terms of sensitivity and specificity. The values for sensitivity and for false-positive rates (1-specificity) are plotted on the y- and the x-axis of the curve and the area under the curve (AUC) represents the probability a measure

correctly classifies patients as improved or unchanged. Analyses were performed using PASW 18 (SPSS/IBM, Chicago, IL, USA) software and P value less than 0.05 was considered statistically significant.

RESULTS

All 100 patients' diagnoses were confirmed histopathologically. Sixty two lesions were malignant and thirty eight were benign. Among the malignant pathologic diagnosis, there were 22 squamocellular carcinomas, 25 adenocarcinomas, 2 large cell carcinomas, 6 small cell carcinomas, 1 metastases, 1 mesothelioma and 5 non-specified NSCLC. There were 3 false negative cases which all of them were adenocarcinomas. Among the benign cases who had lung lesions greater than 2.5 of SUV_{max} , there were 18 acute inflammations (pneumonia), 6 granulomatous disease, 6 chronic inflammations and 4 atelectases. SUV_{max} were less 2.5 in four patients' lesion and evaluated true negative (one lesion was hydatidic cyst and three were pneumonia).

The PET/CT images of a false positive case are presented in Figures 1A, 1B and 1C. This patients' lung mass was diagnosed as an infection histopathologically. All of the patients with benign lesions had mediastinal lymph nodes greater than or equal to 1 cm. The largest mediastinal lymph node was 3.7 cm and was found in a patient who had granulomatous disease. The SUV_{max} values of these benign lymph nodes ranged from 1.2 to 15.3 (Table 1).

A statistically significant relationship between patients' age and malignancy was not detected ($p = 0.094$). The minimum lesion size measured by CT was 1 cm and the largest lesion was 13 cm. The dimensions of malignant masses (4.5 ± 2.5 cm) were larger than benign ones (3 ± 1.6 cm) and the difference was statistically

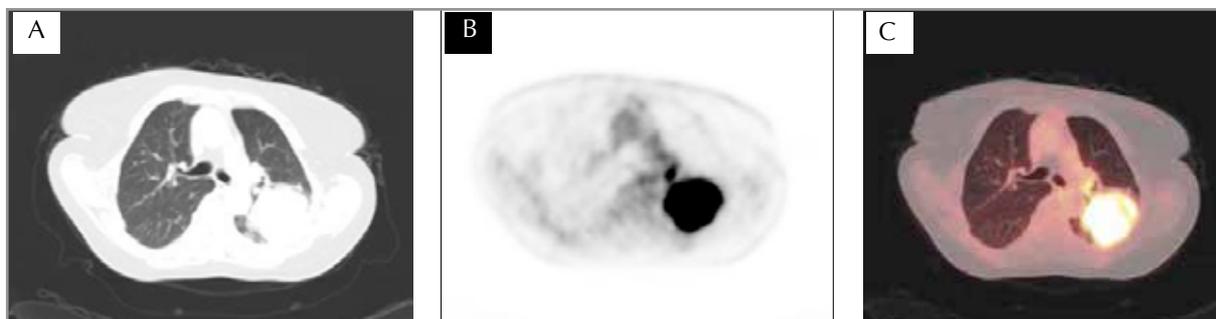
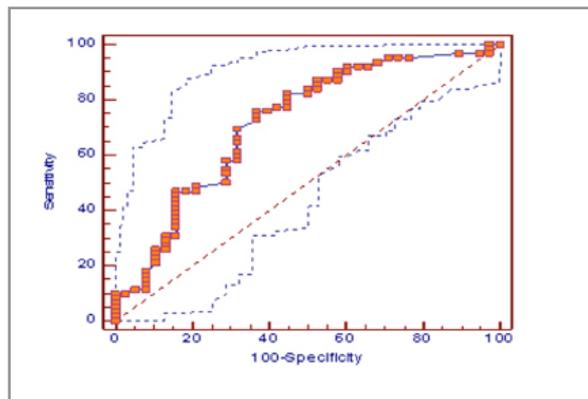
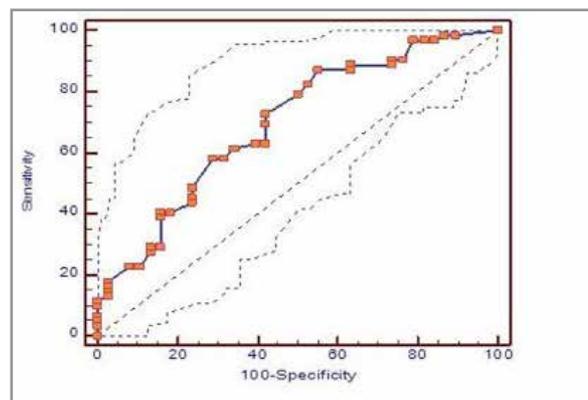


Figure 1. A-C: Imaging of a patient with hypermetabolic lung mass in left lung (SUV_{max} : 22), transaxial CT (A), FDG/PET (B) and fusion (C) images. Histopathological diagnosis was infection.

Table 1. Causes of false positive FDG PET/CT scans; diagnosis and results of SUV_{max} quantifications

	n	SUV _{max} of tumor (range)	SUV _{max} of enlarged lymph node (range)
acute inflammations	18	3.3-22	1.2-10.4
chronic inflammations	6	3.2-13.7	4.1-12.5
granulomatous disease	6	3.6-15.1	2.9-15.3
atelectasis	4	2.7-6.4	2-5.7

*SUV_{max}, maximum standardized uptake value.

**Figure 2.** Area under the receiver operating characteristic curve for standardized uptake value (SUV_{max}). The highest diagnostic accuracy was achieved with an SUV_{max} threshold of > 7.6 (sensitivity 82%, specificity 55%).**Figure 3.** Area under the receiver operating characteristic curve for lesion size. The sensitivity and specificity for the lesion sizes in differentiation of malignant and benign lesions were 87% and 45% respectively.

significant ($p=0.001$). When the cases were evaluated based on tumor metabolism, the SUV_{max} were significantly more elevated in malignant masses (13.1 ± 6.4) than benign masses (8 ± 5.7) ($p=0.000$). The highest

diagnostic accuracy was achieved with an SUV_{max} threshold of > 7.6 and sensitivity 82%, specificity 55% were respectively. The sensitivity was 87% and the specificity was 45% for the lesion sizes in the differentiation of malignant and benign lesions. Sample ROC curves for SUV_{max} and lesion size are shown in Figures 2 and 3.

DISCUSSION

F-18 FDG PET/CT plays an important role in the diagnosis, staging and follow-up of patients with lung cancer. PET images allow both a visual and quantitative evaluation. The glucose utilization of tissues can be semi-quantitatively defined by SUV_{max} (4). Lesions with an SUV higher than 2.5 have been considered malignant (5,6). Although some studies which used SUV evaluation showed no significant difference between the diagnostic performance of visual interpretation and quantitative analyses, the specificity of the visual interpretation was lower than using an SUV threshold of 2.5 (74 vs 90%) (7,8). In one study, authors evaluated the diagnostic value of PET/CT for lung masses and found a sensitivity of 89.9% and specificity of 61.5% for PET imaging using a SUV_{max} cut-off value of 2.5 (9). In our study, we found a sensitivity of 82% and a specificity of 55% for SUV_{max} in the differentiation of benign and malignant lung masses.

One of the most significant limitation of F-18 FDG PET imaging is that abnormal F-18 FDG uptake is not specific for malignancy. Benign lesions such as pneumonia, aspergillosis, abscesses and granulomatous diseases may cause false positive results on PET/CT while low FDG uptake may be appear in slow-growing malignant lesions such as neuroendocrine tumors (10,11). In our study, there were 34 false positive cases, the majority of which were pneumonia. Moreover, the majority of these benign lesions showed a higher SUV_{max} than malignant lesions. Additionally,

there were three false negative cases which were adenocarcinomas, consistent with previous studies which showed a lower SUV in this subtype (12-14).

Although some studies indicated that most lung masses with a diameter larger than 3 cm were malignant, in our study there were 9 cases (8 pneumonia and 1 granulomatous disease) whose tumors were benign and larger than 3 cm (15). We found a statistically significant difference between the sizes of malignant and benign lesions. Lu et al. reported that the size of pulmonary malignant neoplasms was correlated with SUV_{max} , but there was no significant correlation between the size of pulmonary benign lesions and the SUV_{max} (9). They also showed a lot of cases with false positives at PET/CT with tumors larger than 3 cm.

CT and MR were used as diagnostic criteria for metastatic disease in lymph nodes greater than 1 cm. Many studies have shown sensitivities and specificities of 50-70% for this criterion and microscopic metastases may be found in normal sized lymph nodes (3,16,17). An SUV_{max} cut-off value of 2.5 to differentiate benign from malignant lesions has high sensitivity and specificity in PET/CT imaging especially in developed countries. However, in countries where granulomatous diseases are endemic, the diagnostic value of PET/CT may be lower. Kumar et al. evaluated thirty-five patients with mediastinal lymphadenopathies and they found that the SUV_{max} of benign lymph nodes ranged from 2.3-11.8 and the SUV_{max} of malignant lymph nodes ranged from 2.4 to 34 (3). They also showed that F-18 FDG PET/CT has a sensitivity of 93% and a specificity of 40% with SUV_{max} 2.5 as the cut-off. In our study, we evaluated only enlarged lymph nodes in patients with benign pathologies and we found that the SUV_{max} values of these lymph nodes ranged from 1.2 to 15.3. So, we showed hypermetabolic lymph nodes greater than 1 cm do not always reflect malignancies.

Our study has some limitations. First of all, this was a retrospective study which may have resulted in selection bias. We were unable to evaluate enlarged lymph nodes in patients with malignant pathology. So, we couldn't make a comparison between the groups. An additional limitation was calculation of SUV_{max} values of only the lymph nodes with largest short axis despite the possibility that highest SUV_{max} could be found in smaller mediastinal lymph nodes. Using SUV_{max} threshold value of 2.5 which is not specific for

malignancy should be considered as another limitation in this study.

As a conclusion, in this study we found that F-18 FDG PET/CT has good sensitivity and specificity values for determining the character of lung tumors. Although lesion size and SUV_{max} values indicate a good achievement in the differentiation of malignant and benign masses, there are important overlaps between benign and malignant lesions. Specialists should be consider of both false positives and negatives. Additionally, although enlarged lymph nodes with very high SUV_{max} values may be found with benign lesions, these should not be criteria for malignancy, especially in developing countries where granulomatous disease is common.

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