Accuracy of 18-FDG PET/CT in the Differential Diagnosis of Malignant and Benign Pleural Diseases

Kenan C. CEYLAN[1], Deniz AKPINAR[1], Seyda O. KAYA[1], Hakan KOPARAL[2], Ali Kadri CIRAK[3]

[1] Dr. Suat Seren Chest Diseases and Thoracic Surgery Training Hospital, 2nd Thoracic Surgery Clinic, Izmir
[2] Dr. Suat Seren Chest Diseases and Thoracic Surgery Training Hospital, Department of Nucleer Medicine, Izmir
[3] Dr. Suat Seren Chest Diseases and Thoracic Surgery Training Hospital, Chest Diseases Clinic, Izmir, TURKEY

ABSTRACT

Integrated whole-body 18-fluorodeoxyglucose positron emission tomography-computed tomography (PET/CT) is a non-invasive imaging technique for identifying several types of malignant diseases. We evaluated the role of PET/CT in distinguishing malignant from benign pleural diseases. Thirty patients, who had pleural abnormalities on computed tomography (CT), such as thickening, fluid with suspicion of malignant pleural mesothelioma or any other malignancy underwent PET/CT. Maximum standardized uptake values (SUVmax) were calculated separately for pleural thickening and pleural fluid and compared with pathological results obtained by video thoracoscopy. Twenty-two patients with pleural thickening and 25 patients with pleural fluid were assessed with regard to the accuracy of PET/CT. The overall sensitivity,specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET/CT was 81.8%, 54.5%, 64.3%, 75%, and 68.2% for pleural thickening and it was 100%, 56.5%, 41.1%, 100%, and 60% for patients with pleural fluid. When the pleural thickening was evaluated, the SUVmax values were higher in the malignant pleural diseases than in the benign pleural diseases but the difference was not statistically significantly (p = 0.063). When the pleural fluid was evaluated, the SUVmax values were also higher in the malignant pleural diseases than in the benign pleural diseases and the difference was statistically significantly (p= 0.03). The accuracy of PET/CT for detecting malignant pleural fluids was high. However, PET/CT was not adequate to make the differential diagnosis of pleural malignancies especially in case of pleural thickening because of its relatively low sensitivity,specificity,PPV, and NPV. A tissue biopsy is necessary to determine the diagnosis.

Keywords: 18-fluorodeoxiglucose-positron emission tomography, Pleural Disease

ÖZET

Malign ve Benign Plevral Hastalıkların Ayırıcı Tanısında 18-FDG PET/BT'nin Etkinliği

Tüm vücut 18-florodeoksiglukoz pozitron emisyon tomografi /bilgisayarlı tomografisi (PET / BT) birçok malign hastalığın tanısında kullanılan non-invaziv bir hibrid görüntüleme tekniğidir. Çalışmamızda malign ve benign plevral hastalıkların ayırıcı tanısında PET / BT'nin etkinliği değerlendirildi. Bilgisayarlı tomografide malign plevral mezotelyoma ve diğer malignite şüphesi oluşturan plevral kalınlaşma veya plevral sıvısı saptanan 30 hastaya PET / BT uygulandı. SUVmax değerleri plevral kalınlaşma ve plevral sıvı için ayrı ayrı hesaplanarak video torakoskopi ile elde edilen patoloji sonuçları ile karşılaştırıldı. Plevral kalınlaşması olan 22 hasta ve plevral sıvısı olan 25 hasta PET / BT etkinliği açısından değerlendirildi. Plevral kalınlaşma için duyarlılık, özgüllük, pozitif prediktif değer (PPV), negatif prediktif değeri (NPD) ve PET / BT'nin etkinlik oranı sırasıyla %81.8, %54.5, %64.3, %75 ve %68.2, plevra sıvı için sırasıyla %100, %56.5, %41.1, %100 ve %60 idi. Plevral kalınlaşma için bakıldığında SUVmax değerleri malign hastalarda daha yüksek olmakla beraber aradaki fark istatistiksel olarak anlamlı değildi (p= 0.063).

Plevral sıvı için bakıldığında SUVmax değerleri malign hastalarda daha yüksek bulundu ve aradaki fark istatistiksel olarak anlamlı bulundu (p= 0.03). Malign plevral sıvıları saptamada PET / BT etkinliği oldukça yüksektir ancak, düşük duyarlılık, özgüllük, PPV ve NPV değerleri özellikle plevral kalınlaşma durumunda plevral malignitelerin ayırıcı tanısı için yeterli değildir. Kesin tanının belirlenmesinde doku biyopsisi mutlak surette gereklidir.

Anahtar Kelimeler: 18-florodeoxiglukoz-positron emisyon tomografi, Plevral Hastalıklar

INTRODUCTION

Pleural diseases appear as pleural thickening or pleural fluid in the thorax on computed tomography (CT). Pleural diseases, such as infectious pleuritis, pleural fibrosis, malignant pleural mesothelioma (MPM), and lung cancer metastasis, result in pleural effusions and can look similar on CT. When such findings are identified on a CT scan, it is difficult to distinguish whether the disease is malignant or benign. Although lung cancer is the most common cause of pleural effusion, MPM, breast cancer, lymphoma and gastrointestinal tumours can also involve the pleura and cause pleural effusion. Pleural diseases can be diagnosed by pleural biopsy. In some cases, biopsy results are inconclusive; thus, video-assisted thoracoscopic surgery (VATS) or a thoracotomy may be required.

MPM is often seen as pleural thickening or as pleural fluid. Some regions of our country have an increased risk for MPM, a rare, yet aggressive, tumour, which usually has a poor prognosis. Rapidly distinguishing between benign and malignant pleural diseases is important, because a few selected patients may benefit from chemotherapy or trimodal treatment.[1]

Whole-body 18-fluorodeoxiglucose-positron emission tomography (FDG-PET) is a non-invasive imaging technique and diagnostic tool for several types of malignant disease (2). Recent studies have shown that the sensitivity of FDG-PET is within the range 93-96% for diagnosing malignant pleural diseases.[2,3,4]

We compared PET/CT results with pathological results for diagnoses of pleural thickening and pleural fluid.

PATIENTS AND METHODS

Thirty patients who had pleural abnormalities, such as thickening or fluid with suspicion of MPM or any other malignancy on CT scans, underwent PET/CT between April 2007 and March 2010. All patients were investigated by chest physicians, and a blind-needle pleural biopsy was performed. Although a visual analysis by CT, PET/CT, and a blind-needle biopsy was used to distinguish benign from malignant pleural disease, the patients were referred to our clinic for invasive surgical procedures to analyse the accuracy of PET/CT. VATS was considered initially, because the diagnostic value of VATS is greater in diagnosing pleural diseases. All patients were evaluated with a history, physical examination, whole blood analyses, a pulmonary function test, chest radiography, chest CT, and bronchoscopy. Chemical and cytological analyses of the pleural fluid were conducted in all patients. Eligibility criteria for this study were pleural thickening or pleural fluid on chest CT, suspicion of malignancy, and medical fitness for surgical diagnostic procedures (video thoracoscopy or thoracotomy). CT findings, such as pleural thickening and pleural fluid were evaluated in correlation with PET/CT and pathological reports independently. The same patients were analysed for both CT findings to evaluate the accuracy of PET/CT for both pleural thickening and fluid.

This study was approved by the medical ethics committee of Dr. Suat Seren Chest Disease and Chest Surgery Teaching Hospital and was designed prospectively.

PET/CT

PET/CT was performed in our hospital, using a dedicated full-ring scanner (ECAT ACCELL; Siemens Medical Systems, Biograph Duo 2 Slice CT, Erlangen Germany). Plasma glucose values were < 200 mg/dL. FDG activity of 370-555 MBq was injected intravenously, depending on the patient's weight. Attenuation-corrected whole-body PET/CT scans in three-dimensional mode were acquired 60 min after FDG administration, using a machine equipped with lutetium oxyorthosilicate crystals

and a 162 mm axial field of view. Scans were performed from the inferior pelvis to the vertex.

To minimize variability in the standardized uptake value (SUV) due to body composition, the SUV was calculated using lean body mass. Malignant or benign separation was performed according to the interpretations of nuclear medicine specialists. They evaluated the PET/CT results as malignant when the SUVmax value was >2.5, which was considered a positive result; if they evaluated it as benign diseases (SUVmax ≤ 2.5) it was considered a negative result. The SUVmax values for pleural thickening and pleural fluid were calculated for each PET/CT finding separately and compared with appropriate pathological results.

Operation and Pathological Examination

We performed VATS, because a pleural biopsy had already been performed in all patients. VATS was the first option, but a mini thoracotomy was performed in two patients because of strict adherence to the overlying parietal pleura. We used a double-lumen endotracheal tube for intubation. First, the pleural fluid was aspirated, and then multiple biopsies were obtained from different locations in the pleura.

Pathological specimens were sampled from visceral pleura, parietal pleura, and pleural fluid. Pathological examination methods included cytology, histology and, if necessary, immunohistochemistry. Haematoxylin and eosin staining was used for all patient specimens. To verify the differential diagnosis of malignancy, pancytokeratin, vimentin, carcinoembryonic antigen, Tag-72, and calretinin were analysed by immunohistochemistry.

Statistical Analysis: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and PET/CT accuracy were calculated separately for pleural thickening and pleural fluid. A receiver operating characteristic (ROC) analysis was used. A p value < 0.05 was considered to indicate statistical significance.

RESULTS

Thirty patients were included; 19 males and 11 females, with a mean age of 52.5 (range, 32-71) years. Twenty-two of 30 patients (73.3%) had pleural thickening (5 patients had only pleural thickening, 17 patients had pleural thickening with pleural fluid) on CT scans. These 22 patients were examined for PET/CT accuracy of pleural thickening. Twenty-five of the 30 patients (83.3%) had pleural fluid (8 patients had only pleural fluid and 17 patients had pleural thickening with pleural fluid) on CT scans. These 25 patients were examined for PET/CT accuracy of pleural fluid on the basis of pathological examination.

Twenty-eight VATS and two limited thoracotomies were performed. No operative or postoperative mortality was noted. One case of prolonged air leak and one of atrial fibrillation were seen as postoperative morbidities.

Pleural Thickening

Pleural thickening was observed in 22 patients on CT scans. In 17 patients, pleural fluid and thickening occurred together. By PET/CT, 14 malignant (SUVmax > 2.5), eight benign (SUVmax ≤ 2.5) diseases were detected in patients with pleural thickening. The mean SUVmax was 6.7 (range, 2.6-22.0)

Table 1. Sensitivity, Specificity, PPV, NPV and Accuracy of PET/CT

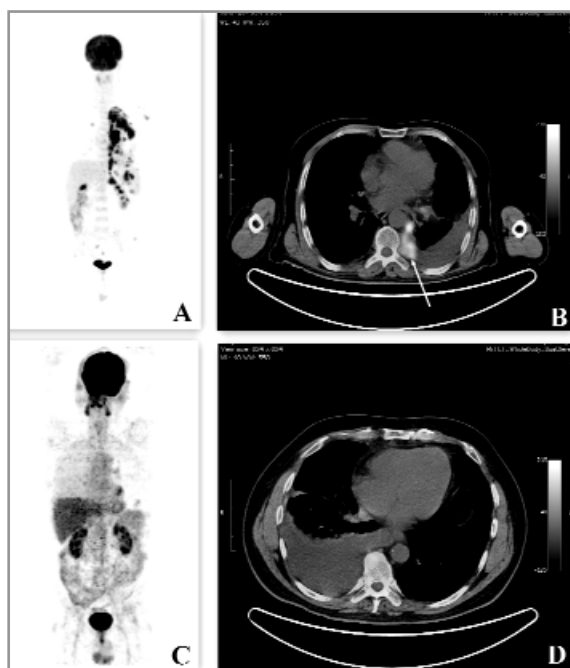| CT Findings	PET Findings		Pathological Results		Sensitivity	Specificity	PPV	NPV	Accuracy
	Negative	Positive	Benign	Malignant					
Pleural Thickening (n= 22)	8	14	11	11	81.8	54.5	64.3	75	68.2
Pleural Fluid (n= 25)	18	7	8	17	100	56.5	41.1	100	60
PPV= Positive predictive value; NPV= Negative predictive value									

Figure 1A, 1B. Positive PET/CT with malignant pleural fluid

Figure 1C, 1D. Negative PET/CT with benign pleural fluid

Figure 2. ROC analysis, the area under the curve for the pleural fluid SUVmax level was 0.735 (p= 0.03)

for PET/CT-positive patients and 1.57 (range, 0.0–2.4) for PET/CT-negative patients, but this difference was not statistically significant (p= 0.063). The pathological diagnoses in the 14 PET/CT-positive patients were nine malignant (2 MPM, 5 adenocarcinoma metastases, and 2 breast cancer metastases) and five benign diseases (4 non-specific pleuritis and 1 case of tuberculosis). The pathological diagnoses in the eight PET/CT-negative patients were six benign diseases (5 non-specific pleuritis and 1 case of tuberculosis) and two with MPM. In the false-negative results observed in patients with MPM, the histological subtype was epithelioid MPM for all, and the SUVmax values were between 0 and 2.4. In the false-positive patients with non-specific pleuritis, the SUVmax values were between 2.7 and 12.0 or 4.2 for tuberculosis. The overall sensitivity, specificity, PPV, NPV, and accuracy for PET/CT was 81.8%, 54.5%, 64.3%, 75%, and 68.2% for pleural thickening (Table 1).

Pleural Fluid

Pleural effusion was observed in 25 patients. The SUVmax values were calculated for pleural fluid. Seven patients had positive PET/CT results with
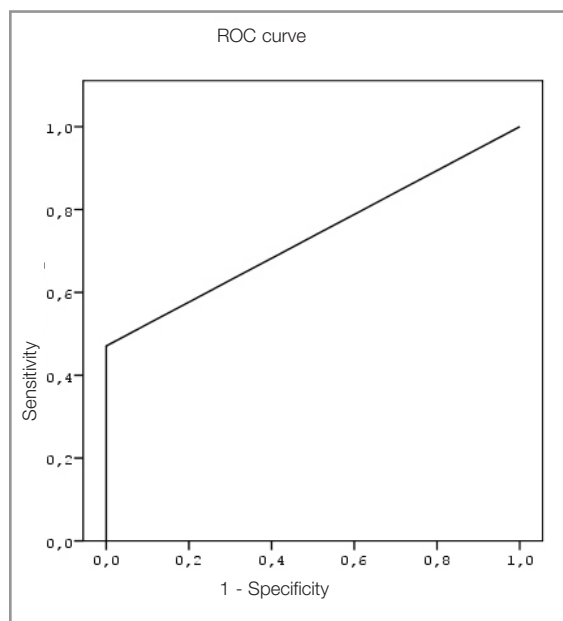
SUV max values of 4.3-11.2. These seven patients were diagnosed pathologically with malignant pleural fluid: two metastatic adenocarcinomas, two MPMs, two adenocarcinomas of the lung and one breast cancer metastasis (Figure 1A, 1B). The PET/CT results were negative in 18 patients with pleural fluid (Figure 1C, 1D). The final pathological results were reported as ten patients with malignant pleural fluid (5 MPM, 4 adenocarcinoma metastases, and 1 breast carcinoma metastasis) and eight with benign pleural fluid (7 with non-specific pleuritis and 1 with tuberculosis). The mean SUVmax value was 7.58 (range, 4.3-11.2) for the PET/CT-positive patients and 0.2 (range, 0.0-2.4) for the PET/CT-negative patients. In the ROC analysis, the area under the curve for the pleural fluid SUVmax level was 0.735 (p= 0.03; Figure 2). The overall sensitivity, specificity, PPV, NPV, and accuracy of PET/CT were 100%, 56.5%, 41.1%, 100%, and 60% for patients with pleural fluid (Table 1).

DISCUSSION

Pleural thickening or pleural fluid can occur in both benign and malignant diseases. The differential di-

agnosis between benign and malignant pleural diseases is crucial because the survival after acquiring a malignant pleural disease is poor, and treatment strategies differ. Some reports have demonstrated that PET/CT is highly accurate in the differential diagnosis of pleural disease and is superior to CT.[5,6,7] Additionally, some authors have reported that PET/CT is highly accurate for staging patients with MPM.[8,9,10] Many studies have evaluated the diagnostic value of PET/CT in malignant pleural diseases, such as lung cancer or MPM[11,12,13,14], but few have evaluated the accuracy of PET/CT in distinguishing malignant from benign disease.

Schaffler et al. reported that the accuracy of PET for detecting pleural malignancies in non-small cell lung cancer is 80% with 100% sensitivity.[15] In Flores et al., 63 patients with proven MPM underwent PET with a 57% PPV and a 63% NPV. They reported that negative PET scans do not rule out the presence of MPM (16). Otsuka et al. reported that the utility of PET/CT was limited for evaluating primary tumour extension and nodal status, but that PET/CT was useful for detecting distant metastases.[17] Additionally, if tumour implants are smaller than 5 mm, they may not be detected by conventional imaging.[18] In our study, the overall sensitivity, specificity, PPV, NPV, and accuracy of PET/CT was 81.8%, 54.5%, 64.3%, 75%, and 68.2% for patients with pleural thickening and 100%, 56.5%, 41.1%, 100%, and 60% for patients with pleural fluid, respectively.

Two patients were diagnosed with epithelioid-type MPM with false-negative PET findings in the pleural thickening group, and five patients were diagnosed with epithelioid-type MPM in the pleural fluid group. The SUVmax value was between 0 and 2.4 in these seven patients. Generally, SUVmax values are lower than other types of lung cancer with lower tumour metabolism, such as in epithelioid-type MPM or adenocarcinoma, in contrast, infectious or granulomatosus diseases can cause false-positive results without malignancy on PET.[19,20,21] Four patients with a false-positive PET result were diagnosed with infectious pleuritis, and one was diagnosed with tuberculosis in the pleural thickening group. We think that the false-negative PET/CT results are due to the low tumour metabolism of MPM, and that the false-positive PET/CT results are due to the infectious process.

Kramer et al. reported that patients with pleural thickening may be followed using CT alone, rather than pathological diagnostic procedures, due to the high NPV percentage of PET (92%) and that positive PET findings should always lead to a tissue verification procedure.[2] The NPV and sensitivity values we found were not high enough to follow-up patients with pleural thickening using PET/CT. Zahid et al. investigated the best method for diagnosing and staging MPM.[22] They searched the literature and found 61 studies. They concluded that pleural biopsy provided the most accurate definitive diagnosis for MPM. We share the same perspective and believe that a tissue biopsy is necessary to determine the diagnosis for patients with PET/CT-negative or -positive pleural diseases. A limitation of our study was the relatively small number of patients.

CONCLUSION

The accuracy of PET/CT for detecting malignant pleural fluid is high. However, PET/CT is not adequate to identify pleural malignancies especially for the patients with pleural thickening because of its low sensitivity, specificity, PPV, and NPV. Thus, a tissue biopsy is also necessary to determine the diagnosis for patients with PET-negative or -positive pleural thickening.

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Correspondence

Dr. Kenan Can CEYLAN

Dr. Suat Seren Göğüs Hastalıkları ve Göğüs Cerrahisi

Eğitim ve Araştırma Hastanesi

Göğüs Cerrahisi Kliniği

Yenişehir, İZMİR / TURKEY

Tel: (+90.232) 433 33 33

Fax no: (+90.232) 458 72 62

e-mail: kcanceylan@gmail.com