Study objectives: To study the ability of positron emission tomography (PET) using 18-fluorodeoxyglucose (FDG) to distinguish between benign and malignant disease in exudative pleural effusions and pleural thickening.

Design: Prospective study of 98 consecutive patients presenting with either pleural thickening or an exudative pleural effusion.

Setting: Department of pulmonary medicine of a university hospital.

Methods: FDG-PET was performed on each subject before invasive procedures were used to determine the etiologic diagnosis. FDG-PET data were analyzed by visual interpretation.

Results: Sixty-three of 98 patients were found to have malignant pleural disease after histologic analysis. Sixty-one of 63 patients with histologically confirmed malignant disease showed FDG uptake within the area of pleural thickening. Uptake was graded as intense in 51 cases and moderate in 10 cases. Only two patients with malignant pleural disease did not show increased FDG uptake. FDG-PET imaging showed an absence of FDG uptake, and correctly classified 31 of 35 benign lesions. For the remaining four lesions, intense FDG uptake was seen in one case of parapneumonic effusion, while moderate and localized uptake was observed in one parapneumonic, one tuberculous, and one uremic pleurisy. The sensitivity of the method to identify malignancy was 96.8% with a negative predictive value of 93.9%, while its specificity was 88.5% and its positive predictive value was 93.8%.

Conclusions: Our results suggest that FDG-PET is an effective tool for differentiating between benign and malignant pleural diseases.

Key words: fluorodeoxyglucose; pleural diseases; positron emission tomography

Abbreviations: CI = confidence interval; FDG = 18-fluorodeoxyglucose; PET = positron emission tomography

Pleural effusion or pleural thickening are the usual radiographic manifestations of pleural diseases, but accurate diagnosis is difficult without resort to invasive procedures. It is often necessary to perform thoracic CT scan; thoracocentesis with biochemical, microbiological, and cytologic analyses; blind-needle biopsies; and sometimes eventually biopsies performed during either pleuroscopy or open-chest surgery. Invasive procedures are justified for several reason. First, there is a lack of accepted and reliable criteria for malignancy only based on morphologic imaging (CT and MRI). Second, the sensitivity of cytologic examination of pleural fluid and blind needle biopsy is weak.1–8 By contrast, thoracoscopy alone was found to be diagnostic in 95% of cases.7 However, this procedure has several drawbacks. It is invasive, must be performed with caution in older patients, and requires surgical facilities and trained staff.

Positron emission tomography (PET) using 18-fluorodeoxyglucose (FDG)9 can accurately differentiate benign from malignant pulmonary tumors using the marked biochemical difference in glucose metabolism between normal and tumor cells. Studies have shown the utility of FDG-PET in the evaluation of solitary pulmonary nodules,10–12 and also in mediastinal staging13,14 and detection of extrathoracic...
metastasis\textsuperscript{15,16} of non-small cell lung cancer. Moreover, residual or recurrent tumor after treatment can also be identified by this metabolic imaging,\textsuperscript{17} making it a useful tool for the follow-up of non-small cell lung cancer.

In a preliminary study assessing 25 patients, we showed that FDG-PET had a sensitivity of 100\% to diagnose malignant pleural disease.\textsuperscript{18,19} To extend this earlier pilot study, we performed a prospective study in 98 patients presenting to our hospital with pleural disease.

**PATIENTS AND METHODS**

**Patient Selection**

Ninety-eight consecutive patients presenting exudative pleural effusion and/or pleural thickening (mean age, 60.9 years; range, 36 to 83 years; 67 men and 31 women) were investigated. In all these patients, the combination of chest radiography, thoracic CT scanning (PQ 2000 Fourth Generation; Picker; Cleveland, OH) and thoracocentesis failed to give an etiologic diagnosis. Sixty-seven patients had pleural effusion, 10 patients had diffuse pleural thickening, 2 patients had localized pleural thickening, and 19 patients had combined effusion and thickening.

**Study Design**

A FDG-PET study was performed on each subject before invasive procedures were carried out. The final diagnosis of the pleural lesion was obtained by invasive procedures including blind-needle biopsy of the pleura, thoracoscopy, or open pleural biopsy. When a diagnosis of benign disease was established, the patients were followed up for at least 3 years to ensure absence of malignant pleural processes.

**FDG-PET Study**

FDG-PET was performed with an UGM Penn PET 240H (UGM Medical Systems; Philadelphia, PA) until 1999 and since 2000 with an ADAC UGM C-PET scanner (UGM Medical Systems). The data were analyzed by visual interpretation of coronal, sagittal, and transverse slices alone and by cross-referencing. FDG-PET images were read independently by two nuclear physicians who only had knowledge of the standard chest radiography. They assessed the presence or absence of FDG uptake in the pleural layer. When increased FDG uptake was observed, activity was classified as either moderate or intense. When a diagnosis of benign disease was established, the patients were followed up for at least 3 years to ensure absence of malignant pleural processes.

**Statistical Analysis**

The efficacy of FDG-PET imaging in differentiating malignant from benign pleural lesions was evaluated using classical sensitivity and specificity criteria. Positive and negative predictive values were calculated. For each parameter, the 95\% confidence interval (CI) was given.

**RESULTS**

The nature of pleural lesion was diagnosed from cytologic and histologic specimens obtained with blind-needle biopsy, thoracoscopy, and open surgical biopsy in 17, 62, and 5 subjects, respectively. In the remaining 14 patients, no specific histologic pattern other than pleural inflammation was observed. Because of the clinical context in these patients, no further invasive procedure was believed to be indicated, and the decision was made to classify the patient as having benign pleural disease.

Table 1 shows the analysis of the diagnoses of benign and malignant pleural lesions, and the interpretation of their FDG-PET uptake. A total of 63 patients had malignant disease, and 35 patients had benign pleural disease. Malignancies confirmed by cytologic and histologic methods included 47 metastatic lesions (34 carcinomas, 1 bronchioalveolar carcinoma, 8 epitheliomas, 3 small cell lung cancers, and 1 thymoma), 13 mesotheliomas, 2 lymphomas, and 1 sarcoma.

The benign lesions were composed of 12 parapneumonic effusions (confirmed by plain radiographic follow-up after invasive exploration), 3 tuberculous pleuritis, 8 chronic inflammatory pleural diseases, 3 effusions after radiotherapy, 1 pleural fibroma, 1 benign neurofibroma, and 1 pleural lipoma. In six cases, the final diagnosis of pleural disease was considered to be benign asbestosis with pleural effusion. All of these had a history of asbestos exposure with a duration (mean ± SD) of exposure of $6 ± 1.2$ years. The mean interval between exposure and presentation was $14 ± 4.2$ years. In four patients, the effusion was asymptomatic, whereas two patients had breathlessness. In all cases, the effusion was small (< 500 mL). Pleural biopsy spec-

<table>
<thead>
<tr>
<th>Etiologic Diagnosis</th>
<th>Metabolic PET Evaluation</th>
<th>Absence of</th>
<th>Moderate FDG Uptake</th>
<th>Intense FDG Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign pleural disease (n = 35)</td>
<td>FGD Uptake</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Parapneumonic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asbestosis</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>After radiotherapy</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lipoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fibroma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Malignant pleural disease (n = 63)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural metastasis</td>
<td>1</td>
<td>9</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
imens obtained by thoracoscopy revealed established pleural fibrosis and/or inflammatory infiltration with fibrinous exudates and benign mesothelial proliferation. The clinical course was that of a benign and self-limiting illness lasting 4 months, with complete resolution in three cases and residual pleural thickening in the others. At present, the follow-up for all patients with benign pleural disease is at least 3 years with no disease progression, recurrence, or pleural malignancy.

FDG-PET imaging correctly identified 61 of 63 cases of malignant pleural disease. The increase in FDG uptake was classified as intense in 51 patients and moderate in 10 patients. The hyperfixation of FDG was intense in all cases of mesothelioma and neoplastic pleurisy associated with a primary lung cancer. In cases of mesothelioma, the hyperfixation appeared to be diffuse and sometimes involved the mediastinal pleura (Fig 1). The metastatic pleural lesions showed a diffuse increase in FDG uptake within the area of pleural thickening that were mainly localized in lower lateral and/or diaphragmatic zones (Fig 2).

Only two confirmed malignant diseases did not show pleural FDG uptake. These included one pleural metastasis of a prostate cancer and one pleural localization of a low-grade lymphoma.

FDG-PET imaging revealed an absence of FDG uptake within the pleura, and correctly identified 31 of 35 benign lesions (Fig 3). In the four patients who showed an FDG uptake, this was moderate and localized in three patients but intense in one case only. The three patients with moderate uptake had parapneumonic effusions, chronic uremic pleurisy, and tuberculous pleuritis, respectively. The patient with intense uptake was a 58-year-old alcoholic woman with a parapneumonic effusion. The fluid obtained by thoracocentesis was a highly cellular exudate with lymphocyte predominance. Results of bacteriologic analysis were negative, and the clinical course was favorable after drainage and antibiotics.

From the above results, the sensitivity of FDG-PET imaging to detect pleural malignancies was 96.8% (95% CI, 89 to 99.6), with a negative predictive value of 93.9% (95% CI, 79.8 to 99.3). The specificity was 88.5% (95% CI, 73.3 to 96.8), with a positive predictive value of 93.8% (95% CI, 85 to 98.3).

**DISCUSSION**

Little is known about application of FDG-PET imaging to the management of pleural disease. Our results indicate that FDG-PET is a useful tool to differentiate between benign and malignant pleural lesions. We confirm in a large series of patients our primary study and the sparse data available involving small number of patients. Indeed, this technique has sensitivity and negative predictive value > 90% in diagnosing malignancy. With a sensitivity of 97%, PET-FDG is by far superior to pleural fluid cytology (62%) and blind pleural biopsy (44%), and is virtually similar to pleuroscopy alone (95%) in diagnosing malignancy. In our study, all benign and malignant primary pleural tumors (n = 16) were correctly identified by this noninva-
sive metabolic technique. Among the 50 cases of metastatic pleural lesions, 48 showed increased FDG uptake. Two pleural metastases were not correctly identified by metabolic imaging with an absence of FDG uptake. The first was a prostate cancer and the second was a low-grade lymphoma, two types of tumors with a low multiplication rate of cells and a low glycolytic activity. As the grading of uptake intensity is dependent on the metabolic activity, it is worth noting that all mesotheliomas showed an intense uptake of FDG, while this pattern was observed in 78% (38 of 49 metastatic pleural lesions), the other 22% showing moderate uptake. The intense uptake that prevailed in the majority of malignancy contrasts with the moderate uptake observed in the rare cases of infections that were found to be positive. Ten of 63 malignant pleural diseases (16%) and 3 of 35 benign lesions (9%) presented with moderate FDG uptake. Therefore, the discriminating value of FDG-PET is clearly weaker when the uptake is moderate. However, this uptake pattern only represented < 15% of cases.

As treatment of pleural malignancy depends on the histologic nature of the tumor, FDG hyperfixation should prompt invasive exploration to guide the treatment. Perhaps the most significant contribution of FDG-PET to management of pleural effusion is its ability to exclude malignant lesions. Because of its high specificity (88%) and negative predictive value (94%), FDG-PET should allow the clinician to avoid performing invasive diagnostic escalation in cases where a benign lesion is suspected by the absence of FDG uptake.

However, there are circumstances under which invasive thoracoscopy or closed biopsies may still be indicated despite negative FDG-PET results. For instance, pleural effusion associated with exposure to asbestos could justify performing thoracoscopy to
obtain an accurate diagnosis in order to benefit from financial government compensation. Also, when clinical context hints at pleural tuberculosis, public health reason would recommend to obtain bacteriologic proof.

In conclusion, we have extended our preliminary results and confirmed, in a large series of patients, that FDG-PET is an accurate method for differentiating benign from malignant pleural diseases. This technique could facilitate decision making as to when to begin invasive procedures.

ACKNOWLEDGMENT: We thank Dr. Garry Harstein for reviewing the manuscript.

REFERENCES