18-FDG positron emission tomography in the evaluation of malignant pleural diseases – a pilot study

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Abstract

Objective: The diagnostic approach to pleural diseases may be difficult. The CT scan, which is the current diagnostic technique, has limited accuracy both in the differentiation between benign and malignant pleural diseases and in the diagnosis of primary and metastatic pleural neoplasms. Invasive procedures, such as thoracoscopy, are therefore frequently required to complete the diagnostic approach. The increasing incidence of malignant pleural mesothelioma has led to the development of new treatment strategies, which still need to be fully validated. There is, therefore, a need for new diagnostic techniques that can lead to a definite diagnosis and a satisfactory evaluation of the response to treatment. Encouraging results have been reported with the F-18-labeled analogue of 2-deoxyglucose (18-FDG) positron emission tomography (PET) in the evaluation of chest tumors such as lung cancer. The aim of this study was to evaluate the role of 18-FDG PET in the diagnostic assessment of pleural diseases.

Methods: Patients with CT scan evidence of pleural thickening, or fluid, entered a study to evaluate the accuracy of 18-FDG PET in diagnosing pleural diseases. Image analysis was performed both with visual interpretation and using a semiquantitative method, standardized uptake values (SUV), on coronal, sagittal and axial reconstructions. The results of PET imaging were compared to histological data. PET was also performed before and after treatment in patients who underwent chemotherapy to evaluate the accuracy of this technique in the assessment of the response. Results: Fourteen patients entered the study. Histology demonstrated a malignant pleural disease in 13 patients; malignant pleural mesothelioma in ten patients, adenocarcinoma in two and liposarcoma in one. Benign pleural disease was diagnosed in the remaining patient. PET assessment demonstrated significant 18-FDG uptake in 12 of the 13 patients with a malignant disease, also revealing distant metastases in two of them. A false-negative result was observed in a patient with an epithelial mesothelioma. The overall accuracy was 92%. A benign pleural disease without significant uptake was correctly diagnosed in another patient. An aspecific uptake was observed in two patients who had undergone pleurectomy and intrapleural chemotherapy. A decreased tracer uptake was observed after chemotherapy in four patients.

Conclusions: These preliminary results demonstrate that 18-FDG PET may have a great potential, both in the differential diagnosis of pleural diseases and in the evaluation of the response to treatment. At present, however, histological thoracoscopic diagnosis remains mandatory before planning treatment. Further studies in larger groups of patients are needed to draw definite conclusions on the role of PET in the assessment of pleural diseases.
raised interest in the diagnostic and therapeutic approach to pleural diseases. Despite the ban on the use of asbestos, the incidence of malignant pleural mesothelioma has grown steadily in recent decades and is expected to increase further [3]. Due to the limited results of the treatments currently available, new therapeutic strategies have recently been proposed. Among these are multimodality oncological treatments combining surgery, radiotherapy and chemotherapy, and experimental treatments, such as immunotherapy, gene therapy and photodynamic therapy [4–7]. However, the evaluation of the results of such new treatments is impaired by the limited accuracy of current diagnostic techniques. The CT scan has limited accuracy, both in differentiating between fibrosis and residual neoplastic tissue after treatment and in identifying tumor recurrence [8]. There is a need, therefore, for new non-invasive techniques capable of obtaining a differential diagnosis between benign and malignant lesions, of performing a complete staging and of evaluating the response to treatment. Positron emission tomography (PET) has been extensively used in the evaluation of chest tumors, particularly of lung cancer [9]. The technique exploits the principle of the increased glucose metabolism that is present in tumor cells. The F-18-labeled analogue of 2-deoxyglucose (FDG) is used as the radiopharmaceutical. It is introduced into cells by facilitative glucose transport and phosphorilated to FDG-6-phosphate, which does not proceed further in the metabolic pathway and is accumulated in the neoplastic cells. This enables benign and neoplastic lesions to be differentiated. In a negative PET examination, no focal, asymmetric or diffuse metabolically-active sites will be evident, and tracer activity will not be higher than that of the normal vascular distribution. Favourable results in terms of differential diagnosis, staging and evaluation of the response to treatment have been reported with PET [10,11]. The possibility of using whole-body PET, instead of the standard assessment with bone scan and brain CT, could also prove to be cost-effective [12]. The role of PET in the assessment of pleural diseases has only been preliminarily evaluated and has to be thoroughly examined [13,14]. The aim of this study was to evaluate the role of 18-FDG PET in the diagnosis of pleural diseases and in the evaluation of the response to treatment in patients with pleural mesothelioma.

2. Material and methods

At our Institution, 14 patients with CT scan evidence of pleural fluid, pleural masses or pleural thickening entered a study to evaluate the accuracy of 18-FDG PET in the differential diagnosis of pleural diseases. The histological diagnosis was obtained by CT-guided biopsy, or by surgical biopsy obtained during VATS or thoracotomy. PET was performed before and after chemotherapy in a group of six patients in order to evaluate the accuracy of PET in the evaluation of the response to treatment.

The results of PET were compared to a CT scan obtained within 7 days of the previous examination.

2.1. PET acquisition and image reconstruction

The synthesis of [18F]FDG was carried out according to the method previously described by Hamacker [15], with a compact automated module connected to the cyclotron (CTI/Siemens RDS 112 cyclotron, Siemens/CPS, Knoxville, TN). After overnight fasting (for at least 8 h), each patient received an i.v. injection of approximately 250–300 MBq of [18F]FDG (3.7 MBq/kg body weight).

PET studies were performed using a dedicated multi-ring tomograph (GE Advance, General Electric, Milwaukee, MI). Patients underwent a whole-body emission scan in 2D mode, performed approximately 60 min after tracer injection. A total of seven bed positions, each lasting 5 min, were acquired from head to pelvis. Transaxial raw data were reconstructed in transaxial images using a filtered back projection algorithm in a 128 × 128 matrix size, 55.0-cm field-of-view, 4.29-mm pixel size, with a Hanning filter with an 8.5-mm cut-off. After the emission scan, two 3-min thoracic transmission scans were acquired with two rotating [68Ge]/[68Ga] pin sources for attenuation correction. A second set of transaxial images was generated in order to obtain the semiquantitative parameter, standardized uptake values (SUV). In particular, images were normalized for injected tracer activity and for body weight. Finally, transaxial files were reoriented into coronal and sagittal views for further analysis.

2.2. Image analysis

Image analysis was performed both by visual assessment and using a semiquantitative method (SUV). Each set of images was scored in a totally blind, random fashion by three independent observers. PET results were graded as follows: 0, absence of activity; 1, presence of moderate activity; and 2, presence of high activity. Controversial findings were solved by consensus. A positive PET result was considered for grades of equal to, or higher than 1. The SUV was calculated in a region of interest drawn around the pleura and the maximum and mean values were measured.

2.3. CT scans

Spiral CT examinations were performed with X-press/sx, Toshiba Medical System. Patients were positioned supine on the couch, with arms alongside the body. During administration of iodinated non-ionic contrast medium (1.5–2.5 ml/kg of body weight; 2 ml/s flow rate), three contiguous helical scans were carried out (120 kV, 150 mA, pitch = 1) to study the pulmonary hila (beam collimation, 5 mm), apices and bases (beam collimation, 7 mm); an additional helical scan was performed to study the adrenal glands (beam collimation, 7 mm). During each diagnostic acquisi-
tion, patients were instructed to hold their breath after maximal inspiration.

3. Results

Fourteen patients entered the study. Eleven were male and three female. The mean age was 58 years (range, 35–73). The histological diagnosis was malignant mesothelioma in ten patients (eight epithelial, one mixoid and one sarcomatous), adenocarcinoma in two, liposarcoma in one and benign pleural fibrosis in another.

A malignant disease was identified at PET in 12 patients with neoplastic disease. A false-negative result was observed in a patient with a mesothelioma of the epithelial subtype (SUV = 0.14; Fig. 1). Benign disease was correctly assessed in the patient with pleural fibrosis, for a sensitivity of 92% and an accuracy of 92%. Distant metastases were observed in two patients; adrenal metastases in a patient with a sarcomatous mesothelioma, and metastases to lymph nodes, lung and ribs in a patient with pulmonary adenocarcinoma.

Surgical treatment was performed in eight patients with pleural mesothelioma, and consisted of a partial pleurectomy in four patients in whom the disease was confined to the parietal pleura. In three patients, the operation was followed by intrapleural treatment with bleomycin through an indwelling catheter. Talc pleurodesis by VATS was performed in four other patients with an inoperable disease. Six of the patients with pleural mesothelioma underwent

Fig. 1. A 48-year-old patient with epithelial mesothelioma. (a) CT scan: right pleural effusion and moderate pleural thickening. (b) FDG-PET (axial and coronal views): absence of significant tracer uptake.
systemic chemotherapy, after surgery in five cases and as the only treatment in one. In this group, PET was performed before and after chemotherapy. In one patient, the first examination was performed after an interval of 3 months from the previous pleurectomy and intrapleural bleomycine administration. An increased uptake was observed in comparison with the preoperative values (from SUV = 0.14 to SUV = 3.16). In another patient the semiquantitative analysis demonstrated a substantially unchanged value after 1 month from pleurectomy compared to the preoperative values (from SUV = 2.9 to SUV = 2.7). The data of these two patients were interpreted as a specific uptake related to surgical or intrapleural treatment, and thus, were excluded from the analysis. In the remaining four patients PET was performed after a mean period of 4 months from previous treatments. A mean reduction in the tracer uptake was observed comparing pre- and post-chemotherapy PET studies (from SUV = 7.2 to SUV = 2.5), which was in accordance with the symptomatic improvement observed in this group of patients (Fig. 2; Table 1). Interestingly, the CT scan remained substantially stable throughout the period of assessment.

4. Discussion

The diagnostic assessment of the pleural cavity is of great importance in the treatment of pleuropulmonaryary diseases. In patients with tumors such as lung cancer, pleural involvement is considered a contraindication to surgical treatment, and has to be differentiated from reactive pleural effusion [16]. Systematic use of VATS as a preliminary step in patients with lung cancer has thus been advocated in order to exclude pleural dissemination of the tumor and avoid unnecessary thoracotomies [17].

The interest in pleural tumors has markedly increased in recent years, due to the growing incidence of pleural mesothelioma both in Europe and the US [3,18]. Current therapeutic modalities provide limited results in the treatment of pleural mesothelioma, a point which has given rise to new forms of diagnostic evaluation and treatment. Among the most promising are multimodality treatments combining extended surgery with chemotherapy and radiotherapy [4]. New chemotherapy drugs and new treatments, such as gene therapy and photodynamic therapy, are also currently being evaluated [5,6,19]. Nevertheless, great difficulty exists in the evaluation of the results of these treatments. A correct histological diagnosis, a complete and accurate staging of the tumor, and the differentiation between residual tumor and pleural fibrosis are in fact essential to evaluate the efficacy of these new therapeutic strategies.

Different histological subtypes of malignant pleural mesothelioma (epithelial, sarcomatous and mixoid) have a different clinical behavior, and should therefore be differentiated [4]. Moreover, complete staging is crucial since pleural mesothelioma may metastatize to hilar and mediastinal lymph nodes and to distant sites [20]. It is also essential to identify residual viable tumors after treatment in evaluating the efficacy of new oncological treatments.

The standard diagnostic assessment of pleural diseases is based on the CT scan, which, however, can be misleading, since it is based on morphological criteria. Difficulty exists both in differentiating between benign and malignant pleural thickening or effusion, and in evaluating the extent of neoplastic disease. The reported specificity of the CT scan in the evaluation of pleural diseases is 83%, with a sensitivity of 72% [1]. In the present series, CT scan evidence of pleural thickening or effusion was present in all patients. However, the CT scan did not allow differentiation between benign and malignant diseases, and between different histologies. These figures may be even lower in the evaluation of residual viable disease after treatment. Other techniques, such as MRI, may slightly improve the evaluation of tumor extent, particularly in the definition of diaphragmatic involvement, but they are also based on morphological criteria, and may be influenced by motion artifacts [21]. Invasive procedures are therefore usually required to complete the diagnostic assessment. Cytology of pleural fluid obtained at thoracentesis, or CT-guided biopsy, may partially improve the diagnostic accuracy [22]. Nevertheless, even with these additional techniques, the differential diagnosis between benign and malignant lesions, and between pleural mesothelioma and tumors, such as adenocarcinoma, may be extremely difficult.

The limits of non-invasive diagnostic techniques have led to the diffusion of VATS in the diagnostic approach to pleural diseases. VATS is currently considered the gold standard technique in the assessment of pleural diseases. However, VATS cannot completely identify lymph node involvement or evaluate distant metastases. Dense pleural adhesions may contraindicate the use of VATS, a mini-thorac-
acotomy being required in these cases to enter the pleural space and perform adequate biopsies. The technique is also inadequate in evaluating the response to treatment. New non-invasive techniques are therefore required to accurately assess pleural tumors.

PET has been extensively used in the diagnosis of chest tumors. Favourable results have been reported, both in the differential diagnosis of indeterminate pulmonary nodules and in the staging of lung cancer [9,23]. A significant improvement in the evaluation of lymph node metastases and distant metastatic spread has been reported in comparison to CT in several trials [10]. Therefore, the use of PET as a whole-body staging technique for lung cancer has been proposed [24]. Moreover, PET seems to have a higher sensitivity than the bone scan in the detection of osteolytic metastases, which could allow an earlier diagnosis to be obtained [25]. If these results are confirmed, PET could be used as a standard staging procedure in NSCLC in the very near future.

A further possible application for PET is in the assessment of the response to oncological treatments in NSCLC. Patz et al. reported a sensitivity of 97% and a specificity of 100% in the detection of persistent or recurrent lung cancer, but pointed out that problems could arise when assessing lesions smaller than 1 cm, or when the evaluation was performed after a short interval from the treatment. Since persistent non-specific increased FDG activity was observed some weeks after oncological therapy, the authors considered findings with PET to be significant only if carried out after 2 months [11]. In our study, an increased uptake in comparison to preoperative values was observed after an interval of 1–3 months in two patients with pleural mesothelioma who underwent pleurectomy and intrapleural treatment with bleomycin. These data were interpreted as an aspecific uptake due to the treatment. An interval of 2 months between treatment and PET, as described by Patz and coworkers, would therefore not suffice in distinguishing aspecific uptake from disease recurrence, a fact which should be taken into account when evaluating results.

Experience with the use of PET in the evaluation of pleural diseases is extremely limited. Preliminary reports have nevertheless demonstrated interesting results in the differential diagnosis of malignant and benign pleural diseases. Bury et al. have reported a specificity of 78% and a sensitivity of 100% in a group of 25 patients with benign and malignant pleural diseases [13]. Bénard et al. have also described favourable results in the differential diagnosis between benign and malignant lesions in a group of 28 patients, reporting a specificity of 100% and a sensitivity of 91% [14]. The authors performed a semiquantitative assessment and observed different degrees of tracer uptake between benign and malignant lesions, and among different subtypes of malignant pleural mesothelioma. A SUV threshold of 2 distinguished benign and malignant diseases with an accuracy of 92%. However, a FDG uptake similar to that of benign lesions was observed in some patients with epithelial mesothelioma. This is in accordance with our experience, as a false-negative result was observed in a patient with epithelial mesothelioma at the semiquantitative analysis (SUV). In our study, PET had an accuracy of 92% in the differential diagnosis of pleural diseases, which again was similar to the findings of other authors. However, besides the difficulty in differentiating tumors with low metabolic uptake, such as epithelial mesothelioma, from benign lesions, PET cannot at present distinguish pleural tumors from metastatic involvement caused by other tumors, such as adenocarcinoma. Histological diagnosis by CT-guided biopsy or thoracoscopy should, therefore, still be obtained before planning treatment. Although encouraging, the results of 18-FDG PET need to be more thoroughly assessed, and do not at present allow this technique to be considered as an alternative to thoracoscopy in the differential diagnosis of pleural diseases.

Interesting results were obtained in our series in evaluating the response to oncological treatment in patients with mesothelioma who underwent chemotherapy. A reduction in PET uptake was observed in comparison to pre-treatment values, thus suggesting a response to chemotherapy. This was in contrast with the CT scan evaluation, which demonstrated stable disease. These data suggest that PET could have a higher accuracy than CT in the detection of residual disease. A longer follow-up and larger groups of patients are needed to confirm this hypothesis.

In conclusion, the diagnostic results obtained with PET, although encouraging, require confirmation in larger trials. Moreover, given the impossibility of differentiating between different histologies with this technique, VATS still remains mandatory in assessing pleural diseases when

### Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Histology</th>
<th>Stage (UICC)</th>
<th>Treatment</th>
<th>Interval to PET control (months)</th>
<th>Pre-chemotherapy SUV</th>
<th>Post-chemotherapy SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Epithelial mesothelioma</td>
<td>III</td>
<td>Intrapleural bleomycin</td>
<td>3</td>
<td>11.1 (3.8)</td>
<td>4.8 (1.3)</td>
</tr>
<tr>
<td>2</td>
<td>Epithelial mesothelioma</td>
<td>I</td>
<td>Pleurectomy, bleomycin</td>
<td>8</td>
<td>3.6 (2.0)</td>
<td>1.0 (0.8)</td>
</tr>
<tr>
<td>3</td>
<td>Epithelial mesothelioma</td>
<td>I</td>
<td>VATS, tuc pleurodesis</td>
<td>3</td>
<td>5.4 (2.5)</td>
<td>2.9 (1.7)</td>
</tr>
<tr>
<td>4</td>
<td>Epithelial mesothelioma</td>
<td>I</td>
<td>Pleurectomy, bleomycin</td>
<td>2</td>
<td>8.9 (3.3)</td>
<td>1.3 (0.4)</td>
</tr>
</tbody>
</table>

*a* Maximum values; mean values in parentheses.

*b* UICC, International Union Against Cancer.
less invasive approaches are inconclusive. The potential of PET in evaluating the response to treatment provides interesting prospects, and should therefore be investigated more deeply, especially in view of the fact that the accuracy of a CT scan in this setting is extremely limited, and the clinical outcome is frequently the most effective means of evaluating the response to treatment. Thus, in the near future PET promises to be an important tool in the follow-up of patients with pleural diseases submitted to oncological treatments.

References


Appendix A. Conference discussion

De T. Godzki (Szczecin, Poland): Congratulations on the nice series. I have one question. The mediastinum PET scan can reduce the number of advantages without a PET scan. So, is it justifiable by costs to use the PET scan? Is it probably related both to the tumor size and different, because video thoracoscopy can provide you with all the advantages without a PET scan. So, is it justified by costs to use the PET scan in the pleural space to make the diagnosis?

De Carretta: I think it cannot substitute VATS. It is justified as far as we have to evaluate new treatments, and also, of course, if it is demonstrated that PET may have a prognostic value in patients that are submitted to surgery or to chemotherapy or radiotherapy.

De A. Lerut (Leuven, Belgium): One of your conclusions was that you can differentiate between different types of tumor, which, of course, is not exactly what you would expect from PET scan. I think the most important message is that PET is indeed accurate in diagnosing malignancies, and that is a very important message. The problem is that you won’t like to have false-negatives. In your two patients who were false-negative, what was the reason for it? Was it because the tumor was too small, or was there another?
approach, so that is why we think that VATS cannot be substituted by this method in this setting.

Dr A. Ritchie (Cambridge, UK): Do you think that the role of PET scanning in this group of mesothelioma patients really lies in the follow-up of those who have had a pleural pneumonectomy, in order to detect evidence of recurrent disease?

Dr Carretta: Well, I think it is important before surgery to detect lymph nodes, because this method could possibly also detect metastasis to hilar and mediastinal lymph nodes. This is, of course, to select patients before surgery and to define prognosis after treatment. Of course, it may be very useful in the follow-up of these patients after surgery.

Dr J. Dussek (London, UK): It can be very difficult, even with VATS and sometimes open pleural biopsy, to actually get representative tissue when you have widespread pleural thickening. Have you used PET scanning to target your biopsies?

Dr Carretta: No, we did not use it this way.

Dr Dussek: It can be invaluable.