Positron Emission Tomography/Computed Tomography for the Pleural Staging of Malignant Pleural Mesothelioma: How Accurate Is It?

Valentina Pinelli, Elisa Roca, Silvia Lucchini, Sophie Laroumagne, Anderson Loundou, Hervé Dutau, Fabien Maldonado, Philippe Astoul

Division of Pneumology, Hospital S. Bartolomeo, Sarzana, Italy; Division of Nuclear Medicine, Spedali Civili, Brescia, Italy; Division of Thoracic Oncology, Pleural Diseases, and Interventional Pulmonology, Hôpital Nord, and Department of Public Health and Biostatistics and Faculty of Medicine, Aix-Marseille University, Marseille, France; Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minn., USA

Abstract

Background: Careful clinical staging in patients with malignant pleural mesothelioma (MPM) is fundamental in management planning. Positron emission tomography/computed tomography (PET/CT) is increasingly recognized as an important staging modality.

Objectives: The purpose of this study was to assess whether the metabolic activity of the pleural tumor detected with PET/CT correlates with specific endoscopic features and pleural distribution of the lesions as assessed by medical thoracoscopy.

Methods: Consecutive patients with MPM and available PET/CT performed before thoracoscopy were separated into 2 groups, according to their standardized uptake value (SUV). Kaplan-Meier analysis for survival was performed on groups with low and high SUV. Agreement between PET/CT and thoracoscopy evaluation was analyzed using Cohen’s kappa coefficient. The Wilcoxon test was used to compare the median SUV, and the \( \chi^2 \) test was used to evaluate differences in endoscopic findings.

Results: A total of 32 patients were included. The median maximum SUV (SUV max) was 6.1 and patients were separated into 2 groups based on this cutoff. Patients with SUV max <6.1 had a better survival than those with SUV max \( \geq 6.1 \) \((p = 0.005)\). The comparison between PET/CT and thoracoscopy showed a fair agreement for visceral and diaphragmatic pleural involvement and moderate agreement for the presence of nodular lesions. There was a statistically significant association between median SUV max and visceral pleural involvement; nodular lesions and visceral pleural involvement were more common in the high-SUV group than in the low-SUV group \((p = 0.0012 \text{ and } p = 0.03, \text{ respectively})\).

Conclusions: PET/CT data may be predictive of thoracoscopic features of MPM associated with prognosis and staging, but the correlation is moderate at best. A degree of disagreement exists between these two modalities, which supports thoracoscopy as the gold standard for assessment of local invasion in MPM.

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive neoplasm arising from mesothelial pleural cells with increasing incidence and high mortality \([1, 2]\). Accurate
Few studies have been ing malignant pleural lesions and in the assessment of MPM. FDG-PET is generally considered useful in detecting (FDG)-positron emission tomography and complementary assessment of the local extension of MPM guides decisions on appropriate therapeutic strategies.

Pleural mesothelioma can involve both parietal and visceral pleura and quickly spreads to adjacent structures such as the diaphragm, chest wall and mediastinum. Although MPM is a tumor with a predominantly ‘local spread’, in some cases lymph node and distant metastases may occur such as kidney, brain and liver metastases. The tumor originates from the parietal pleural surface and only secondarily involves the visceral pleura. This extension, particularly to the visceral pleura, represents a more advanced stage and consequently an important prognostic factor [3–5]. The place of computed tomography (CT) scan and magnetic resonance imaging in the diagnosis and staging of MPM remains unclear. In recent years several radiological assessment tools have been proposed, but neither the WHO criteria nor the more recent Response Evaluation Criteria in Solid Tumors (RECIST) are firmly established for the assessment of local extent of the disease [6, 7]. Few studies have been published on the role of combined 18F-fluorodeoxyglucose (FDG)-positron emission tomography and computed tomography (PET/CT) scan in the diagnosis of MPM. FDG-PET is generally considered useful in detecting malignant pleural lesions and in the assessment of tumor involvement [8].

To our knowledge there are no data available on the comparison between thoracoscopic and PET/CT evaluation of pleural lesions in patients with MPM. The purpose of this study was to assess whether tumor metabolic activity of the pleural tumor detected with PET/CT correlates with specific endoscopic features and pleural distribution of the lesions, in particular with regards to the invasion of the visceral pleura as assessed by medical thoracoscopy.

**Methods**

**Study Design and Data Analysis**

From 2006 to 2009, all consecutive patients with histologically confirmed MPM after medical thoracoscopy who underwent PET/CT scanning before diagnosis were identified from an institutional database of a single tertiary center (Spedali Civili, Brescia, Italy).

FDG-PET scanning was done as part of their initial staging evaluation. Patients with pleurodesis were excluded from this study, since it may affect PET findings.

All clinical and radiological data were also obtained from a prospective institutional database. Data acquisition and analysis were approved by the hospital institutional review board. Collected data included demographics (age and gender), thoracoscopic findings such as free cavity or presence of adhesions, extent of the tumor to the different pleural areas (parietal, diaphragmatic, visceral, mediastinal), pattern (nodules, thickening, multiple lesions), date of death, and date of last follow-up at which the patient was confirmed alive.

The pathological diagnosis of MPM was done by histology using immunohistochemistry, and all histological specimens were centrally reviewed according to European guidelines [5].

**Thoracoscopy Evaluation**

Thoracoscopy was standardized in accordance with current European practice as previously described [9]. It was performed under local anesthesia with 1% lidocaine and moderate sedation or general anesthesia after tracheal intubation with the patient in the lateral decubitus position and spontaneously breathing. A 7-mm trocar was inserted in the appropriate intercostal space, with or without ultrasound guidance, and a 0° telescope was introduced through the trocar and connected to a video camera. The parietal, diaphragmatic and visceral pleural appearance and the extent of their involvement were carefully examined with the thoracoscope (R. Wolf GmbH, Knittlingen, Germany) [9].

Multiple biopsies were taken from the parietal pleura for histological diagnosis. Abnormal findings at thoracoscopy were defined by the presence of one of the following characteristics: macroscopic visceral pleural involvement, diaphragmatic pleural involvement, nodules, and thickening. The thoracoscopy was considered negative if there were no pleural involvement (visceral or diaphragmatic), nodular lesions or pleural thickening. All cases with uncertain macroscopic pattern of pleural invasion (e.g. thin pleural thickening, minimal alteration of visceral or diaphragmatic pleura) or those with poor quality of thoracoscopic examination (due to the presence of pleural adhesions or partial lung collapse) were excluded from the study. Visceral pleural biopsies were not performed because of evidence for malignant lesion on the parietal pleura.

**PET Evaluation**

PET/CT was performed on a Discovery ST (General Electric, Fairfield, Conn., USA) tomograph (CT multislice, 80 mA, 140 kV; 4 min per PET bed) after the intravenous administration of 5.5 MBq/kg of 18F-FDG and fasting for at least 6 h. CT was used for the attenuation correction and anatomical localization. Serum glucose levels were lower than 150 mg/dl and scans were performed 60 min after injection starting from the mid-thigh region to the base of the skull. We performed a visual and semiquantitative analysis of the PET/CT scans. Standardized uptake value (SUV) was calculated according the standard methods based on the FDG uptake corrected for injected dose, patient’s body weight and blood glucose level at the injection time. The maximum SUV (SUV max) was measured from a region of interest drawn electronically on the hottest voxel of the tumor burden seen on the attenuation-corrected transaxial slices. In the absence of a validated standard for normal SUV in MPM, the median SUV max was used to divide patients into 2 groups defined as those with low and high SUV max.

**Statistical Methods**

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 10 software; SPSS Inc., Chicago, Ill., USA) program. Data are expressed as medians with standard deviations (SD). Differences were considered statistically significant at p < 0.05. Patients were separated into 2 groups on the basis of median
SUV max: those with SUV max $\geq 6.1$ (high-SUV group) and those with SUV max $<$6.1 (low-SUV group). The Kaplan-Meier method was used to estimate the probability of survival and compared using the log-rank test. Both PET and thoracoscopy recordings were reviewed separately by a blinded radiologist and a blinded respiratory physician, respectively. Agreement between PET and thoracoscopy results was analyzed using Cohen’s kappa coefficient ($\kappa$) for categorical data. The kappa coefficient values were interpreted as follows: $<0.20$ indicates poor agreement, $0.21–0.40$ fair agreement, $0.41–0.60$ moderate agreement, $0.61–0.80$ good agreement, and $0.81–1$ very good agreement, according to Landis and Koch [10].

The Wilcoxon test was used to compare the median SUV max of patients with or without visceral and diaphragmatic pleura involvement. The same test was also used to analyze the difference between the median SUV max of patients with or without thickenings or nodular lesions. Differences in endoscopic pleural involvement between the 2 groups of patients (high- and low-SUV groups) were evaluated using the $\chi^2$ test.

### Results

A total of 32 consecutive previously untreated patients with MPM were included in the study. These patients included 24 men and 8 women (25%), with a median age of 63 years (range: 45–74). Among these mesothelioma patients, 29 had tumors of epithelioid subtype, 2 of mixed subtype and 1 of sarcomatoid subtype. The characteristics of the patients are shown in Table 1.

<table>
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<th>Characteristic</th>
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<td>Female</td>
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<td>MPM</td>
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MPM: IMIG (International Mesothelioma Interest Group) classification.

SUV max: the overall median survival of patients with SUV max $<$6.1 (34.07 months) was better than for those with SUV max $\geq 6.1$ (12.50 months). The difference was statistically significant ($p = 0.005$).

The Wilcoxon test was used to compare the median SUV max of patients with or without visceral and diaphragmatic pleura involvement. The same test was also used to analyze the difference between the median SUV max of patients with or without thickenings or nodular lesions. Differences in endoscopic pleural involvement between the 2 groups of patients (high- and low-SUV groups) were evaluated using the $\chi^2$ test.

### Table 1. Characteristics of patients (n = 32)

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The presence of nodular lesions was found in 19 patients with a median SUV max of 9.10 ± 3.88, and 13 patients without nodules had a median SUV max of 4.80 ± 3.33 ($p = 0.009$; fig. 2b).
Therefore, the results showed a statistically significant difference of the median SUV max between patients with and without visceral pleural involvement (p = 0.032). A statistically significant difference was also found between the median SUV max in patients with and without nodular aspect of pleural lesions (p = 0.009).

Visceral and diaphragmatic pleural involvement and the presence of nodular lesions and/or pleural thickening were assessed by PET/CT and thoracoscopy. A fair agreement between PET/CT and thoracoscopy was found with regards to the visceral or the diaphragmatic pleural involvement (κ = 0.375 for visceral pleura and κ = 0.313 for diaphragmatic pleura). With respect to pleural thickening, there was very poor agreement between the images obtained by PET/CT and the thoracoscopy findings (κ = -0.188). Finally, a moderate agreement between PET/CT and thoracoscopy was found with regards to the presence of nodular lesions (κ = 0.563).

In the high-SUV group (16 patients), thoracoscopy demonstrated visceral pleural involvement in 12 of 16 patients (75%), diaphragmatic pleural involvement in 13 subjects (81%), pleural thickening in 11 cases (68%), and nodules in 14 patients (87%).

Conversely, in the low-SUV group (16 patients), thoracoscopy revealed visceral pleural involvement in 6 of 16 patients (37%), diaphragmatic pleural involvement in 8 subjects (50%), pleural thickening in 14 cases (87%), and nodules in 5 patients (31%).

Nodular lesions and visceral pleural involvement were more present in the high-SUV group than in the low-SUV group and the difference was statistically significant (p = 0.0012 and p = 0.03, respectively). Diaphragmatic pleural involvement was more frequent in the high-SUV group compared to the low-SUV group but the difference did not reach statistical significance (p = 0.06). Pleural thickening was more numerous in the low-SUV group but the difference was not statistically significant. PI = Pleural involvement. * p < 0.05, ** p < 0.01.
group, although it did not reach statistical significance (p = 0.06). On the other hand, pleural thickening was more frequent in the low-SUV group in comparison to the high-SUV group but the difference was not statistically significant (p = 0.08; fig. 3).

Discussion

The purpose of this study was to analyze whether tumor metabolic activity assessed by PET/CT scanning correlates with endoscopic pleural findings of MPM focusing on visceral pleural involvement, which is an important prognostic factor for this disease. In fact this study analyzes the relationship between imaging results and endoscopic findings, comparing the information obtained from 'looking from outside' to that from 'looking inside'.

The assessment of the local extension of MPM is paramount for appropriate treatment decisions. However, while available imaging techniques can typically accurately detect extra thoracic metastases, they sometimes fail to reliably characterize local pleural involvement. Consequently, approximately 20–30% of patients undergoing thoracoscopy for MPM are found to be suitable candidates for resection due to discrepancy between preoperative radiological and operative findings [11–14]. More recently, several studies aimed to define the role of PET/CT in pretherapeutic MPM staging and showed good accuracy for mediastinal lymph nodes assessment as well as extra thoracic metastases, but with comparatively poor evaluation of the pleural cavity [15–19].

False-negative PET/CTs for pleural evaluation in histologically proven MPM patients have also been reported. It has been hypothesized that endoscopic patterns of the tumor, not only the extent but also the shape, may have an impact on the ability of the $^{18}$F-FDG-PET/CT scan to detect such lesions. In this previous study, these false-negative PET/CT lesions were flat or nodular and located on the parietal pleura or, for flat lesions, the visceral pleura [20].

However, in the literature, an SUV max cutoff is usually assessed to distinguish MPM from benign pleural disease. Conversely, in the setting of MPM, if PET/CT is useful to predict the prognosis of MPM with an independent prognostic value of FDG uptake measured at diagnosis by SUV, there is no clear cutoff for SUV max predicting survival in prognostic studies. Benard et al. [16] found an SUV max cutoff of 4.03 (equal to the median value) to distinguish the overall survival of patients. On the other hand, Flores et al. [21] proposed an SUV max cutoff >10 as a main prognostic parameter with a high SUV max (>10) associated with shorter survival than a low SUV max (<10). For several authors, a high SUV was associated with shorter survival and greater death risk than a low SUV and can be used to stratify patients for survival and outcome, separating patients into good and poor prognosis groups [22–24].

In our study, the demographic data are consistent with those usually observed in MPM. The majority of patients were males, and most tumors were of epithelioid histological subtype. Patients with SUV max ≥6.1 had a better survival than those with SUV max ≥6.1. This difference was statistically significant, and confirms that PET imaging could separate patients into high- and low-risk groups. While an optimal cutoff for SUV remains to be determined, this finding is not unexpected given the fact that SUV is a reflection of the tumor metabolic rate and usually correlates with more biologically aggressive tumors and poor survival.

We also found that SUV ≥6 at PET/CT scanning was associated with endoscopic findings of visceral pleural involvement and pleural nodules. While the involvement of the visceral pleura is a recognized prognostic factor in MPM and corresponds to a higher pathological stage, the potential significance of particular types of lesions, such as nodular lesions, remains to be determined.

We analyzed SUV as a prognostic factor and its relationship with thoracoscopy findings. Patients with SUV max ≥6.1 at PET/CT had thoracoscopy evidence of visceral pleural involvement in 85% of cases (fig. 4a) but, conversely, only 35% of patients with SUV max <6.1 at PET/CT presented visceral pleural involvement at thoracoscopy evaluation (p = 0.03; fig. 4b). Also, nodular lesions were more common in the high-SUV group in comparison to the low-SUV group (p = 0.0012), suggesting a correlation between endoscopic pleural findings of MPM and tumor metabolic activity assessed by PET/CT. The results of PET/CT and thoracoscopy were also compared using the Cohen’s kappa coefficient (κ) test, in order to analyze the concordance or discrepancy between the two procedures. Agreement between imaging uptake and endoscopic results was fair for the visceral or diaphragmatic pleural involvement and moderate for the presence of nodular lesions.

This study has several weaknesses. It is a small study, and it may therefore be difficult to generalize our results for the MPM patient population at large. However, MPM
is a rare tumor, and our series represents one of the largest series on imaging and thoracoscopic findings published. We also acknowledge that we arbitrarily defined an SUV cutoff based on the median SUV observed in our group, which may not be clinically relevant. In the absence of a validated cutoff for SUV in MPM, we believe that our analysis is valid and hypotheses generating, but we acknowledge that the chosen cutoff may not be clinically relevant.

Our results show that the prognostic value of SUV max cutoff can be related to visceral pleural invasion or nodular aspects of the lesions. However, there is only a fair agreement between PET/CT and thoracoscopy, with discrepancy between these two tests due to false-negative PET/CT’s as previously reported. This study suggests that PET may be more helpful than previously thought in determining the local extent of mesothelioma but that it is still not accurate enough to obviate endoscopic evaluation of the pleural cavity. Therefore, thoracoscopy remains the gold standard for the diagnosis and local pleural staging in MPM patients according to current European guidelines [5].

**Financial Disclosure and Conflicts of Interest**

The authors have no conflicts of interest to declare.
References


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Pinelli/Roca/Lucchini/Laroumagne/
Loundou/Dutau/Maldonado/Astoul