Preoperative staging of mesothelioma by 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography fused imaging and mediastinoscopy compared to pathological findings after extrapleural pneumonectomy

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Abstract

Objectives: Extrapleural pneumonectomy (EPP) in MPM may be confined with both morbidity and mortality and careful preoperative staging identifying resectable patients is important. Staging is difficult and the accuracy of preoperative CT scan, 18F-FDG PET/CT scan (PET/CT), and mediastinoscopy is unclear. The objectives were to compare these staging techniques to each other and to surgical—pathological findings.

Methods: Patients had epithelial subtype MPM, age <70 years, and lung function test allowing pneumonectomy. Preoperative staging after 3—6 courses of induction chemotherapy included conventional CT scan, PET/CT, and mediastinoscopy. Surgical—pathological findings were compared to preoperative findings.

Results: Forty-two consecutive patients were without T4 or M on CT scan. PET/CT showed inoperability in 12 patients (29%) due to T4 (7 patients) and M1 (7 patients). Among 30 patients with subsequent mediastinoscopy, including 10 with N2/N3 on PET/CT, N2 were histologically verified in 6 (20%). Among 24 resected patients, T4 occurred in 2 patients (8%), and N2 in 4 (17%), all being PET/CT negative. PET/CT accuracy of T4 and N2/N3 compared to combined histological results of mediastinoscopy and EPP showed sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios of 78% and 50%, 100% and 75%, 100% and 50%, 94% and 75%, not applicable and 5.0, and 0.22 and 0.67, respectively.

Conclusions: Non-curative surgery is avoided in 29% out of 42 MPM patients by preoperative PET/CT and in further 14% by mediastinoscopy. Even though both procedures are valuable, there are false negative findings with both, urging for even more accurate staging procedures.

Keywords: Mesothelioma; Staging; PET/CT scan; Mediastinoscopy; Extrapleural pneumonectomy

1. Introduction

Malignant pleural mesothelioma (MPM) is an uncommon tumour with approximately 3500 new cases annually in the USA, 1800 in UK, and 300 in Scandinavia (Denmark, Norway, and Sweden) [1]. Staging, the assessment of the anatomical extent of MPM, determines treatment and prognosis and is mandatory for selecting the relatively few patients who are candidates for intended curative surgery by extrapleural pneumonectomy (EPP). Various imaging techniques have been utilised to stage MPM, which is difficult to evaluate radiologically because of its tendency to grow locally along tissue planes. Computed tomography (CT) and magnetic resonance imaging (MRI) are helpful in identifying the location and extent of the involved area [2]. However, these imaging techniques often fail to detect non-resectable tumour invasion in the chest wall, mediastinal structures, or the diaphragm (T4) [3]. It can also spread to N2 mediastinal lymph nodes, which in many centres is considered to be a sign of inoperability, or N3 glands may be missed [4].

The surgical procedure of EPP for early stages of MPM is a procedure confined with considerable morbidity and also a 30-day perioperative mortality rate around 3—5% in recent series [5—7]. In addition, approximately 20—30% of patients have exploratory thoracotomy or pleurectomy/decortication only because the staging procedures underestimate the extent of tumour spread [8]. Improved methods for
determining resectability are thus needed. Fluorine-18-labelled deoxyglucose (18F-FDG)-positron emission tomography (PET) is a newer imaging technique based on changes in glucose metabolism, which have been evaluated for use in the staging of malignant tumours [9]. An increased uptake of 18F-FDG in MPM has been shown [10], and PET has been evaluated as a staging method [11,12].

Anatomical details are difficult to interpret on PET scans but a more recent technique using image fusion with simultaneous PET and CT scanning (PET/CT) allows for more detailed anatomical information [13]. Mediastinoscopy is the standard for obtaining preoperative histological evaluation of tumour involvement in mediastinal lymph nodes [14] though the nodes in the para-aortic and AP window are inaccessible. Further evaluation of mediastinal lymph node involvement together with histological verification of local tumour spread is obtainable by the surgical procedure of EPP. The purpose of this study was to evaluate the ability of PET/CT compared to conventional preoperative CT to detect inoperable stages of MPM in order to avoid futile surgery. Another purpose was to validate the results of preoperative PET/CT staging results by the histological results from both subsequent mediastinoscopy on all patients referred to surgery and also by the surgical—pathological results from EPP.

2. Patients and methods

2.1. Patients

Patients with histologically confirmed MPM of epithelial subtype were included. All histological specimens were reviewed centrally at the Department of Pathology at the Copenhagen University Hospital in Copenhagen. The upper age limit was 70 years, the patients had no prior or concomitant other malignancies, had normal organ function (liver, renal, and bone marrow) as evaluated by biochemistry and performance status ECOG/WHO of 0—1. Total lung function test and regional lung function test was carried out preoperatively in all patients and only patients with an estimated postoperative FEV1 of 40% or more and an estimated DLCO diffusion capacity of 40% or more of normal values according to gender, height, and age were included for further preoperative examination.

All patients gave written informed consent after thorough information, the treatment was approved by the participating departments ethical review board and the standards of the Helsinki Declaration were fulfilled.

2.2. Treatment

Patients received 3—6 courses of neoadjuvant platinum-based chemotherapy together with either pemetrexed or vinorelbine according to guidelines at their local hospital in Denmark, Sweden, or Norway. Cisplatin-based treatments were recommended but not mandatory; carboplatin-based treatments were allowed. The number of neoadjuvant treatment courses was at the discretion of the local investigator with three courses being the recommendation. A CT scanning of chest and upper abdomen was performed locally at completion of chemotherapy. If the apparent stage according to the staging system by the International Mesothelioma Interest Group (IMIG) [15] allowed surgery, i.e. IMIG stages T1—3N0—2M0, the patient was referred to further examination at the National University Hospital in Copenhagen, Denmark, where preoperative staging, surgery and postoperative radiotherapy were centralised in this trial.

The surgical procedure was extrapleural pneumonectomy with complete dissection of the parietal pleura and an ipsilateral mediastinal lymph node dissection. The pleura was removed from the ipsilateral diaphragm and the pericardium was resected. Gore-Tex patches were placed to re-construct the diaphragm and the pericardium. Postoperative radiotherapy with IMRT technique was embarked on 6—8 weeks postoperatively.

2.3. Preoperative staging procedures

An 18F-FDG PET/CT scanning was performed when patients following neoadjuvant chemotherapy at their local hospital were referred for preoperative staging in order to take account for a possible downstaging by the chemotherapy. In all cases there was an interval of at least two weeks between chemotherapy and the examination. The CT scanning was interpreted separately and blinded from the result of the PET/CT scanning. The patients were judged inoperable based on PET/CT in case of either extensive non-resectable invasion of the chest wall or invasion of mediastinal structures (T4), or distant metastases (M1) and were referred back to the local hospital for further systemic treatment. All other patients went on to preoperative mediastinoscopy, including patients with N2 (ipsilateral mediastinal) or N3 (contralateral mediastinal) lymph nodes on the PET/CT. Biopsies from lymph nodes in position 2L, 2R, 4L, 4R, and 7 were done during the mediastinoscopy. The patients were judged inoperable in case of positive histological examination in either of these lymph node positions while all other patients went on to surgery with EPP.

2.4. PET/CT imaging parameters

Integrated PET/CT scanners (GE Discovery LS PET/CT scanner, GE Medical Systems, Milwaukee, WI, U.S.A. and Siemens Biograph, Siemens Medical Solutions, Knoxville, TN, U.S.A.) were utilised. The patients fasted for at least 6 h prior to intravenous injection of 400 MBq FDG (2-[18F]fluoro-2-deoxy-o-glucose). The examination was performed approximately 60 min post injection with the patient positioned supine with the arms placed over the head.

CT scans were performed immediately prior to the PET scan with the multi-detector spiral CT scanner. CT scans were acquired as diagnostic CT scans. With a delay of 40 s, intravenous contrast media (100 ml Ultravist 300 mg I/ml, Schering) was injected with an automatic injection system (Medrad Envision CT injector, Pittsburgh, PA, U.S.A.) with a flow rate of 2.5 ml/min. The CT scan was performed during shallow breathing with a rotation time of 0.5 s, speed 15.0 mm/rotation, helical thickness 5 mm, pitch 1.5:1, and kV and mA depending on the size of the patient.

The PET scan followed immediately with an acquisition time of 3 min per bed position during shallow breathing. It consisted of imaging from the base of the skull to the pelvis.
including the upper abdomen using 3—4 axial fields of view with coverage of 14.5 cm.

2.5. Surgical procedures

Surgical staging procedures and EPPs were performed jointly by the same two experienced thoracic surgeons throughout the study. Mediastinoscopies were in all cases performed preoperatively irrespectively of the PET/CT mediastinal staging results. Specimens were classified according to the mapping system by Mountain and Dresler \[16\] and patients with histological positive N2 or N3 lymph node obtained by mediastinoscopy were precluded from surgery. Thus, patients having PET/CT positive left-side nodes in the para-aortic or AP window which are inaccessible to biopsy by mediastinoscopy also went to EPP and perioperative biopsy from these nodes. Staging laparoscopy was not used routinely.

2.6. Staging considerations

Patients were staged according to the IMIG staging system \[15\] and stages I to III MPM (T1—3N0—1M0) were eligible for EPP, whereas those with stage IV (any T4, any N3, any M1) were not. Also histologically verified N2 diseases were non-eligible for surgery. This included patients with T4 disease due to extensive invasion of the thoracic wall. The decision to obtain pathologic confirmation of non-lymph node signs at PET/CT of T4 disease or metastatic disease was at the discretion of the treating physician. Histologic confirmation of the inoperable lesions were preferred but was abstained from if localised in difficult assessable locations in which biopsies may induce a risk for the patient. Only lesions unequivocally positive on PET-scan and a clearly defined mass on CT scan were considered proof of either inoperable T4 or M1 disease. In no cases were positive mediastinal lymph nodes on PET/CT scan alone considered proof of inoperability without histologic verification.

2.7. Statistical methods

Comparisons are done by two-tailed Fisher’s exact test. Confidence intervals of 95% of frequencies are given.

3. Results

3.1. Patients

A total of 42 patients from Denmark, Norway, and Sweden were included from October 2003 to October 2006. Patients’ characteristics are shown in Table 1. The majority were men (93%), 67% had performance status 1, 59% had a history of asbestos exposition, 69% were from Denmark and 24% and 7% from Sweden and Norway, respectively. Median age was 61 years (range 30—70 years).

3.2. Postinduction chemotherapy CT versus PET/CT

The results of CT alone after induction chemotherapy and of PET/CT according to the IMIG staging system is shown in Table 2. A total of seven patients (17%) had T4 disease on PET/CT compared to none on CT alone (p = 0.0119). Fourteen patients (33%) had N2 or N3 disease (p = 0.1295) and seven patients (17%) had M1 disease (p = 0.0119) on PET/CT compared to seven patients (16%) and none on CT alone, respectively. This resulted in a stage migration from one case (2%) of IMIG stage IV with CT alone (due to N3 disease) to nine cases (21%) with PET/CT (p = 0.0146). Fig. 1 shows a case of metastatic spread to two para-aortic lymph nodes in upper abdomen discovered by PET/CT.

PET/CT revealed 12 out of 42 patients to be non-resectable (29%), due to either T3 disease too extensive

Table 1

<table>
<thead>
<tr>
<th>IMIG-stage</th>
<th>CT alone, n (%), 95% c.l.</th>
<th>PET/CT, n (%), 95% c.l.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9 (21, 10—37)</td>
<td>4 (10, 3—23)</td>
</tr>
<tr>
<td>II</td>
<td>14 (33, 20—50)</td>
<td>12 (29, 16—45)</td>
</tr>
<tr>
<td>III</td>
<td>19 (43, 30—61)</td>
<td>17 (41, 26—57)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (2, 0—13)</td>
<td>9 (21, 10—37)</td>
</tr>
</tbody>
</table>

95% c.l.: 95% confidence limits.
\[ p < 0.0119.\]
\[ p = 0.1295.\]
\[ p = 0.0146.\]
for resection or because of T4 or M1 disease (Table 3), which is significantly fewer anatomically resectable than discovered by CT alone \( (p = 0.0011) \). Three patients had more than one sign of inoperability.

### 3.3. PET/CT versus mediastinoscopy

The 30 patients judged resectable based on PET/CT scan without T4 or M1 went on to mediastinoscopy. Signs of N2 or N3 without histological verification were not considered proof of inoperability. Mediastinoscopy showed malignant involvement of mediastinal lymph nodes in six patients (20%), all being in the N2 position (Table 3). Thus, of a total of 42 patients initially considered resectable following induction chemotherapy judged on CT alone, PET/CT scan revealed 12 cases (29%) to be unresectable due to T4 or M1 disease and another 6 cases had histologically mediastinal N2 disease during mediastinoscopy, leaving 24 (57%) patients for EPP while a total of 18 patients (43%) avoided futile surgery (Table 4).

### 3.4. PET/CT versus EPP surgical—pathological staging results

#### 3.4.1. Accuracy of T4 prediction

The overall EPP surgical—pathological staging results are shown in Table 4. Two out of 24 resected patients (8%) had unexpected T4 disease despite PET/CT without signs of this. The surgical—pathological T-stage was lower in 1 out of 24 patients (4%), equal in 13 patients (54%), and higher in 10 patients (42%) (Table 5). The 24 operable patients are compared with respect to preoperative PET/CT results and final surgical—pathological results in Table 5. The fraction of patients in stages I and II were diminished from 63% to 21% and stage IV increased from 4% to 12% from preoperative PET/CT to final surgical—pathological staging. Fig. 2 shows a case of preoperative T2N0M0 on PET/CT which proved to be T4N0M0 at surgery.

The accuracy of PET/CT for T4 disease was a sensitivity of 78%, specificity of 100%, positive predictive value of 100%, while a total of 18 patients (43%) avoided futile surgery (Table 4).

### Table 3

Results of preoperative staging programme in MPM patients of epithelial subtype

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional CT ((n = 42))</td>
<td></td>
</tr>
<tr>
<td>Potentially resectable( (\text{no T4 or M1}) )</td>
<td>42 (100)</td>
</tr>
<tr>
<td>PET/CT ((n = 42))</td>
<td></td>
</tr>
<tr>
<td>Potentially resectable( (\text{incl. N2/N3, no other inoperability signs}) )</td>
<td>30 (71, 55—84)</td>
</tr>
<tr>
<td>Non-resectable due to( a ):</td>
<td>12 (29, 16—45)</td>
</tr>
<tr>
<td>T4</td>
<td>7 (22, 7—31)</td>
</tr>
<tr>
<td>M1</td>
<td>6( b ) (14, 5—29)</td>
</tr>
<tr>
<td>Mediastinoscopy ((n = 30))</td>
<td></td>
</tr>
<tr>
<td>Non-resectable due to histologically positive N2</td>
<td>6 (20, 8—39)</td>
</tr>
<tr>
<td>Potentially respectable</td>
<td>24 (80, 61—92)</td>
</tr>
</tbody>
</table>

95% c.l.: 95% confidence limits.

\( a \) Some patients had more than one sign of inoperability.

\( b \) One additional patient had port metastasis considered respectable.

\( \text{CT alone versus PET/CT operability, } p = 0.0011. \)

### Table 4

Overall results of preoperative staging programme and surgical results in MPM patients of epithelial subtype

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative staging, total no.</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Excluded by PET/CT( a )</td>
<td>12 (29, 16—45)</td>
</tr>
<tr>
<td>Excluded by mediastinoscopy (N2 disease)( b )</td>
<td>6 (14, 5—29)</td>
</tr>
<tr>
<td>Potentially resectable (T1—3N0—1M0)( c )</td>
<td>24 (57, 41—72)</td>
</tr>
<tr>
<td>Resected by EPP</td>
<td>24 (100)</td>
</tr>
<tr>
<td>T4 surgical—pathological</td>
<td>2 (8, 1—27)</td>
</tr>
<tr>
<td>N2 surgical—pathological</td>
<td>4 (17, 5—37)</td>
</tr>
<tr>
<td>M1 (seed in port)( \text{d} )</td>
<td>1 (4, 0—21)</td>
</tr>
</tbody>
</table>

95% c.l.: 95% confidence limits.

\( a \) Excluded from surgery due to T4, or M1, but not due to N2 or N3.

\( b \) No patients had N3 disease.

\( c \) Includes one patient having preoperatively known metastatic seed in thoracoscopy port, completely resected during EPP.
negative predictive value of 94%, a positive likelihood ratio not applicable, and a negative likelihood ratio of 0.22.

3.4.2. Accuracy of N2 prediction

PET/CT accurately established N-stage compared to mediastinoscopy in 20 out of 30 cases (67%) and in 16 out of 24 cases when compared to EPP surgical—pathological results (67%). The overall accuracy of PET/CT in assessing the correct N2 status as compared to mediastinoscopy alone was a sensitivity of 60%, specificity of 80%, positive predictive value of 60%, negative predictive value of 80%, a positive likelihood ratio of 3.0, and a negative likelihood ratio of 0.5. When comparing PET/CT to the final histological results obtained by mediastinoscopy and surgical—pathological results together a sensitivity of 50%, specificity of 75%, positive predictive value of 50%, negative predictive value of 75%, a positive likelihood ratio of 5.0, and a negative likelihood ratio of 0.67 were revealed.

3.4.3. Mediastinoscopy versus EPP surgical—pathological staging results

Four out of 24 resected patients (17%) had N2 disease despite negative preoperative mediastinoscopy (Table 4). Mediastinoscopy accurately established the N-stage in 20 out of 24 cases (83%) when compared to EPP surgical—pathological results (Table 6).

4. Discussion

Previous trials have shown PET alone to be useful in the staging evaluation, given additional data that could clarify...
doubtful CT findings, especially regarding distant lesions and also with respect to lymph node involvement though not compared to findings by mediastinoscopy. Nanni et al. compared PET stage to CT stage in 15 MPM patients and found no difference with respect to stage in 9 patients (60%) [11]. In 2 of 15 (13%) patients, PET upstaged the disease, while in 4 of 15 (27%) patients PET downstaged MPM. These findings correspond well to those reported for other solid tumours [17].

PET has the limitation of being imprecise with respect to the anatomical localisation of the lesion, which may especially be a problem with respect to preoperative staging. Combined PET and CT with fused imaging has been developed to improve accuracy [13]. The integration of PET and CT provides precise localisation of the lesion on the FDG PET scan within the anatomic reference frame provided by CT, thereby increasing specificity of the examination. Current available data in solid tumours indicate that PET/CT is more sensitive and specific than either of its constituent imaging methods alone [13], and its benefit in the staging of non-small cell lung cancer has been demonstrated [17]. Similar studies in MPM are however scarce.

The results of the current study show that PET/CT improves the accuracy of preoperative staging in MPM as compared to CT alone. Futile surgery was avoided in 12 out of 42 patients (29%), due to either distant metastases (10%) or T4 disease (22%). Also other studies have evaluated either PET alone [18, 19] or PET/CT [20] in the preoperative setting of MPM. The study by Flores et al. [18] using PET alone in 60 MPM patients of all histological subtypes did not reveal data on the fraction of patients who avoided futile surgery. However, the study by Erasmus et al. [20] using PET/CT in 29 patients of all histological subtypes of MPM provided information in 11 cases (38%) that precluded EPP, which corresponds to the 29% in the current study solely evaluating patients having epithelial subtype of MPM. Schneider et al. [19] also reported the usefulness of PET in detecting occult metastases in 2 of 18 patients with MPM who were precluded from surgery. Others have reported that distant metastases may be the initial site of relapse after EPP, and this could possibly reflect limitations in conventional staging with CT scan alone [21]. An improvement in the accuracy of M staging by use of PET/CT scan may possibly lead to more appropriate selection of patients for surgery and thus decrease the fraction of patients experiencing early relapse following EPP. The preclusion of some patients having T4 or M1 disease from surgery without histological confirmation may theoretically be a false positive signal in some patients, thereby overestimating the positive predictive value of PET/CT. However, biopsies in some of these patients were not possible without considerable risks or morbidity and was accordingly not felt possible to perform for ethical reasons.

The occurrence of T4 disease is confined with inoperability and is thus important to rule out. In the current study, the sensitivity of PET/CT in detecting T4 disease was 78% compared to 67% in another study using PET/CT scan by Erasmus et al. [20] and 19% using PET alone reported by Flores et al. [18]. Also Schneider et al. [19] observed limitations in PET alone, which failed to detect transdiaphragmatic invasion in one of 18 patients because PET alone lacks the spatial resolution to detect these kinds of findings. One solution to detect such infradiaphragmatic spread may be to do routine laparoscopy in the preoperative assessment which is done in some centres [22, 14] but was not included in the staging programme in this study. A peritoneal recurrence rate of 26% after EPP has previously been reported [23], but out of 78 patients who received peritoneal lavage in a staging study by Rice et al. [14] only 2.6% were positive for malignant cells. Such low yield may give rise to the question whether the procedure should be used routinely or confined to more selected patient groups and further illumination of this point is needed.

Spread of MPM to mediastinal lymph nodes is a poor prognostic sign [24], which in many centres prevail EPP. The occurrence of spread to N2 nodes was understaged by PET/CT in 3 of 30 patients (10%) when compared to mediastinoscopy alone and in 7 of 30 patients (23%) when compared to the combined results of mediastinoscopy and EPP. The sensitivity of PET/CT in detecting N2 spread was 50% which corresponds to 38% reported by Erasmus et al. [20] also using PET/CT and to 11% when using PET alone [18]. Thus, both PET and PET/CT.
are inaccurate in evaluating nodal MPM spread. One of the reasons for the unsatisfactory sensitivity of mediastinoscopy is the inability to reach certain lymph nodes, especially in the para-aortic region and the aortopulmonary window. This emphasizes the need for careful mediastinal lymph node mapping during EPP in order to accurately stage the patient.

In conclusion, 18F-FDG PET/CT increases the accuracy of staging in MPM, improves the selection of patients for EPP and avoids a significant number of futile operations. Even though PET/CT currently may be the preferred preoperative non-invasive staging procedure, it does not render mediastinoscopy and other invasive staging procedures unnecessary and further development of accurate, preferably non-invasive, staging methods in MPM remains of great importance.

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