Is malignant pleural mesothelioma a surgical disease? A review of 83 consecutive extra-pleural pneumonectomies

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Abstract

Objective: To report on the experience with radical surgery, with emphasis on the long-term outcome, for malignant pleural mesothelioma (MPM) at a single institution. Methods: From our prospective database over a 17-year period, we reviewed 83 consecutive patients undergoing radical surgery for MPM in a multimodality programme. The long-term overall survival was analysed using the Kaplan—Meier method. Results: A total of 83 patients (65 males, median age: 60 years) underwent an extra-pleural pneumonectomy (EPP) with a curative intent. Epitheliod MPM was the most frequent (82%) cause. A right-sided disease was present in half of the cases (n = 42). The International Mesothelioma Interest Group (IMIG) stage of the disease was 2 in 36%, 3 in 45% and 4 in 9% of the cases. Preoperative chemotherapies consisting of a doublet cisplatin—pemetrexed (mean of three cycles) was offered to 10 patients (12%). Postoperative therapies, either chemotherapy or radiotherapy, were given in 25 patients (30%). The 30-day and 90-day mortality rates were 4.8% and 10.8%, respectively. Postoperative complications occurred in 39.8% and were major in 23 patients (27.7%). Re-operation was necessary in 12 cases (14.5%) for one of the following reasons: broncho-pleural fistula (n = 4), bleeding (n = 3), diaphragmatic patch rupture (n = 3), oesophago-pleural fistula (n = 1) and empyema (n = 1). The mean hospital stay was 43 days. The median survival was 14.5 months, while the overall 1-, 2- and 5-year survival rates were 62.4%, 32.2% and 14.3%, respectively. Conclusions: These results concur with the published data of the most experienced centre with regards to the mortality and morbidity after EPP for MPM. In line with the biggest series reported in the past, the observed 5-year survival rate of almost 15% is disappointing.

Keywords: Extra-pleural pneumonectomy; Malignant pleural mesothelioma; Overall survival; Prognostic factors

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare, but constantly fatal, tumour linked with asbestosis. The incidence of the disease is increasing and is expected to peak in 10–15 years. The inherent prognosis of MPM is extremely poor, and median survival never exceeds 1 year — this is associated with a major negative impact on the quality of life. Unfortunately, there is currently no evidence-based effective therapy for this neoplasm. Neither surgical resection nor medical treatment or any local therapies have been proved to significantly improve survival. Obviously, there is a lack of multicentre randomised trials comparing these different options. The therapeutic management of MPM is mainly supported by retrospective series and the longitudinal experience of international centres with high volumes of patients. The primary goal of surgery remains the excision of the complete gross tumour in order to achieve a macroscopic complete resection. Extra-pleural pneumonectomy (EPP) has been intuitively considered the procedure of choice, which makes it possible to potentially achieve this target. However, the benefit on survival of such a major procedure has to be put in perspective with its high morbidity and mortality. When a single-agent treatment is no longer adequate, there is still doubt on what kind of therapeutic scheme could be the most effective and what the real place for radical surgery such as EPP may be. Therefore, in this context, we analysed our experience with EPP in the therapeutic management of MPM and compared our results with recent published data.

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2. Patients and methods

From September 1989 to August 2007, we reviewed 83 consecutive patients treated in a single institution for MPM based on data from our prospective database. All the patients underwent radical surgery in the form of an EPP using the standard surgical technique. During the same period, 40 patients underwent a pleurectomy/decortication (P/D) for MPM at our institution.

2.1. Patients

There were 65 men (78%) and 18 women (22%) with a median age of 60 years (range: 31—81 years). Nineteen patients (23%) were aged over 65 years. There were 52 patients (63%) with right-sided disease and 31 (37%) with left-sided disease. Occupational asbestosis was found in 48 patients (58%) and was unreported for 18 cases (22%).

2.2. Preoperative work-up

Diagnosis was pathologically proved in all cases following several pleural biopsies during a thoracoscopic approach. Talc pleurodesis was performed during the same time in four patients (49%). The mean gap between diagnosis and radical surgery was about 11.5 weeks.

All patients underwent preoperative investigations including a chest X-ray and a contrast-enhanced computed tomographic (CT) scan of the chest and the abdomen to evaluate the stage of the disease. Only 10 patients (12%) had a positron emission tomography (PET) scanning in order to detect distant metastasis. None of these patients had disease that was situated outside the thorax. A brain CT or MRI was also performed.

Moreover, an invasive surgical staging was performed in 16 patients (19%). A cervical mediastinoscopy was done in 10 cases (12%) exploring lymph node stations 2R, 4R, 7 and the contralateral lymph node stations of the disease. None of the patients who underwent a mediastinoscopy had lymph node involvement.

The operability was evaluated clinically on the basis of the performance status and additionally with pulmonary function tests, ventilation—perfusion scan and echocardiography.

2.3. Operative techniques

An EPP was performed using the standard technique. After an extra-pleural dissection, an en bloc resection of all the pleurae, the lung, the pericardium and the ipsilateral hemidiaphragm was performed. The reconstruction of the pericardium and the hemidiaphragm was done using Vicryl® and Prolene® meshes. A radical mediastinal lymph node dissection and the excision of previous port sites were also done systematically. A macroscopic complete resection was always obtained.

2.4. Statistical analysis

The statistical analysis was performed using the SPSS software package (SPSS, version 13.0, Inc., Chicago, IL, USA). The quantitative variables were expressed as mean ± standard deviation (SD). Demographic variables in the three groups were compared using the chi-square test. Survival was evaluated from the date of diagnosis up to the date of the last follow-up for the living patients or the date of death for the others. The Kaplan—Meier method was used to analyse the overall survival of all patients including the postoperative mortality. The differences in survival between the groups were tested using the log rank test. Significance was defined as a p-value ≤0.05.

A multivariate analysis was performed using a forward step-wise Cox’s model regression. This analysis pointed out the independent factors influencing overall survival and determined hazard ratios (HR). Sex, cell type, preoperative mediastinoscopy, side of the disease, previous talc pleurodesis, pre- or postoperative chemotherapy were considered as categorical variables. Age, pathological node (pN) stage, pathological tumour (pT) stage, the International Mesothe-lioma Interest Group (IMIG) stage and in-hospital stay were treated as continuous variables. For these continuous data, the HR represented the risk of death when the variable increased, step-by-step.

3. Results

3.1. Histology

The type cell was epithelial in 68 (82%) patients, biphasic in 13 patients (16%) and sarcomatoid in two cases (2%). The pathological T umour—Node—Metastasis (pTNM) staging was established using the TNM classification [1] and is reported in Table 1.

The IMIG stage [2] was II in 30 cases (36%), III in 37 patients (45%) and IV in 7 patients (9%). We did not have any patients with early-stage disease (Table 2) in our cohort.

3.2. Surgery

Postoperative complications occurred in 33 patients (40%). The major complications included broncho-pleural fistula (n = 4), diaphragmatic patch rupture (n = 3), acute respiratory distress syndrome (ARDS) and multi-organ failure.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Pathological stage of the MPM (pTNM).</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1</td>
<td>pT2</td>
</tr>
<tr>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>pN0</td>
<td>pN1</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>IMIG stage.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IMIG</td>
<td>N</td>
</tr>
<tr>
<td>Stage I</td>
<td>—</td>
</tr>
<tr>
<td>Stage II</td>
<td>30</td>
</tr>
<tr>
<td>Stage III</td>
<td>37</td>
</tr>
<tr>
<td>Stage IV</td>
<td>7</td>
</tr>
<tr>
<td>Unknown stage</td>
<td>9</td>
</tr>
</tbody>
</table>
(n = 3), cardiac failure (n = 3), bleeding (n = 3), oesophago-pleural fistula (n = 1), chylothorax (n = 1), and sepsis (n = 1).

Re-operation was necessary in 12 patients (14.5%). The indications for re-operation included broncho-pleural fistula (n = 3), bleeding (n = 3), diaphragmatic patch rupture (n = 3), oesophago-pleural fistula (n = 1) and empyema (n = 1).

Minor complications occurred in 17 patients and included atrial fibrillation (n = 7), arterial thrombosis (n = 1), fever (n = 1), urinary retention (n = 2), chest infection (n = 2), recurrent nerve palsy (n = 2) and atelectasis (n = 2).

### 3.3. Multimodality therapy

Most of the patients were included in a multimodality programme therapy. Ten patients (12.5%) had undergone chemotherapy preoperatively, including two cycles of a cisplatin-based regimen associated with pemetrexed. Thirty-five patients (42%) received chemotherapy postoperatively and postoperative radiotherapy was administered to 35 patients (42%). Radiotherapy was limited to the wound sites for 25 patients (30%), whereas a high-dose hemi-therated to 35 patients (42%).

### 3.4. Overall survival

The median survival of all patients was 14.5 months (95% confidence interval (CI): 11.5—17.6). The 1-, 2- and 5-year overall survival rates were 62.4%, 32.2% and 14.3%, respectively (Fig. 1). The 30- and 90-day mortality rates were 4.8% (95% CI: 1.6—12.5) and 10.8% (95% CI: 5.4—20.1), respectively. The causes of postoperative deaths (n = 4) included ARDS followed by multi-organ failure (n = 2), sepsis (n = 1) and cardiac failure, in the last patient.

On univariate regression analysis, sex (p = 0.4), age (p = 0.2), preoperative mediastinoscopy (p = 0.38), pT stage (p = 0.52), pn stage (p = 0.30), IMIG stage (p = 0.36), side (p = 0.18), previous talc pleurodesis (p = 0.15), preoperative chemotherapy (p = 0.39) and postoperative chemotherapy (p = 0.34) did not significantly impact the outcome. Only postoperative radiotherapy (p = 0.04) and cell type (p = 0.014) were found to be significant prognostic factors (Table 3).

On multivariate regression analysis, three variables were found to be poor independent prognostic factors: age (p = 0.028, HR: 1.1 (1.01—1.13), a non-epithelial cell type (p = 0.034, HR: 4.2 (1.1—15.7)) and a lymph node involvement (p = 0.002, HR: 2.3 (1.4—3.9)) (Table 4).

### 4. Discussion

MPM is a lethal malignancy with an extremely poor prognosis. In the absence of treatment, median survival ranges from 4 to 12 months from the time of diagnosis [3].

Few therapeutic options are available for MPP. Unfortunately, no therapy of choice has been validated yet due to the lack of consistent multicentric randomised trials comparing these different options.

The assessment for radical surgery for MPM is still controversial. The EPP was initially considered the procedure of choice, enabling the removal of the entire gross tumour, and has, therefore, been extensively developed worldwide. The first historical surgical series of 29 EPP, published in 1976 by Butchart et al., reported a high morbidity (>50%) and a high operative mortality rate (31%) while reporting a limited benefit on overall survival [4]. For more than 30 years, the management of patients with EPP has improved and morbidity and mortality rates have decreased. However, the best-experienced centres still report on an operative morbidity higher than 50% [5].

With regards to the best published figures, the median survival varies from 10 to 19 months and the associated overall 5-year survival rates have never reached 20% [5—9]. Our survival results are very similar (14.5 months and 14.3%, respectively), but are extremely disappointing. At 2 years,

### Table 3
Results of the univariate analysis in the 83 patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>65/18</td>
<td>78/22</td>
<td>0.4</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>–</td>
<td>–</td>
<td>0.2</td>
</tr>
<tr>
<td>Cell type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial/mixt/sarcomatoid</td>
<td>68/13/2</td>
<td>82/16/2</td>
<td>0.01</td>
</tr>
<tr>
<td>Preoperative mediastinoscopy (Y/N)</td>
<td>10/73</td>
<td>12/88</td>
<td>0.4</td>
</tr>
<tr>
<td>Stage pT</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Stage pn</td>
<td>–</td>
<td>–</td>
<td>0.3</td>
</tr>
<tr>
<td>Stage IMIG</td>
<td>–</td>
<td>–</td>
<td>0.4</td>
</tr>
<tr>
<td>Side of the disease R/L</td>
<td>42/41</td>
<td>50/50</td>
<td>0.2</td>
</tr>
<tr>
<td>Previous talc pleurodesis (Y/N)</td>
<td>41/42</td>
<td>50/50</td>
<td>0.15</td>
</tr>
<tr>
<td>Preoperative chemotherapy (Y/N)</td>
<td>10/73</td>
<td>12/88</td>
<td>0.4</td>
</tr>
<tr>
<td>Postoperative chemotherapy (Y/N)</td>
<td>35/48</td>
<td>42/58</td>
<td>0.3</td>
</tr>
<tr>
<td>Postoperative radiotherapy (Y/N)</td>
<td>35/48</td>
<td>42/58</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Table 4
Results of the multivariate analysis in the 83 patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>83</td>
<td>1.1</td>
<td>1.01—1.13</td>
<td>0.03</td>
</tr>
<tr>
<td>Cell type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial/mixt/sarcomatoid</td>
<td>68/13/2</td>
<td>4.2</td>
<td>1.1—15.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Stage pn</td>
<td>83</td>
<td>2.3</td>
<td>1.4—3.9</td>
<td>0.002</td>
</tr>
</tbody>
</table>

![Fig. 1. Overall survival of the 83 consecutive EPP.](image-url)
only one-third of the cohort (32%) was still alive. Since a median survival of 14 months is less than two times the median without treatment, these results on overall survival are unsatisfactory and, obviously, not acceptable in a curative intent when less than one patient out of five is still alive after 5 years. Nevertheless, as mentioned previously, these results are in line with those reported for locally advanced mesothelioma by international expert centres.

It is our opinion that it is questionable to consider patients with MPM for EPP in a curative scheme without evidence-based treatment guidelines and a 5-year survival rate that is less than 15% when, at the same time, the oncological thoracic community tend to regard as patients with non-small cell lung cancer and a bulky or multi-station N2 disease as non-operable although they are known to have at least similar survival rates (5-year overall survival rates of 17% and 23%, respectively) [10,11].

In these circumstances, the benefit of performing EPP in the management of MPM should be revisited. In concurrence with the main international series, we failed to demonstrate a substantial benefit on survival with EPP. We do not yet know if we could pretend an impact on control symptom or quality of life. There is no ongoing prospective randomised trial currently studying quality of life after surgical resection in MPM, especially comparing the different options such as: pleural biopsy alone and talc pleurodesis, subtotal pleurectomy, radical debulking P/D and EPP. Some data on debulking surgery and its impact on symptom control are available in the literature at present [12], but are not yet sufficiently strong to compare favourably with active symptom control alone or palliative radiotherapy. Encouraging results have been reported from centres defending radical P/D removing all pleurae, the hemidiaphragm and the pericardium but sparing the underlying lung [13–15]. This procedure is basically judged as an incomplete resection with a high rate of local disease progression [16]. However, it offers a hopeful alternative to EPP in patients with poor performance status or insufficient cardiopulmonary reserve [13,17].

Obviously, with regards to the high postoperative morbidity reported after EPP (25–63%), there is no rationale in considering EPP in a palliative intent [18–22].

Although many efforts are made to select the best candidates, especially using invasive preoperative staging, there are no consensus and well-defined indications for EPP. Consequently, most centres carry on managing MPM based on their own experience. Additionally, the surgical management of MPM appears inconsistent. For example, some institutions are continuing with EPP in patients aged 75 years whereas others refuse to perform EPP in patients beyond 65 years of age. The mediastinal lymph node disease draws a large part of the controversy in this debate. Should we still operate in case of lymph node involvement when a median survival of only 10 months [13,15,23] is expected? In this situation, several centres favour radical pleurectomy/decortication [13,15].

Obviously, radical P/D is considered as a palliative debulking procedure only. However, when the overall survival and quality of life represent the primary end-points, no significant difference has yet been demonstrated in favour of either. The benefit of palliative debulking in MPM, either by open radical P/D or video-assisted thorascopic (VATS) P/D, has been suggested in terms of pleural drainage, lung re-expansion and pleurodesis. Its benefit on survival is more controversial. The effective impact on the quality of life and pulmonary function of lung-sparring procedures has not yet been evaluated fully in the context of MPM [12,14,15,24,25]. Although EPP is an invasive procedure with a high morbidity rate, it could remain an interesting option for early-staged MPM when a complete resection (R0) could be attainable and median survival increased to more than 29 months [23]. To date, in the absence of any organised screening in a well-defined high-risk population, this situation remains extremely rare. Indeed, patients with Stage I or II MPM represent less than 30% of most surgical series at best [5,15,22]. In our cohort, we predominantly operated on patients with locally advanced MPM (45%), and did not identify any patients with Stage I disease. Even in recent series with a greater number of patients with Stage I MPM, the median survival still stands at 11.3 months [5] and the overall survival at 5 years never reaches 25% [6]. Moreover, no significant difference on survival after EPP could be established between early-stage and Stage II or III disease [5].

In future, efforts should probably focus on the early detection of pre-neoplastic conditions such as mesothelial hyperplasia and/or very early invasive disease. The follow-up of those patients who are occupationally exposed to asbestosis has to be improved. The role of PET scanning in this setting seems an exciting challenge.

5. Conclusions

The EPP in MPM does not provide a dramatic benefit on survival, especially in case of a locally advanced disease. Unfortunately, MPM is an insidious disease, and patients are rarely diagnosed with early-stage disease. After undergoing a major procedure such as EPP, a median survival of 15 months and a 5-year overall survival rate of less than 15% are discouraging. Nevertheless, our own results are consistent with others from international expert centres. The subgroups of patients with lymph node involvement or sarcomatoid histological cell type have been widely identified as having the poorest prognosis. In these subgroups, EPP is no longer justifiable, especially when the associated median survival (7 months) is similar to that with active symptom control alone. Surgery should not be confined in a curative scheme, but could be part of palliative therapies where priority is given to the quality of life. Active symptom control should involve surgical procedures in order to provide effusion drainage, pleurodesis and lung re-expansion. Debulking surgery in the form of radical pleurectomy/decortication is currently increasing. Proponents of radical P/D underline the advantage of an adequate cytoreduction procedure, a lower morbidity and mortality rate, the opportunity of additional therapies in a multimodality programme and a potential impact on the quality of life. When surgery and chemotherapy have previously failed in the treatment of mesothelioma, new therapeutic agents have to be explored quickly and patients included in randomised trials while there are still candidates to treat.
Acknowledgements

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References


