Three decades of experience in the surgical multi-modality management of pleural mesothelioma

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Abstract

Background: Optimal management of diffuse malignant pleural mesothelioma (DMPM) remains unclear. We report our 30-year surgical experience with DMPM with emphasis on surgical procedure and post-operative adjuvant therapy. Methods: During the period of the study, 217 patients with DMPM were referred for surgical opinion. Patients who only had pleural biopsies were excluded (n = 78). Consecutive patients who underwent surgical treatment were included (n = 139). Surgical options were extra-pleural pneumonectomy (EPP) for Butchart stage I disease in clinically fit patients (n = 49) or pleurectomy/decortication in patients who were either not fit for EPP or had advanced disease (Butchart stage II and III) or both (n = 90). Post-operative adjuvant therapy included either chemotherapy, radiotherapy, both or none. Results: The median follow-up was 10.0 months. The longest survival (median 26.0 months, IQR: 11.1–40.9 months) occurred in the pleurectomy/decortication group who received both post-operative chemotherapy and radiotherapy (n = 24) (p < 0.001). EPP whether or not combined with adjuvant therapy provided no significant survival advantage in comparison to pleurectomy/decortication (overall median survival 10.3 months vs 10.1 months, p = 0.09). On univariate analysis, pleurectomy/decortication combined with chemotherapy and radiotherapy was the strongest predictor of prolonged survival (Hazard Ratio = 3.6). Multivariate analysis with the inclusion of histological type, surgical procedure and type of adjuvant therapy, EPP without adjuvant therapy was an independent risk-factor for decreased survival (Hazard Ratio = 9.2).

Conclusions: In this series, cytoreductive surgery combined with post-operative adjuvant therapy provided better survival despite either advanced disease or surgically less fit patients. Thus, pleurectomy/decortication may be the procedure of choice, given that neither surgical procedure (EPP or PD) is not curative.

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1. Introduction

The incidence of diffuse malignant pleural mesothelioma (DMPM) is still rising and is expected to peak within this decade [1]. In the UK, the mortality has increased 10-fold over the last two decades. Meanwhile, the management of DMPM is still being modified as the evidence emerges concerning the survival benefit of various treatment modalities. Unfortunately, many patients with DMPM present late and the only modality of treatment is supportive. However, in a small percentage of patients treatment modality can improve their survival. The best combination of treatment and the optimum type of surgery remain to be defined.

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We reviewed our 30-year experience with the surgical management of DMPM paying particular attention to the survival benefit of post-operative adjuvant therapy.

2. Methods

A retrospective analysis of all patients who underwent surgical treatment for DMPM in our unit was undertaken. Staging and resectability were assessed pre-operatively by CT scan (with contrast) but modified by the operative findings. The Butchart staging classification was used [2] during the initial data collection (pre 1995) and continued thereafter so as to maintain consistency of the staging data. Thus we report our results using the Butchart classification rather than IMIGs.

During the period of the study, 217 patients with DMPM were referred for surgical opinion. Patients who underwent surgical pleural biopsy alone were excluded (n = 78). All
patients undergoing surgery for mesothelioma were included in the study \((n = 139)\). This included 90 patients who underwent pleurectomy and decortication (PD) where 90—95% of the tumour was excised. Consistently throughout the period of analysis, parietal pleurectomy included chest wall pleura and mediastinal pleura up to the hilum. Bulky tumour on the surface of the diaphragm was removed but the diaphragm was never resected. Decortication was used to remove as much tumour as possible from the surface of the lung and fissures and to achieve full lung re-expansion by also removing the thick organised fibrin deposited by the pleural effusion.

Forty-nine patients underwent extra-pleural pneumonectomy (EPP) where the lung, ipsilateral hemidiaphragm and pericardium were excised en-bloc with the parietal pleural. For the PD group, the remaining tumour bulk was marked with metal clips for targeted radiotherapy treatment. This was usually around the hilum and at the costophrenic angle.

Cardiovascular work-up in later years included echocardiography and Bruce protocol exercise tolerance test. Patients who were fit and appeared to be in Butchart stage I (on CT scan) were listed for EPP but some underwent PD if stage II or III disease was encountered during operative assessment. Patients with significant co-morbidities and/or were known to be stage II or III pre-op were listed for PD.

Peri-operatively all patients received a loading dose of digoxin (500 mcg 8 hourly, two doses pre-op) and digoxin was continued post-operatively for six weeks.

All thoracotomies were performed through the bed of the excised sixth rib. If EPP was feasible, then a second level thoracotomy through the same skin incision was performed through the bed of the excised tenth rib for better access to the periphery of the diaphragm to ensure complete extra-pleural excision and preservation of diaphragmatic peritoneum. In some right sided EPP, no prosthetic material was used to reconstruct the diaphragm if the diaphragmatic peritoneum was completely intact. Otherwise and for left sided EPP, dacron/silastic mesh or bovine pericardium with biological glue was used for diaphragmatic reconstruction (Fig. 1).

Pathological confirmation and sub-type analysis was based on histology and immuno-histochemical analysis.

Post-operatively all patients were referred to their local oncology team for consideration of chemotherapy and radiotherapy. External beam radiotherapy was targeted to Ligaclips-marked areas (usually at the costophrenic angle and around the hilum), thoracotomy wound and drain sites.

Although all patients were referred for post-operative adjuvant treatment, the following factors influenced the decision to proceed: (1) patient’s choice, (2) presence of infection, (3) poor performance status post-operatively and (4) oncologist’s reluctance, in the absence of Level I evidence in terms of benefit.

The chemotherapy regimen changed considerably over the years and now includes cisplatin, pemetrexed and vinerelbine. Radiotherapy treatment was via linear accelerators to a total dose of 50—55 Gy. Because of small numbers of patients within each drug regime, no attempt was made to analyse survival in relation to individual drugs. Instead the groups were categorised as having had either chemotherapy, radiotherapy or both.

All patients were followed in the out-patients department. Death dates were confirmed with the respective Cancer Registries in the UK. The causes of death for the early mortality group included sepsis (3 patients), pulmonary embolism (2 patients), ARDS (1 patient) and aspiration pneumonia (1 patient). The cause of death of most of these patients was recorded as being due to mesothelioma and this included those who developed BPF. Whether the BPF was the direct cause of death was not registered.

3. Statistical methods

Data was analysed with SPSS 15.0 and expressed as mean (standard deviation), median (interquartile range) and percentages as appropriate. Survival was calculated from the date of surgery to either date of death or date of last follow-up and was analysed by the Kaplan–Meier method with log-rank test for statistical significance. A \(p\)-value of less than 0.05 was considered statistically significant. The \(p\)-values for the data expressed as percentages were calculated by either Chi-Squared or Fisher’s exact tests for small groups. The median in-hospital length of stay for the various groups were compared using Kruskal–Wallis test while the median survival and 95% confidence intervals were obtained from the K–M analysis with the log rank as the \(p\)-value. Factors which were found to be significant on univariate analysis, namely mesothelioma type, surgical procedure and type of adjuvant therapy were then entered in the multi-variate analysis model (Cox regression).

4. Results

Overall, the mean age (SD) was 58.9 (9.8) years with 87% males. Two-thirds of the patients had right sided disease.

Patients’ groups were PD alone \((n = 34)\), PD with chemotherapy \((n = 13)\), PD with radiotherapy \((n = 19)\), PD with both chemotherapy and radiotherapy \((n = 24)\), EPP alone \((n = 12)\), EPP with chemotherapy \((n = 14)\), EPP with radiotherapy \((n = 8)\), and EPP with both chemotherapy and radiotherapy \((n = 15)\).
Patients in the PD alone group were older than EPP with chemotherapy and radiotherapy. The patients’ demographics are shown in Table 1.

The 30-day mortality was 1.1% for the PD group and 8.2% for the EPP group (p = 0.03). A further two patients (one from the EPP and one from the PD group) died after 30 days within the same hospital admission. The overall median follow-up was 10 months. Patients undergoing EPP experienced more post-operative complications especially immediate post-operative infections (16% - 8/49) and the development of broncho-pleural fistula after hospital discharge (14% - 7/49). The incidence of post-operative atrial fibrillation was 1% for PD and 4% for EPP.

Three patients required early re-operation following EPP. One patient developed cardiac herniation and required re-operation to patch a pericardial defect. A second patient needed re-operation due to herniation of large bowel and omentum through a small defect between the patch and the chest wall following a left-sided EPP. A third patient underwent a right sided EPP without diaphragm patch as the peritoneum was intact but required patch insertion due to excessive migration of the liver within the right pleural space.

Due to selection criteria, all patients in EPP group were in Butchart stage I pre-operatively but at the time of surgery some did have metastatic lymph node involvement. Post-operative staging confirmed 12% of PD group and 65% of EPP group to be Butchart stage I disease.

There was a tendency for patients who underwent PD to live longer than those who underwent EPP (p = 0.09) (Fig. 2). Patients with epithelial type of mesothelioma on histological diagnosis also experienced better survival (p = 0.002). However, Butchart staging did not influence long-term survival (p = 0.78).

The use of adjuvant therapy (radiotherapy, chemotherapy or both) was associated with an increased post-operatively survival (Fig. 3).

The longest survival (median 26.0 months, 95% CI: 11.14—40.9 months) occurred in the pleurectomy/decortication group who received both post-operative chemotherapy and radiotherapy (n = 24) (log rank < 0.001).

On univariate analysis, pleurectomy/decortication combined with chemotherapy and radiotherapy was the strongest predictor of prolonged survival (Hazard Ratio = 3.6). On multivariate analysis EPP alone was an independent risk-factor for decreased survival (Hazard Ratio = 9.2).

Post-operative survival data are summarised in Table 2 and illustrated by Fig. 4.

5. Discussion

The results of our series compare favourably with the reported literature in terms of early mortality and morbidity after either PD or EPP for DMPM. However, the overall survival of patients diagnosed with DMPM remains poor.

![Fig. 2. Kaplan–Meier survival curve comparing EPP with PD.](image_url)

![Fig. 3. Kaplan–Meier survival curve showing the survival benefit of pleurectomy/decortication when combined with adjuvant therapy.](image_url)
The post-operative incidence of AF in this series was relatively low and may reflect our protocol using digoxin prophylactically to maintain sinus rhythm. The incidence of broncho-pleural fistula (BPF) in the EPP group (14%) was probably due to the post-operative effect of the combination of chemotherapy and radiotherapy. Unfortunately the patient numbers were too small to define the associated factors statistically.

According to a recent trial, chemotherapy alone (cisplatin and pemetrexed) offers a median survival of 12.1 months and a 2-year survival of 22% [3]. More recently a Turkish group reported on the improved survival with chemotherapy (median 11.3 months) when compared with best supportive care (median 8 months) [4]. Radiotherapy may have a role in symptom palliation but radical radiotherapy alone has not been shown to be beneficial [5]. Debulking surgery alone via VATS is reported to result in a median survival of around 13 months [6]. The same group reported a median survival of 16.5 months and a 2-year survival of 42% in 19 patients with epithelial cell DMPM [7].

Thus far, the best survival option had been provided by a combination of surgery followed by adjuvant therapy. The most recent series reported by Sugarbaker et al. showed a median survival of 19 months when EPP was followed by chemotherapy and radiotherapy [8]. Moreover, Sugarbaker suggested that the primary goal of surgery should be complete macroscopic resection followed by chemotherapy and radiotherapy [9]. In patients with N2 disease, EPP is reported to have no survival benefit when compared to PD [10]. More recently the use of neo-adjuvant chemotherapy followed by EPP and radiotherapy has shown some promising results with a median survival of up to 23 months [11].

The combination of PD and chemoradiation has been reported in a small group of patients (n = 26) by Lee et al. [12]. In their series, radical PD and intra-operative radiotherapy was followed by external beam radiation therapy with or without chemotherapy. They reported a median survival of 18.1 months. More recent data from Borasio et al. (n = 26) showed a 14.5 months median and 29.6% 2-year survival in patients undergoing either EPP or PD followed by chemotherapy [13].

Intensity modulated radiotherapy (IMRT) seems to have some effect both on control of local disease and overall survival. Reporting on their experience in 63 patients with IMRT, Rice et al. showed an improved survival in patients with mesothelioma, with a median and a 3-year survival being 14.2 months and 20% respectively [14].

More recently, combining experience from three institutions, Flores et al. [15] reported that PD had an improved survival when compared to EPP in 663 patients with median survival of 23 and 19 months respectively. However, the effect of adjuvant therapy post surgery was not documented. In a subsequent study, the same group reported on the overall median survival of patients treated either with EPP or PD and post-operative chemotherapy, radiotherapy or both (n = 207) as being much better compared with other treatment modalities, with a median survival of 20.1 months [16].

In an attempt to assess the benefit of multi-modality treatment of DMPM prospectively, Rea et al. enrolled 21 patients with DMPM to induction chemotherapy followed by EPP and then post-operative radiotherapy. They report a 25.5 months median survival and 33% 3-year survival [17].

In our patient group, PD followed by chemoradiotherapy offered the best survival benefit with a median survival of 26 months. This compares favourably with the current reported literature (Table 3). Tumour debulking by pleurectomy/decortication allows for local control of the disease especially when combined with targeted radiotherapy to

![Fig. 4. Kaplan–Meier survival curve for the two surgical modalities (PD and EPP) when combined with various adjuvant therapy modalities.](image-url)
remaining tumour. When followed by chemotherapy, the above strategy also seems to provide the best control of both local and systemic effects of DMPM.

Survival benefit was optimised in the patient group who underwent the combination of post-operative chemotherapy and radiotherapy following pleurectomy/decortication, despite (a) clinically less fit patients, (b) more advanced disease and (c) an adjuvant regime which have changed significantly over the years. We believe that with the current improved adjuvant regime (including pemetrexed and IMRT), survival could be further improved in the pleurectomy/decortication group.

According to our results and those of others comparing EPP and PD, EPP may have only a limited role in DMPM, particularly as neither operative procedure is curative. Ultimately the place of EPP will only be determined by a randomised trial in comparison to PD in stage I disease with both groups receiving adjuvant therapy. Randomisation would need to take place in the operating room once initial operative assessment had confirmed Stage I disease.

### 6. Limitations

This study is a retrospective analysis and thus no randomisation was carried out. Analysis of the effect of tumour volume in stage I disease was also not feasible. During the study period, the chemotherapy and radiotherapy regimens changed significantly and thus the effect of specific regimens could not be assessed. Many of the EPP patients were not considered well enough to receive post-operative adjuvant therapy. Although this undoubtedly influenced survival, the overall results represent 'real life' situations when comparing EPP to PD.

### References


Table 3 Comparison of survival with other published data.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimta and cisplatin [3]</td>
<td>12.1</td>
<td>22</td>
</tr>
<tr>
<td>EPP + IMRT [14]</td>
<td>14.2</td>
<td>—</td>
</tr>
<tr>
<td>EPP/PD and adjuvant therapy [13]</td>
<td>14.5</td>
<td>30</td>
</tr>
<tr>
<td>EPP [15]</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>PD (epithelioid) [7]</td>
<td>16.5</td>
<td>42</td>
</tr>
<tr>
<td>PD + radio + chemo [12]</td>
<td>18.1</td>
<td>—</td>
</tr>
<tr>
<td>EPP + chemoradiation [8]</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>EPP [15]</td>
<td>19</td>
<td>—</td>
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<tr>
<td>EPP/PD and adjuvant therapy [16]</td>
<td>20.1</td>
<td>—</td>
</tr>
<tr>
<td>PD [13]</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td>Induction chemo + EPP + radio [17]</td>
<td>25.5</td>
<td>—</td>
</tr>
<tr>
<td>PD + chemo + radio [our data]</td>
<td>26</td>
<td>55</td>
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