Palliative surgical debulking in malignant mesothelioma
Predictors of survival and symptom control

A.E. Martin-Ucara, J.G. Edwards, A. Rengajaran, S. Muller, D.A. Waller

Department of Thoracic Surgery, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK
Department of Pathology, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK

Objective: Malignant mesothelioma (MM) typically presents at an advanced stage. In the UK surgical intervention has been mostly reserved for tissue diagnosis or chemical pleurodesis. However, the role of debulking surgery in symptom control has not been fully explored.

Methods: In a prospective cohort study, 51 consecutive patients presenting with MM underwent palliative surgical debulking for symptomatic relief (all patients presented with dyspnoea, 39 also had pain and two had a co-existing pleural empyema). Patients with early disease who underwent extrapleural pneumonectomy were excluded. The treatment aims were pleural drainage, lung re-expansion, pleurodesis and pleural debulking for symptom control. If the lung re-expanded after drainage of the effusion a subtotal parietal pleurectomy was performed via Video Assisted Thoracic Surgery (VATS). If the lung remained entrapped, a parietal and visceral decortication using VATS or thoracotomy was performed. The changes in subjective dyspnoea and pain scores were recorded at 6 weeks and 3, 6 and 12 months after surgery. Prognostic factors were analyzed to determine their influence on survival and symptom control.

Results: VATS pleurectomy was possible in 17 patients (34%), whilst decortication was required in the remainder (three by VATS and 31 by thoracotomy). Median postoperative stay was 7 days (range 2–17) with 30-day mortality of 7.8% (four of 51 patients). Morbidity included postoperative empyema in two patients (4%) and prolonged air-leak in five (9.8%). Overall significant symptomatic benefit was obtained up to 3 months after surgery but subsequently increasing mortality offset these benefits. Epithelial cell type and absence of weight loss prior to surgery were found to predict longer survival and successful symptom control.

Conclusions: Debulking surgery has a beneficial role in symptom control for unresectable MM. However, this surgery should be reserved for those patients who present with epithelial cell type and before significant loss of weight.

Keywords: Malignant pleural mesothelioma; Video assisted thoracoscopic surgery; Decortication; Trapped lung

1. Introduction

Patients with malignant mesothelioma (MM) usually present at an advanced stage with dyspnoea due to effusion (in most patients), and pain (approximately 70% of patients) because of invasion of the chest wall by tumour [1]. With the exception of a reduced number of patients undergoing radical surgery for local control of the disease, the primary aim of treatment is palliation of dyspnoea by drainage of the pleural effusion and prevention of fluid re-accumulation by chemical pleurodesis. Talc pleurodesis has been shown to achieve the best results and is successful in 80–95% of patients [2–4], but pain, respiratory failure and acute pneumonitis has been reported following its instillation in the pleural cavity [5]. Subtotal parietal pleurectomy provides a lasting and effective pleurodesis, and gives the opportunity to obtain large volumes of tissue in cases of difficult histological diagnosis. Unfortunately when performed through a thoracotomy it has been associated with high morbidity and is therefore generally avoided [6]. However, the use of Video Assisted Thoracic Surgery (VATS) pleurectomy has been shown to give symptom control with low morbidity [7].

A dilemma occurs in patients with advanced malignant pleural disease when the lung is entrapped by tumour cortex and remains collapsed following drainage of the effusion. Chemical pleurodesis or parietal pleurectomy is insufficient to relief symptoms in these cases where pleural apposition cannot be obtained. The use of pleuroperitoneal shunts has been described in an attempt to palliate symptoms [8]. However, it does not achieve lung re-expansion, and complications such as shunt blockage or infection, occur in up to 15% of patients [9,10]. Long-term indwelling pleural drainage catheters have also been employed in the
management of malignant pleural effusions, but re-expansion does not occur in cases of trapped lung and the complication rate approaches 20% [1].

In these situations we have adopted a protocol of visceral pleural decortication to treat an entrapped lung in operable patients, in an attempt to reduce dyspnoea by obtaining pleural apposition. The aims of this prospective cohort study were to evaluate the risks and benefits of a protocol of tumour debulking in MM. We have assessed the impact of prognostic factors, which we have previously validated [11], in an attempt to predict patients who fail to get benefit from surgery.

2. Methods

2.1. Patients

Over the 4-year period between April 1997 and March 2001, 116 patients with diagnosis of MM were assessed in our unit. Fifty-one patients (47 males, four females), mean age of 62.5 years (range 43–79), underwent palliative surgery for symptomatic control (43%) and form our study group. Indications for surgery included dyspnoea in 51 (100%), chest pain in 37 (72.5%) and empyema in two patients. The pathological diagnosis was MM in all cases (epithelial type in 34, mixed cell type in nine and sarcomatous type in eight). This study does not include the group of 22 patients with early disease who underwent radical extrapleural pneumonectomy during the same time period (19% of total).

2.2. Surgical protocol

We have followed a protocol of simultaneous VATS assessment and symptom control in patients with pleural effusions, who were deemed operable on preoperative assessment and in whom a positive pathological diagnosis of MM (by cytology or closed pleural biopsy) had been made. All these patients were unresectable as per computerized tomography ± magnetic resonance imaging (CT ± MRI) scan. General anaesthesia was employed with double lumen intubation and thoracic epidural analgesia at T5/6/7 levels using a combination of bupivacaine and fentanyl. Initial thorascoscopic assessment was performed at T5/6/7 levels using a combination of bupivacaine and fentanyl. Initial thorascoscopic assessment was performed with univariate analysis were subject to multivariate, forward, stepwise, binary logistic regression analysis. The prognostic variables entered in the different models are clinicopathological and radiological indices were derived immediately prior to surgery. Patients were assessed preoperatively and at 6 weeks and 3, 6 and 12 months postoperatively. Assessment consisted of chest radiography and subjective scores of dyspnoea and chest pain. The Medical Research Council (MRC) Dyspnoea Score, as recently validated [12], was used. Pleuritic chest pain was assessed on a four-point scale (not at all, a little, moderate and severe). Changes in symptom score and radiographic recurrence of effusion were recorded. Radiotherapy and chemotherapy was withheld in these patients until clinical evidence of disease progression occurred. Postoperative survival was calculated from the date of the surgery.

2.4. Statistical analysis

Postoperative survival was plotted according to the Kaplan–Meier method and the difference in survival between groups was evaluated with the log–rank test. Prognostic variables significant in univariate analyses were included in a multivariate, forward, stepwise, Cox proportional hazards model. Cases dying within 30 days were excluded from multivariate survival analysis to exclude bias from perioperative death. The Wilcoxon signed-rank test was used to compare symptom score changes in each individual patient between preoperative values and those at follow-up. For the purposes of analysis, patients who had died by the assessment point were assigned the maximum scores of both pain and dyspnoea. To identify the impact of clinicopathological variables on symptomatic benefit, we compared groups of patients: (1) who had obtained symptomatic benefit and (2) who were dead or did not achieve symptomatic control at the different assessment time-points. In univariate analysis, clinicopathological variables were assessed with Fisher’s exact test. Variables significant with univariate analysis were subject to multivariate, forward, stepwise, binary logistic regression analysis. The prognostic variables entered in the different models are presented in Table 1. Statistical significance was defined throughout by P values of less than 0.05.

3. Results

3.1. Operative details

Parietal pleurectomy was possible in 17 and visceral tumour decortication was required in 34 patients (31 by thoracotomy and three by VATS). The median postoperative hospital stay was 7 days (range 2–17).

3.2. Early postoperative complications

No patient required re-operation for bleeding. Postopera-
tive empyema developed in two patients (4%) in which full lung re-expansion was not obtained even after decortication. One of these patients required rib resection but the other one was treated successfully with intercostal drainage. There were four deaths within 30 day of surgery (7.8%). These include all in-hospital mortality. No patient died in hospital after 30 days without being discharged. One patient who presented with a malignant empyema that required open decortication died on day 18 of bronchopneumonia and respiratory failure. Two of the deaths were due to pulmonary embolism following open decortication and occurred on days 10 and 24 after surgery. The remaining death from respiratory failure followed VATS decortication and occurred in a patient with concomitant chronic obstructive pulmonary disease. Five patients (15%) of the open decortication group suffered from persistent air leaks for more than 7 days following surgery.

3.3. Follow-up and survival

Follow-up assessment was complete in all patients at 6 weeks and 3, 6 and 12 months. At 6 weeks the overall mortality was 14% (43 survivors). Thirty-six patients survived 3 months, 24 survived 6 months and 13 were still alive after 1 year. There were no radiological recurrences of effusions at follow up. Due to the lack of trial protocols locally for the use of chemo and radiotherapy, neither of these modalities of treatment was employed early as prophylaxis. During the follow-up four patients received radiotherapy and two patients have entered a chemotherapy regime.

Median survival was 215 days (95% confidence interval (CI) 152–278). Overall survival at 6 weeks was 89%, and at 3, 6 and 12 months 71, 56 and 31%, respectively. The type of procedure performed did not significantly influence survival ($P = 0.07$). Survival was significantly better with epithelial than mixed or sarcomatoid cell types (median survival of 302 versus 131 days, $P = 0.0001$) and also in patients who had not lost weight ($P = 0.004$). However, in a multivariate analysis, weight loss did not contribute to the cell type as an independent predictor of survival, and only

![Fig. 1. Relative survival plots for good and poor prognostic groups. The number of patients alive at 1 and 2 years is quoted for each group.](image-url)
epithelial cell type did (hazard ratio 3.6 (95% CI 1.7–7.8) (P = 0.0008)).

When patients with non-epithelial cell type and/or weight loss were analyzed against who had neither, a significant difference in survival was seen (P = 0.0003, Fig. 1; Table 2).

3.4. Symptom relief

Significant improvement in the dyspnoea and pain score was achieved at 6 weeks and 3 months. However, despite good symptom control in the surviving cases, mortality outweighs the benefits after 3 months (Tables 3 and 4). In binary multivariate regression analysis, cell type and weight loss were predictors of symptom control (Table 5). Patients with epithelial cell type and no weight loss were significantly more likely to retain symptomatic control than those with neither of these features (P < 0.01).

4. Discussion

These results suggest that a protocol of debulking surgery incorporating VATS and open surgery is useful in providing relief of symptoms caused by MM in selected patients. Improvement in dyspnoea was due not only to drainage of the effusion but also to expansion of the underlying lung, which pleurodesis alone could not achieve. Although not measured in this study, there is evidence from surgery for empyema that decortication of an entrapped lung increases vital capacity, forced expiratory volume and lung perfusion [13,14]. The reasons for the relief of chest wall pain observed are unclear but this may be due to relief of intercostal nerve compression. The improvements in dyspnoea and pain scores are both consistent with other studies [15,16]. Symptom improvement remains until tumour progression: we presume that failure of symptom control occurs due to local recurrence, since we did not encounter re-accumulation of effusion. The morbidity and mortality that we have demonstrated is comparable to that of other methods of effusion control. Our 30-day mortality rate of 7.8% is similar to that quoted for talc pleurodesis, which is typically between 5 and 16% [17,18].

The use of VATS procedures for the management of MM has been reported in the literature with a high success rate in the radiological control of effusions and in the confirmation of histological diagnosis [7,19]. We have recorded the same results in the control of the effusion but also an improvement in subjective symptom scores over a prolonged period of time. Our low incidence of complications in VATS pleurectomy compares with these previous experiences.

The symptomatic control observed in this series of selected patients challenges the view that thoracotomy, in the palliative treatment of malignant pleural effusion, is not justified. Although we accept that careful consideration has to be given before performing thoracotomy and decortication, due to the increased risk of prolonged air-leak (15%) and the development of empyema (6%) if the lung fails to re-expand, no other method has proven superior in achieving lung expansion and symptom control in the trapped-lung syndrome. This radical approach should be contrasted with the less invasive use of pleuro-peritoneal shunts. This technique is not universally applicable because of pleural sepsis and the shunt does not relieve the effect of an entrapped lung on pulmonary function nor does it relieve chest wall pain.

Future studies should include prospective randomized trials to compare different surgical approaches in similar stages of this disease. One study should compare VATS pleurectomy against talc pleurodesis, if the lung expands and pleural apposition can be obtained. In the situations in which pleural apposition is not possible, the relative risks and benefits of decortication, pleuroperitoneal shunt and long-term drainage should be assessed. Other modalities of treatment also have to be considered in these trials.

The results of this series suggest that patient selection can be improved to maximize the benefits of palliative surgery in mesothelioma. Those with epithelial cell types and without weight loss appear to derive most benefit in terms of symptom control achieved by surgical debulking, mostly due to prolonged survival. Every effort to investigate treatments of MM is required, particularly with the prospect of the incidence of the disease rising up to 9000 deaths per year in Western Europe by 2018 [20].

---

### Table 2
Survival data for the group of patients with epithelial cell type and without weight loss, compared to the group with non-epithelial cell type and/or weight loss (95% CI in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Epithelial cell type and no weight loss</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>32</td>
</tr>
<tr>
<td>Median survival (days)</td>
<td>496 (331–661)</td>
<td>158 (96–220)</td>
</tr>
<tr>
<td>6-month survival</td>
<td>95% (90–100%)</td>
<td>44% (35–52%)</td>
</tr>
<tr>
<td>1-year survival</td>
<td>63% (51–75%)</td>
<td>14% (8–20%)</td>
</tr>
<tr>
<td>2-year survival</td>
<td>42% (30–54%)</td>
<td>4.5% (0–9%)</td>
</tr>
</tbody>
</table>

### Table 3
Dyspnoea relief

<table>
<thead>
<tr>
<th></th>
<th>Dead</th>
<th>Alive</th>
<th>Improved</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>8</td>
<td>43</td>
<td>39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3 months</td>
<td>10</td>
<td>38</td>
<td>35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 months</td>
<td>20</td>
<td>26</td>
<td>22</td>
<td>0.3</td>
</tr>
<tr>
<td>12 months</td>
<td>32</td>
<td>13</td>
<td>11</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 4
Pain relief

<table>
<thead>
<tr>
<th></th>
<th>Dead</th>
<th>Alive</th>
<th>Improved</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>8</td>
<td>43</td>
<td>39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3 months</td>
<td>10</td>
<td>38</td>
<td>35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 months</td>
<td>20</td>
<td>26</td>
<td>22</td>
<td>0.3</td>
</tr>
<tr>
<td>12 months</td>
<td>32</td>
<td>13</td>
<td>11</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Some of the patients did not present with pain.
References


Table 5
Multivariate binary logistic regression analysis of symptom control

<table>
<thead>
<tr>
<th>Symptoms controlled</th>
<th>Variables</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 weeks</td>
<td>40 of 51 (78.4%)</td>
<td>Non-epithelial cell type</td>
<td>4.78 (1.5–15.6)</td>
</tr>
<tr>
<td>At 3 months</td>
<td>36 of 48 (70.6%)</td>
<td>Non-epithelial cell type</td>
<td>9.0 (2.4–33.2)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>21 of 46 (41.2%)</td>
<td>Non-epithelial cell type</td>
<td>3.7 (1.0–13.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight loss</td>
<td>3.7 (1.0–13.3)</td>
</tr>
<tr>
<td>At 1 year</td>
<td>13 of 45 (25.5%)</td>
<td>Weight loss</td>
<td>4.4 (1.2–13.8)</td>
</tr>
</tbody>
</table>


