Open lung-sparing surgery for malignant pleural mesothelioma: the benefits of a radical approach within multimodality therapy

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Abstract

Objectives: To identify the optimal debulking procedure in patients with malignant pleural mesothelioma who are not suitable for extrapleural pneumonectomy (EPP).

Methods: We reviewed 102 consecutive patients (93 male; 9 female, mean age 63 years) who were not suitable for EPP because of either advanced tumour stage or suboptimal fitness. Patients underwent either a non-radical tumour decortication to obtain lung expansion (group NR) or latterly a radical pleurectomy/decortication to obtain macroscopic tumour clearance (group R). We analysed the comparative perioperative courses and long-term survival.

Results: The two groups were similar for age and gender distribution but epithelioid type was more predominant in group R: 78% compared to 55% epithelioid in group NR. Thirty-day mortality was similar (5.9% in group R and 9.8% in the group NR, \( p = 0.36 \)) but 90-day mortality was significantly higher in the group NR (29.4% vs 9.8% in group R, \( p = 0.012 \)). More patients in group R received adjuvant chemotherapy (65% vs 28%, \( p = 0.000 \)) and radiotherapy (65% vs 26%, \( p = 0.000 \)). Median survival for all cell types was significantly higher in group R (15.3 months vs 7.1 months, \( p < 0.000 \)). Group R survival rates at 1, 2, 3 and 4 years were 53, 41, 25 and 13%, respectively while for group NR they were 32, 9.6, 2 and 0%, respectively. For epithelioid cell type there was still a significant median survival advantage in group R (25.4 months vs 10.2 months, \( p < 0.000 \)), but there was no difference for sarcomatoid (9.3 months vs 3.2 months, \( p = 0.16 \)) or biphasic cell types (9.4 months vs 7 months, \( p = 0.38 \)).

Conclusion: If a patient with epithelioid MPM is fit enough to tolerate a thoracotomy then macroscopic clearance of the tumour is the preferred option as part of a multimodality regime including chemotherapy.

Keywords: Malignant pleural mesothelioma; Radical surgery; Pleurectomy/decortication

1. Introduction

Extrapleural pneumonectomy (EPP) is considered by many to be the best surgical option as part of a trimodality treatment as it is associated with the longest reported survival in carefully selected patients [1]. Selection criteria for EPP are restrictive and include: age, cell type, locoregional extent and cardiopulmonary reserve. In cases that were unsuitable for EPP because of tumour extent or comorbidity we have offered an open, non-radical tumour decortication to achieve lung expansion and alleviate symptoms of chest wall pain and dyspnoea. However, we found that any symptomatic benefit was curtailed by limited survival [2]. We therefore introduced a more radical policy of extending the decortication to achieve macroscopic tumour clearance by excising the diaphragm and pericardium if necessary [3].

In this study we have compared the short- and long-term results of these two operative strategies in patients unsuitable for EPP.

2. Materials and methods

We identified in our prospective database 102 consecutive patients who underwent parenchyma sparing debulking surgery for MPM over a 10-year period. Their ineligibility for EPP included: clinical stage T4 or M1, mediastinoscopy proven stage N2, age >70 years, predicted postoperative FEV1 <40%, right or left ventricular systolic dysfunction or estimated mean pulmonary artery pressure higher than 35 mmHg.

2.1. Patient demographics

The full cohort of 51 patients undergoing radical P/D (group R) was compared with the last cohort of 51 patients who had undergone tumour decortication alone (group NR). There were no statistically significant differences in the
distribution of age or gender between the two groups but there was a larger proportion of epithelioid MPM in group R (Table 1).

Forty-one patients (40%) confirmed positive asbestos exposure history.

2.2. Preoperative workup

Definitive pathological diagnosis was established in 67 patients (66%). The remaining 35 (29 in group NR and 6 in group R) had pleural biopsies that were highly suspicious but not diagnostic for MPM. The median delay from diagnosis to surgery was 50 days. All patients had staging thoracic and abdominal CT (although CT PET was not used) and pulmonary function tests to assess resectability and operability. From June 2004 onwards all candidates for EPP had invasive mediastinal staging (cervical mediastinoscopy) and if N2 nodal disease was found patients were offered radical P/D instead of EPP [3,25]. In group R 13 of the patients were initially candidates for EPP but 5 of them were found to have mediastinal lymph node involvement. The remaining eight either opted for radical P/D (two patients) or were unfit for pneumonectomy (six patients).

2.3. Operative techniques

Open tumour decortication was more frequently performed earlier in the series. The operative objective was to remove the bulk of the tumour including both visceral and parietal pleura, to re-expand the trapped lung and achieve effusion, dyspnoea and pain control [2]. The diaphragmatic and mediastinal surfaces were spared.

With radical P/D the surgical objective was to achieve complete macroscopic clearance of the tumour with removal of the pericardium and diaphragm if required. Pericardium and diaphragm were reconstructed using prosthetic patches (Marlex mesh for the pericardium and Gore-Tex for the diaphragm) (Fig. 1). Fibrin glue is routinely used nowadays to control air leakage and bleeding from the lung [3].

2.4. Statistical analysis

Statistical analysis was performed using the SPSS version 11.0 software package (SPSS Inc., Chicago, Ill). Differences between groups were tested with the chi-square and the t-test. Survival was calculated from the day of pathological confirmation until either the date of death or the date of last follow-up. The patient’s general practitioner was contacted in most of the cases so that we could ensure the accuracy of the data used for analysis. Actuarial survival was calculated with the Kaplan–Meier method, included perioperative deaths and the differences between the groups were tested with the log-rank test.

3. Results

3.1. Patient demographics and cell type

The gender and age distribution was similar in the two groups: median age for group R was 62 (53–75) years and for group NR 63 (46–77) years, \( p = 0.7 \). There were 46/51 males in the radical group and 47/51 in group NR, \( p = 0.5 \). There was a difference though in the distribution of the histological subtypes of the disease: there were proportionately more patients with epithelioid cell type in group R (40 epithelioid, 4 sarcomatoid and 7 biphasic) than in group NR (28 epithelioid, 11 sarcomatoid, 12 biphasic), \( p = 0.035 \) (Table 1). The patients that had radical P/D were staged according to the WHO and IMIG staging systems but this was not appropriate for group NR (Table 2). The resection margins could only be assessed in group R and they were negative in 32 cases (63%), microscopically involved (R1) in 17 (33.3%) and macroscopically involved (R2) in 2 (3.8%). All cases in group NR were assumed to be R2.

3.2. Surgery and perioperative events

There was no significant difference in the 30-day mortality between the two groups: three (5.9%) deaths for group R and
five (9.8%) for group NR, $p = 0.36$. Most common causes of early deaths were pleural sepsis, chest infection, acute myocardial event and acute pulmonary embolism. More patients in group R suffered from moderate to severe early morbidity (28 patients, 55%) than in group NR (14 patients, 28%), $p = 0.023$. The major complications that occurred requiring re-exploration were: chylothorax ($n = 1$), oesophageal rupture ($n = 1$), bleeding ($n = 1$) and diaphragmatic patch disruption ($n = 1$). Other major complications were: acute myocardial infarction ($n = 4$), pulmonary embolism ($n = 1$) and renal impairment ($n = 2$). Non-fatal complications included persistent air leak for longer than 7 days ($n = 73$), blood transfusion, chest infection ($n = 10$), atrial fibrillation ($n = 6$), wound infection ($n = 4$), urinary retention ($n = 2$) and ileus ($n = 1$).

It is interesting that although there were significantly more patients with persistent (>7 days) air leak in group R ($n = 41$, 80% compared to $n = 32$, 63% in group NR, $p = 0.039$) the duration of drainage was marginally longer (mean 14.4, SD 10.4 days for group R and 11.2, SD 7.2 days for group NR, $p = 0.087$). Subsequently, the length of stay was also similar; median 12 (6–35) days for group R and 10 (4–30) days for group NR, $p = 0.99$.

Although 30-day mortality was not significantly different, there was significantly higher 90-day mortality in group NR: 15 (29%) versus 5 (10%).

### 3.3. Multimodality therapy

More patients in group R than group NR received postoperative chemotherapy ($n = 33$, 65% vs 14, 28%)

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<tr>
<th>Table 2</th>
<th>Pathological stage in radical P/D (group R)</th>
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<tr>
<th>Table 3</th>
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<td>Actuarial Survival (months)</td>
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p = 0.000) and similarly for postoperative radiotherapy (n = 33, 65% in group R and n = 13, 26% in group NR, p = 0.000).

3.4. Survival

The median follow-up for the entire group was 12 (1—60) months and at the end of the observed period 81 patients (80%) had died. The median survival for group R was significantly higher (15.3 months) than group NR (7.1 months, p < 0.000) (Table 3, Fig. 2). When we split the patients into subgroups according to cell type, radical P/D continued to be associated with prolonged survival compared to tumour decortication, but only for epithelioid cell type: 25.4 months versus 10.2 months, p < 0.000 (Fig. 3). There was no statistically significant difference in the survival for the non-epithelioid cell types (Table 3). The estimated survival rates for epithelioid disease were 66%, 54%, 33% and 16.3% at 1, 2, 3 and 4 years from diagnosis when the operation was radical P/D compared to 45%, 16%, 4% and 0%, respectively, when it was tumour decortication (Table 3).

4. Discussion

For some people, the role of surgery in the management of MPM remains undetermined. There are no established practice guidelines and although many centres have demonstrated promising results employing trimodality treatment, many medical professionals, including a significant proportion of thoracic surgeons, remain nihilistic when dealing with the disease. Because of the generally poor prognosis associated with MPM [4], radical surgery, with high mortality (3.4—5%) and morbidity (22—50%) in the best series [5—8] should be reserved for the fittest patients with early disease, since evidence exists that bad prognostic factors for mesothelioma include N2 disease [3,9—11], sarcomatoid cell type [5,12—14], poor performance status [12] and advanced (>65 years) age [12]. Nevertheless, without treatment patients are expected to survive an average of 7—9 months or 12.1 months with the best non-surgical treatment available [23]. Therefore the majority of patients with mesothelioma could benefit from surgical options that could prolong life with lower risk than the widely accepted alternative of EPP [3,15]. Since pneumonectomy, especially in the form of the extrapleural variety, is widely accepted as the thoracic operation with the worse physiological impact on the human body, it appeared reasonable to surgeons dealing with MPM that preserving the lung would lower the risk. Pleurectomy/decortication could be the surgical alternative to EPP [14,15,16].

One of the important milestones in our practice was when we started using cervical mediastinoscopy as a routine selection tool before EPP. For patients with N2 disease EPP does not impact significantly on survival [3,10] therefore we ceased offering it to these patients. Instead we offered radical P/D because we felt that the possible compromise in radicality compared to EPP would be offset by the decrease in pneumonectomy associated morbidity and mortality [3]. We have always considered radical P/D a radical approach, since it was aiming to achieve complete macroscopic tumour clearance. We had performed tumour decortications for MPM and initial analysis of our results had indicated that it was not necessarily associated with lower morbidity and mortality. There exists evidence to support the non-radical decortication [2,17—19,21,22] but we hypothesised that the superior local control of a more radical approach would offset any increased morbidity.

Many surgeons do not consider pleurectomy/decortication radical surgery and in many studies it was not expected to prolong survival but just to alleviate symptoms [17]. This criticism is the assumption that pleurectomy/decortication fails to achieve complete macroscopic clearance resulting in an increased incidence of local recurrence [9,17—19]. We have not found this in our series of radical pleurectomy/decortication (group R) since only 2 patients had macroscopically positive (R2) resection margins; 17 (33%) had microscopically involved margins (R1) and 32 (63%) were reported to have complete microscopic clearance with negative resection margins (R0). It is important to record that in our series of patients who had radical P/D there was only 1 patient staged pT1 with 14 pT2, 20 pT3 and 16 pT4. When staged according to the IMIG staging system there were no stage I patients, 8 were stage II, 26 stage III and 17 stage IV (Table 2). This is in contrast to other reported series of this.
operation [20]. It should also be noted that the prognostic importance of R1 resection margins has only rarely been found to be important [6].

Most importantly, radical P/D was associated with significantly better survival figures than symptomatic tumour decortication, although this was only so in those patients with epithelioid cell type (Table 3). It remains to be determined whether there is a role for therapeutic surgery in non-epithelioid tumours.

Although there were more patients with prolonged air leak in the radical group (80% vs 63% in group NR, p = 0.039) the duration of drainage was only marginally longer (mean 14.4 days for group R compared to 11.2 days for group NR, p = 0.087). There was however higher overall postoperative morbidity in the radical group (55% vs 28%) due to technical complications of the radicality of the procedure, including haemorrhage, chylothorax and diaphragmatic patch dehiscence.

The 30-day mortality was no higher in the patients undergoing the more radical procedure (5.9% in group R, 9.8% in group NR). Indeed at 90 days after surgery 29.4% of the patients that underwent tumour decortication had died, compared to 9.8% dead in the radical group. This may be due to tumour progression or from morbidity resulting from failure to re-expand the affected lung (Table 3).

Postoperative pleural sepsis is a clinical challenge in these patients, which resulted in mortality in both groups although there were proportionately more cases in the non-radical group. The increased dependency and morbidity of the early postoperative period in radical P/D though is not translated into increased mortality and is rewarded with superior survival benefit.

We have not had an established protocol regarding adjuvant treatment following pleurectomy/decortication since these decisions are at the discretion of our referring oncologists.

In our series 65% of patients in the radical P/D group had adjuvant chemotherapy and postoperative wound and drain site radiotherapy. In contrast, only 28% of the patients in the non-radical group had adjuvant chemotherapy and 26% adjuvant radiotherapy. These figures partially reflect the higher 90-day mortality in the latter group.

As a result of our cumulative experience we have now ceased to perform an open non-radical tumour decortication [2,23]. The median survival of 7.1 months (10.1 for epithelioid, Table 3) are no better than best supportive care or chemotherapy alone [12,23]. For palliation, if videothoracoscopic approach is possible, it is potentially the best surgical option with lowest morbidity, shorter drainage time and it provides good symptomatic relief [24].

In the increasingly common group of patients who are unsuitable or unwilling to undergo EPP, if they are fit for thoracotomy, radical pleurectomy/decortication with the aim to achieve macroscopic clearance is now our treatment of choice as part of a multimodality program [15].

References


Appendix A. Conference discussion

Dr P. van Schil (Antwerp, Belgium): What kind of technical complications do you encounter during VATS debulking and how do you manage them? For example, when you do pleurectomy on the pericardium or the diaphragm, did you have any technical problems doing the operation?

Dr Trousse: For the VATS approach, we are only doing a parietal pleurectomy and a visceral pleurectomy to free the lung.

Dr van Schil: So you do not touch the diaphragm?

Dr Trousse: We do not touch the diaphragm and pericardium. It is only in the radical pleurectomy decortication that we remove the diaphragm and pericardium.

Dr van Schil: The radicality of the operation was not significant anymore in a multivariate analysis.

Dr Trousse: I know. I asked the statistician this question. Because I was, well, a little disappointed about that. But finally, perhaps the number of patients wasn’t sufficient, as he explained to me. Because it was really hardly significant in univariate analysis and, well, perhaps, the numbers were small and the follow-up period short. Because in the early years we were doing much more open non-radical decortications that we do now. But as soon as we found out that the results were bad our management practice changed. And finally, the radical group has probably to be studied furthermore and the follow-up will help us to know exactly what is the impact on longer term survival. But it appears like good results.

Dr S. Guth (Rotenburg, Germany): I have a question concerning your adjuvant therapy. I’m getting right that you put people only to chemotherapy or only to radiotherapy, or did you apply a combination of both?

Dr Trousse: Well, some have got just chemo, others had radiotherapy, and really few patients had both. But we don’t have any impact on this decision. In our opinion, all patients should be offered adjuvant treatment because now we have proof that this is of benefit to them. But the decision was not our decision. It was left to the discretion of the oncologist. And in this study about 10 different centres were included. Because every oncologist has a different opinion, we couldn’t really influence the decision. We always refer patients for postoperative treatment, but we can’t have any real impact on what would be decided after surgery.