The role of video assisted thoracoscopic pleurectomy/decortication in the therapeutic management of malignant pleural mesothelioma

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Abstract

Objective: Extrapleural pneumonectomy (EPP) has high mortality and morbidity; radical pleurectomy decortication (P/D) carries less mortality but still significant morbidity. This surgery is not suitable for many patients with malignant pleural mesothelioma (MPM) for whom video assisted thoracic surgery (VATS) offers a minimally invasive alternative. We aimed to assess the role of VATS decortication for MPM.

Methods: Over a 9-year period 208 patients underwent therapeutic surgery for MPM in our unit. One hundred and twelve of the patients underwent EPP, 29 had a P/D and 67 had VATS decortication. Sixty-three of the 208 patients (EPP n = 13, P/D n = 8 and VATS decortication n = 42) were 65 years of age or older at the time of the operation (57 males and 6 females, age 70 (65—80) years). In this group we analyzed perioperative morbidity and mortality and long-term survival data using the Kaplan—Meier method.

Results: Postoperative stay and 30-day mortality was significantly lower for VATS P/D than for EPP (14.3 days vs 36.6 days, p < 0.05 and mortality 7.1% vs 23%, respectively). There was no significant difference in the overall mean survival between the two groups (11.5 months for EPP and 14 months for VATS P/D, p = 0.6).

Conclusion: VATS decortication should be considered in the therapeutic strategy for MPM.

Keywords: Mesothelioma; Surgery; Pleuropneumonectomy; Decortication; Pleurectomy

1. Introduction

Surgical treatment of malignant pleural mesothelioma (MPM) remains controversial. In a systematic review and evidence summary published in 2004 by Maziak et al. no randomized trials comparing surgery with an alternative treatment or comparing pleurectomy with extrapleural pneumonectomy (EPP) were identified [1]. However, there are published series that demonstrate that there is benefit in survival and/or symptom control in the patients that undergo extrapleural pneumonectomy (EPP) [2], radical pleurectomy decortication (radical P/D) [3,4] and VATS pleurectomy decortication (VATS P/D) [5,6] as part of a multimodality treatment. What all these studies have also demonstrated is that EPP and radical P/D are associated with significant treatment-related mortality and morbidity.

There appears to be a consensus that older age is a poor prognostic factor [7,8] and that the sarcomatoid cell type is an important prognostic factor [2]. Some authors argue that extrapleural nodal status and cell type determine the postoperative long-term survival in patients that undergo EPP [2,9] while others do not believe that nodal status is important [10]. In our institution EPP was offered to all the patients that fulfilled the widely accepted resectability and operability criteria, based on the British Thoracic Society guidelines for pneumonectomy [11]. Radical P/D was offered to patients who fulfilled similar resectability criteria but with either suboptimal respiratory reserve (unable to tolerate pneumonectomy) or mediastinoscopy proven extrapleural lymph node involvement [3,12] while VATS P/D was reserved for the older and less fit patients.

In theory VATS P/D should provide good palliation in the subgroup of patients who were unfit for a radical procedure (EPP or radical P/D) and it could possibly prolong survival. The aim of this study was to examine whether VATS P/D is a procedure that is feasible and should be considered in the therapeutic management of malignant pleural mesothelioma. Since the majority of the patients who underwent VATS P/D were over the age of pension (65 years) we also wanted to assess whether patients of similar age who underwent EPP or radical P/D had better survival with the more radical procedure.
2. Patients and methods

2.1. Patient groups

Over a 9-year period (1997–2006) 208 patients underwent therapeutic surgery for MPM in our institution. One hundred and twelve had extrapleural pneumonectomy (EPP) performed, 29 had radical pleurectomy/decortication (radical P/D) and 67 had video assisted pleurectomy decortication (VATS P/D).

Sixty-three of these patients (57 males and 6 females) were 65 years of age or older at the time of operation (mean 70 years, range 65–80). The demographics of the older than 65 (> 65) group and the cell type distribution are detailed in Table 1.

The VATS P/D > 65 group (n = 42) patients were significantly older than both the EPP > 65 (n = 13) (p = 0.007) and the radical P/D > 65 (n = 8) (p = 0.03) groups. There was no difference in age distribution between the EPP > 65 and the radical P/D > 65 groups (p = 0.96). There was no statistically significant difference for gender (p = 0.26) or cell type (p = 0.29) distribution between the groups. Only 1 patient in the EPP > 65 group had preoperative chemotherapy (see Table 1).

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2.2. Preoperative assessment and patient selection

All patients were staged with CT scanning and in some selected cases MRI scanning to assess mediastinal or transdiaphragmatic invasion [13]. All candidates for radical surgery (EPP or radical P/D) had echocardiographic assessment and pulmonary function tests. In the last 4 years all VATS P/D candidates were undergoing routine cervical mediastinoscopy and if found to have mediastinal lymph node involvement were offered radical P/D instead of EPP [12]. VATS P/D was offered only to patients who were not fit for a radical procedure or had an already infected pleural space since this prohibited the use of synthetic materials (diaphragmatic and pericardial patches). Tumor stage, cell type or involvement of the fissure were not decisive factors in determining whether the patient would undergo VATS P/D but overall fitness was. Very unfit patients were offered only talc pleurodesis. When needed, quantitative radionuclide scintigraphy was used to assess the lung function on the diseased side.

2.3. Operative techniques

2.3.1. Extrapleural pneumonectomy

EPP is performed with standard techniques resecting lung, pleura, pericardium and diaphragm en bloc and reconstructing the diaphragm with a Gore-Tex patch (W.L. Gore and Associates, Inc.) and the pericardium with a non-absorbable mesh patch. In the last 4 years all right-sided EPPs were performed through a median sternotomy [14]. The space is drained with a single 28F drain which is removed on the 3rd–4th postoperative day, depending on the rate of space filling.

2.3.2. Radical pleurectomy decortication

The extrapleural dissection is performed in the same fashion as an EPP. Following that the pleura is incised and a full visceral decortication of the lung is performed. Pericardium and diaphragm are removed in the same way as in an EPP. The lung is sprayed with aerosolized fibrin-based glue to control the air leak and the pleural space is drained with three 32F drains [3].

2.3.3. VATS pleurectomy decortication

The standard access with three ports is usually employed [15]. After draining the effusion with suction and breaking down any loculations a parietal pleurectomy is performed using blunt dissection with arterial forceps. Following that, positive airway pressure is applied and the visceral pleura is decorticated using peanut gauze mounted on long curved artery forceps or Rampley’s ring forceps (Figs. 1 and 2). We use a 32F chest drain mounted on the same forceps and connected to suction which provides continuous aspiration of the fluid during the procedure (Fig. 3). When lung apposition to the chest wall is achieved, 10 ml of aerosolized fibrin-based glue is sprayed to the surface of the lung. The pleural
cavity is drained with 2–3 32F drains which are connected to 5 kPa of suction.

2.4. Data acquisition and statistical methods

Data for all the patients were obtained from the prospective mesothelioma database held in our institution. Medical notes were reviewed retrospectively to retrieve data that were not immediately available from the database. Up-to-date survival data was obtained from the hospital’s patient’s information system and from the patient’s general practitioners. Statistical analysis was carried out using the software application SPSS for Windows version 12, SPSS Inc., Chicago, USA. Survival curves were estimated using the Kaplan–Meier method and the statistical significance for differences between the groups was assessed with the log rank test for survival, Student’s t-test for quantitative data and the Chi-square, Fisher’s exact test and Cramer’s V-test for qualitative data.

3. Results

3.1. Perioperative events and hospital stay (Table 2)

There were three perioperative deaths in the EPP >65 group, one in the radical P/D and three in the VATS P/D group. The mean postoperative stay for this group was significantly longer than for both the radical P/D and the VATS P/D groups. Two of the deaths in the EPP >65 group were due to lower respiratory tract infection and one due to pulmonary embolism. The single death in the radical P/D group occurred due to pulmonary embolism and the three deaths in the VATS P/D group were all a result of pleural and/or lung sepsis and associated complications. Only one patient in the EPP group did not experience major non-fatal complications. The most common complications were atrial fibrillation in 4 patients, rapid space filling and mediastinal shift in 1, two re-explorations, one for bleeding and one for chylothorax, two episodes of paralytic bowel ileus and one of acute renal failure requiring temporary dialysis. The most common cause of postoperative morbidity in the radical P/D >65 group was persistent air leak, with 3 patients requiring intercostal drainage for more than 1 week. The frequency of postoperative air leak was at least as high, if not higher in the VATS P/D >65 group where 20 patients required intercostal drainage for more than 1 week.

3.2. Adjuvant treatment and long-term survival

There was no significant difference in the proportion of patients receiving adjuvant postoperative chemotherapy between the groups but the patients in the EPP >65 group were less likely to receive adjuvant postoperative radiotherapy than the patients in the radical P/D and the VATS P/D groups (Table 2). There were 12 patients in the VATS P/D group who received between two and four cycles of adjuvant chemotherapy and 22 patients in the same group who received a total dose of between 20 and 30 Grays of postoperative radiotherapy targeted at the port and drain sites. The rest of the patients did not receive adjuvant treatment as a result of either prolonged or suboptimal...

<table>
<thead>
<tr>
<th></th>
<th>EPP &gt; 65 (n = 13)</th>
<th>Radical P/D &gt; 65 (n = 8)</th>
<th>VATS P/D &gt; 65 (n = 42)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative stay days</td>
<td>36.6 (9–184)</td>
<td>14 (9–24)</td>
<td>14.3 (10–28)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>3 (23%)</td>
<td>1 (12.5%)</td>
<td>3 (7.1%)</td>
<td>p = 0.28</td>
</tr>
<tr>
<td>Preoperative chemotherapy</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>p = 0.14</td>
</tr>
<tr>
<td>Postoperative chemotherapy</td>
<td>5</td>
<td>4</td>
<td>12</td>
<td>p = 0.45</td>
</tr>
<tr>
<td>Postoperative radiotherapy</td>
<td>3</td>
<td>6</td>
<td>22</td>
<td>p = 0.05</td>
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<tr>
<td>Mean survival months</td>
<td>11.5</td>
<td>12.4</td>
<td>14</td>
<td>p = 0.6</td>
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EPP: pleuropneumonectomy; radical P/D: radical pleurectomy/decortication; VATS P/D: video assisted pleurectomy/decortication.
postoperative recovery sometimes because some of the oncologists demonstrated a rather nihilistic approach to adjuvant treatment in patients with mesothelioma in this age group. There were four cases where the patients declined chemotherapy because of the associated toxicity. The actuarial survival for all groups is summarized in Table 2 and plotted in Fig. 4. Actuarial survival estimation includes the perioperative mortality.

We did not formally assess the results on quality of life but data regarding the impact of VATS P/D on pain and shortness of breath was available for 24 patients. Fourteen (58%) patients reported significant improvement from pain and 20 (83%) improvement of dyspnea following VATS P/D.

Disease progression in all the VATS P/D patients occurred as local recurrence (pleural effusion and tumor progression) with port site recurrence developing first in 9 of the patients that did not receive port site radiotherapy as adjuvant.

4. Discussion

Over the years various forms of radical (EPP), less radical (pleurectomy/decortication, P/D) and debulking (VATS P/D) operations have demonstrated encouraging results. Whilst initially P/D was considered by some to have better results than EPP [16], in a second study by the same authors 3 years after the first the type of surgical resection was not significant for the survival [17]. Other studies have demonstrated the efficacy of P/D in symptom control and/or survival [18–20]. We have always believed that planned debulking, leaving macroscopic residual disease is not ideal but can be justified [21]. VATS P/D can achieve lung re-expansion and effusion control with acceptable morbidity in selected groups of patients [19]. Radical P/D is offered to patients who are pN2 positive on mediastinoscopy and therefore have limited prognosis or do not have the respiratory reserve for a pneumonectomy. However, it remains a major procedure with significant physiological impact [3].

In our series overall 30-day mortality for EPP was 6.75% with a 60% complication rate [22]. Our arbitrary cut off point for EPP had been 70 years of age but we were not sure that the operation had any impact on survival in the older group of patients. The question remained whether we should continue to offer EPP in the patients above the age of pension (65 years of age) or if a less invasive procedure would offer these patients comparable survival with fewer treatment-related complications. Analysis of our results demonstrates that the 30-day mortality rate of EPP in our patients who were older than 65 at the time of diagnosis (n = 13) was 23% compared to an observed mortality of 6.75% in the general EPP population (n = 112), and 12.5% in the radical P/D >65 group (n = 8) and 7.1% in the VATS P/D group (n = 42). We wished to test the hypothesis that the reduction in treatment-related mortality would offset the inferior tumor clearance. The patients in the VATS P/D group still experienced significant mortality (7.1%) but they were significantly older and, by definition, had a larger probability of significant co-morbidity since they were not deemed suitable for a more radical resection. Their survival proved to be at least as good if not better compared to the more radical procedures and the length of hospital stay was significantly shorter than in the EPP group (Table 2).

Symptom control was also achieved in a significant proportion of these patients: 58% improvement in pain and 83% in shortness of breath.

The 23% mortality in the EPP >65 group might be higher than expected but we do not believe it is a coincidence. Age is an important prognostic factor for the post pneumonectomy prognosis [11], therefore it is reasonable to expect higher mortality at the older age group. Also, the sample is small; therefore even a single death is influencing the results disproportionately.

What we already know from previously published studies is that VATS parietal pleurectomy is feasible and effects good symptom control [5]. We also know that VATS P/D improves diagnosis and symptoms in patients with MPM [23] and is better than biopsy only [6]. The combined parietal pleurectomy and visceral decortication should have superior results compared to pleurectomy and talc pleurodesis since it aims to release the trapped lung and control the pleural effusion by eliminating the space.

The MesoVATS study opened in the UK in September 2003 and aimed to compare VAT pleurectomy with conventional talc pleurodesis for treatment of pleural effusion in patients with MPM. Endpoints of the trial were: survival in 1 year, control of effusion and quality of life. The trial aimed to recruit 196 patients but the accrual to date (August 2007) is only 27% in the single center involved in the trial. The trial is now extending to other centers, including our unit and hopefully, the question whether pleurectomy and/or decortication is superior to talc pleurodesis will be answered.

There are published studies that report similar survival times for patients treated with combination chemotherapy: 12.1 months with Pemetrexed and Cisplatin [24] and 11.4 months with Raltitrexed and Cisplatin [25]. Both these studies have found the combination regimes to be superior to single agent (Cisplatin) chemotherapy but they also both reported significant chemotherapy-related toxicity. In one of the studies the mortality for the combined agent arm was 6.2% with these patients dying while on study therapy or
within 30 days of the last dose of study drug [24]. Both these
studies have established the superiority of combination over
single agent chemotherapy but did not assess the potential
effect of cytoreductive surgery combined with chemother-
apy. In both studies the patients were younger than in our
study: median age 61 in [24] and 58 in [25], median age 71 in
our VATS P/D >65 group. The reported survivals of 12.1 and
11.4 months, respectively, are probably on par with our
actuarial survival of 14 months. It would be interesting,
though, to be able to compare patients undergoing VAT
debulking surgery with adjuvant chemotherapy to a control
group that would receive chemotherapy only.

A limiting factor in our study is that the follow-up period is
short (median 12, 1—36 months), but this appears to be a
common problem in many mesothelioma studies. When some
time lapses we might be able to get results for the longer
term survival.

The three groups of patients we compared demonstrated
similar survivals but the conclusion that we have drawn from
these results is that VATS pleurectomy decortication is not a
substitute for radical surgery in the older than 65 patients
with MPM. In our institution we still offer EPP and radical P/D
to patients who are older than 65 years of age but we are
reluctant to offer EPP to patients who are above 70.

In conclusion, we believe that VATS P/D is the only method
to effectively palliate this subgroup of malignant meso-
thelioma patients with trapped lung who are not candidates for
radical surgery without the complications of thoracotomy
[19]. It can alleviate symptoms and appears to prolong
survival but further research is needed to assess its role in the
management of malignant pleural mesothelioma. It is
expected that the MesoVATS trial is going to provide much
needed answers to these important questions.

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perioperative mortality with the mortality which has been reported by other groups? A perioperative mortality rate of 23% is difficult to justify and I fully understand that you stop the procedure. But there might be selected patients who may profit more from the radical approach.

Dr Nakas: Thank you for your question. I could not find any data or any study done in patients within this specific age group. I don’t think that anyone targeted the older patient’s group and tried to identify which is the best procedure they can have. What we tried to say is not that VAT Decortication is a better operation for mesothelioma, we tried to say that if someone is above 65 or 70 and is not fit for a radical procedure we are going to offer them VAT Decortication.

Dr H.B. Ris (Lausanne, Switzerland): I did not really understand the aim of the study. You do a VATS pleurectomy/decortication for relief of symptoms and effusions in a disease accessible to VATS. Why do you do a decortication and not only a simple talcage in these patients?

Dr Nakas: We feel that if you reduce the tumor bulk you might improve the symptom control. It has also been published that if you free the lung when it’s trapped, as it was in most of these cases, and the lung expands, then you have better symptom control.

Dr Ris: That is exactly what I mean, because the majority of these patients would require an open decortication in these situations. Everybody who deals with this disease knows that only a small proportion of patient with mesothelioma-related complicated effusion and entrapped lung is accessible for ATS debridement/decortication. What is the percentage of patients in your series accessible for a VATS decortication? I feel that these are probably the same patients who can also be treated by simple talcage as well.

Dr Nakas: The answer is that we have a lot of patients that underwent an open non-radical decortication. There are approximately 50 patients in this group. If a patient was suitable and it was feasible then obviously he underwent a VAT decortication. If a patient had an open decortication, then obviously I would not include him in this study. We are currently looking at what happens with this group of patients (open decortications) and we will compare them with the other groups.

Dr P. Nafteux (Leuven, Belgium): Thank you for this very nice presentation. I have one question. Especially if you look at the substance of patients with very bad prognoses my question will be: did you look specifically on quality of life, especially compared to a control group of patients having had a best supportive care or only chemotherapy for example?

Dr Nakas: We did not compare with a control group of patients, and we did not formally assess the quality of life. There were only two markers of improvement in quality of life that were the pain and the symptom control. Most of these patients are not from our own catchment area. We get patients from all over the country and we loose many of them to the follow-up, so it is not easy to have a full assessment of quality of life. We are not comparing them with best supportive care because we believe that this question has already been answered. We believe if you do something, even if it is a VATS talcage, they do better. We believe that the papers that were published have proved that patients with VATS pleurectomy do better than patients with VATS biopsy alone.

Dr R. Berrisford (Exeter, U.K.): To palliate those patients with a trapped lung who are not going for radical treatment, do you offer them pleurx catheter as an option for a trapped lung?

Dr Nakas: We have used the pleurx catheter in a couple of patients but it did not improve their symptoms. We do not offer it routinely.

Dr S. Bo¨lückbas (Wiesbaden, Germany): It is only a comment: as one of the youngest surgeons here in this session, I have to act as an advocate of the elderly. I know even octogenarians have life expectancy of 8 years in Germany, therefore I suppose we have to make the same efforts for elderly as for younger patients.

Dr Nakas: We do make the same efforts for elderly patients. We are offering them the procedure that we believe is best for them.

Dr P. Goldstraw (London, U.K.): I have been asked to make a comment on the origins of the Brompton prize. It was inaugurated in 2000 when I hosted this meeting in London and is funded from my research funds. Since that time the standard of the submissions for this award has been extremely high indeed. Dr Van Raemdonck was the first receptor and he is a great example to the young researchers of today. From what we have heard today I am sure that the successful paper from today’s session will further enhance the reputation of this award. Thank you very much for your attention.