The management of malignant pleural mesothelioma; single centre experience in 10 years

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Abstract

Background and Objectives: Malignant pleural mesothelioma (MPM) is an asbestos-related disease of the pleura with a survival time without treatment ranging from 4 to 12 months. The objective of this study is to review our experience in selection of MPM patients for various modalities of treatment.

Methods: Between 1989 and 1999, 302 patients with MPM have been referred to our Centre for assessment. Majority (191 patients, 61%) of them received no specific treatment. Forty-seven patients were treated by decortication/pleurectomy and 64 had a radical extra-pleural pneumonectomy (EPP). Intrapleural chemotherapy and systemic post-operative chemotherapy was employed only in the last 51 patients following radical surgery.

Results: The average survival was 8.9 months for those treated by palliative care only. The average survival was 13 and 14 months for patients treated by radical surgery only or by decortication/pleurectomy, respectively. However, survival has improved to a mean of 35 months for patients treated by radical surgery followed by systemic post-operative chemotherapy. In this group, the survival prevalence was 90 and 70% for T1 patients and 85 and 36% for T2 patients at 1 and 3 years, respectively (P = 0.002). Survival was surprisingly not affected by lymph node involvement (P = 0.08) or pathological type of MPM (P = 0.07). The operative mortality was 9% for EPP and 0% for decortication/pleurectomy.

Conclusion: In selected patients with MPM, complete surgical resection by EPP represents an important initial step in their management. Systemic chemotherapy improves survival in surgically treated patients. Further trials are needed to improve on the adjuvant treatment regimes.

Keywords: Malignant pleural mesothelioma; Extra-pleural pneumonectomy; Chemotherapy

1. Introduction

Malignant pleural mesothelioma (MPM) is a mesodermally derived neoplastic disease that arises in the pleura and grows relentlessly into adjacent structures (namely the lungs chest wall and heart), until it ultimately results in the death of the patient [1]. Asbestos is causally related to the pathogenesis of this malignancy with up to 80% of patients having a history of asbestos exposure [2]. Although MPM is thought to be a rare neoplasm, approximately 3000 patients continue to be diagnosed with MPM in the United States every year and one should consider that over the next 20 years, 80,000 new cases of mesothelioma MPM are expected in the United States alone [3]. In Scotland, UK, the incidence of MPM has been continuously rising from 2.7/100,000 in the population in 1976 to 8.9/100,000 in the population in 1996 and nearly 10,000 new patients with MPM are expected to be diagnosed in the UK during the next decade. Therefore, the development of innovative treatment strategies should be pursued. In most reports the median survival time for patients with this disease without specific treatment is less than 1 year [4]. At the present time, no standard approach exists for the treatment of this disease. Recommended approaches range from supportive care only, to single modality therapy (e.g. operation or radiotherapy, or chemotherapy) and rarely trimodality therapy [6–8].

In the absence of randomised trials, it is not possible to define optimal treatment. This retrospective study looks at guidelines for selection of MPM patients for appropriate treatment considering their clinical and radiological status at presentation.

2. Patients and methods

2.1. Patient assessment

Between 1989 and 1999, 302 patients were observed at
2. No mediastinal or chest wall invasion.

3. No co-morbidity preventing major surgery.

4. Good function in opposite lung.

5. No abdominal or distant metastasis.

6. Age less than 60 years.

2.3. Operative technique

EPP was performed as described by Butchart et al. in their classic paper in *Thorax* [6]. Briefly, The resected specimen includes the entire parietal and visceral pleura en bloc with the underlying lung and the ipsilateral pericardium and diaphragm. Blunt dissection is used to separate the diaphragm from the peritoneum underneath, which is left intact. The diaphragm is reconstructed using a prosthetic patch of two-way stretch Dacron velour sewn circumferentially at the level of the rib incision. The ipsilateral pericardium in contact with the affected pleura is excised dividing the phrenic nerve between ligatures high in the mediastinum at an early stage. The pericardium is reconstructed using a prosthetic patch of mericile mesh, inserted loosely like a hammock to prevent cardiac herniation. We have been using Trasylol (Bayer) routinely since January 1993 to prevent fibrinolysis and have thus reduced average blood loss by about 1 L in cases since. Two intercostal drains are used, one above and the other below the newly constructed diaphragm, to measure post-operative blood loss accurately.

2.4. Adjuvant chemotherapy

The initial 13 patients had a radical resection (EPP) only without adjuvant chemotherapy (Group I). Their mean survival was only slightly better than for those who received no definitive treatment. Subsequent 51 patients therefore received chemotherapy post-operatively (Group II). A platinum based combination of Carboplatin and the anthracycline drug Epirubicin was used in all patients in Group II.

2.4.1. Intrapleural chemotherapy

Post-operatively Carboplatin 1 g (Faulding DBL) was instilled intrapleurally into every patient in Group II before chest drain removal.

2.4.2. Systemic chemotherapy

Systemic adjuvant chemotherapy was given to the 51 patients in Group II who underwent EPP after 1992. Depending on how well the patients recovered from the operation they were given their first treatment about 3–5 weeks after operation. The chemotherapy regime consisted of intravenous bolus of Carboplatin (1 g) followed by an intravenous infusion of Epirubicin (Pharmacia and Upjohn) 50 mg/m²/body surface area. The treatment was repeated every 4 weeks for four treatments. Appropriate hydration and antiemetic regimes were used for all patients. Close haematological and biochemical monitoring of the patients was practised and the next chemotherapy course was postponed if nausea, vomiting, or anorexia was present or if

### Table 1

<table>
<thead>
<tr>
<th>Tumour staging</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>T1</td>
<td>28</td>
</tr>
<tr>
<td>T2</td>
<td>30</td>
</tr>
<tr>
<td>T3</td>
<td>6</td>
</tr>
<tr>
<td>N0</td>
<td>25</td>
</tr>
<tr>
<td>N1</td>
<td>22</td>
</tr>
<tr>
<td>N2</td>
<td>17</td>
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<td>N3</td>
<td>0</td>
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<td>0</td>
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myelosuppression persisted at the time chemotherapy was next due. However, no dose modification was made.

2.5. Follow-up policy

Patients were followed up regularly as an outpatient at our institution as long as they lived. Follow-up consisted of clinical assessment and a chest radiograph with CT scan of chest annually or as required. Confirmation of suspected disease recurrence was also documented histologically whenever possible (80% of the recurrences). If recurrence was documented, repeating the course of systemic chemotherapy was considered if the patient was fit. Where chest wall masses were present, visible shrinking of the tumour with the chemotherapy was often noted. In some cases the symptoms such as ascites and signs of recurrent disease regressed or were kept under control for the duration of treatment and for 3–6 months thereafter suggesting tumour control rather than cure. If the patient was not fit or active at the time of recurrence, palliative care was initiated.

2.6. Statistical analysis

Survival time was calculated from the date of the operation (radical EPP, decortication/pleurectomy or open pleural biopsy for unoperated patients) to the date of death or last follow-up, and survival curves were constructed using Kaplan–Meier method. The relationships of patient, MPM, and treatment variables to the outcome of survival and recurrence were univariately examined using the two-sided Log rank test. Fisher’s exact test was used to examine associations between patient groups and treatment variables.

3. Results

3.1. Patients demography

3.1.1. All study population

Between 1989 and 1999, 302 patients with MPM have been referred to our institution for assessment. The median age was 57 years (range 34–77 years). Sixty-one patients (20%) were females and history of smoking was reported in 202 patients. Clear history of asbestos exposure was documented in 288 patients and the median duration between asbestos exposure and development of MPM was 26 years (range 19–37 years). The mode of presentation is shown in Fig. 1.

3.1.2. Patients for best supportive care

The majority of patients (191 patients, 63%) had locally extensive or metastatic disease at the time of referral to us or were in quite poor health. They tolerated an open pleural biopsy to establish the diagnosis beyond doubt, thus strengthening their compensation claims. They were offered no specific treatment other than best supportive (palliative) care. Their median survival was 7 months (1–19 months) and this group will not be considered here any further.

3.1.3. Patients undergoing decortication/palliative pleurectomy

This lesser procedure was employed in 47 (15%) patients who were reasonably fit but had locally extensive disease. The aim of this procedure was to attempt palliation of troublesome symptoms particularly chest pain and pleural effusion. This number included three patients who had been planned to undergo EPP but the operative plans were modified to pleurectomy in view of operative findings (extensive mediastinal invasion in three patients). There was no operative mortality in this group. The benefits in terms of relief of symptoms were not impressive but admittedly difficult to assess in this small retrospective study.

3.1.4. Patients selected for radical surgery

Sixty-four patients were clinically and radiologically in stage I–II MPM and fulfilled the criteria set out above, and were treated by extra pleural pneumonectomy. The first 13 patients did not receive systemic chemotherapy (Group I), while the remaining 51 patients did receive systemic chemotherapy (Group II).

Pre-operative CAT scan identified pleural thickening in all patients. Sub-diaphragmatic, chest wall and contralateral pleural involvement was excluded prior to radical surgery. According to IMIG staging system, 28 patients had T1 tumour, 30 patients had T2, and six had T3. Thirty-nine patients had nodal metastases of which 25 had only N1 and 14 patients had ipsilateral mediastinal lymph nodes (N2). None of our study population was proved to have N3 or M1 disease. The histological tumour type was epithelial in 35/64 patients (54%), fibrosarcomatous in 22/64 patients (35%) and mixed cellularity in 7/64 patients (11%). Thirty-eight patients underwent right EPP while 26 patients required a left-sided procedure.
3.2. Operative outcome

3.2.1. Mortality

The 30 days operative mortality for EPP patients was 6/64 (9.1%). No significant differences in mortality were found with regard to patient sex, pre-operative forced expiratory volume (FEV₁), mediastinal lymph node involvement, or pre-operative oxygen saturation. However, survival was inversely affected by patient age and right-sided EPP. Five out of six patients died of adult respiratory distress syndrome from 9 to 30 days after operation. One patient died of acute myocardial infarction on the third post-operative day and significant coronary artery stenosis was revealed in his post-mortem examination.

There was no operative mortality in the 47 patients who underwent pleurectomy or decortication.

3.2.2. Major post-operative complications following EPP

Including the six patients who died, the major morbidity rate was 14 out of 64 (21%). Major complications included pulmonary oedema, or adult respiratory distress syndrome (six), re-operation for bleeding (four), pneumonia or empyema (four), reintubation and ventilation (two). Univariate analysis identified age greater than 60 and right-sided procedures were associated with major complications following EPP. The major complications following pleurectomy procedures were re-exploration for bleeding (one), and pneumonia (one).

3.2.3. Minor post-operative complications following EPP

Eighteen patients (28%) had minor complications including atrial dysrhythmia (eight), wound infection (four), sputum retention needing bronchoscopy (three), and contralateral pneumothorax (one). The median length of hospital stay was 17 days. The duration of hospital stay was not affected by the minor complications but was significantly increased with a major complications (29 days).

3.2.4. Post-operative chemotoxicity

Including nausea (63%), hair loss (71%), anaemia (32%), leukopenia (21%), and thrombocytopenia (9%). Generally, myelosuppression was mild to moderate mostly after the third or fourth cycle. Most patients with nausea and vomiting responded well to orally administrated anti-emetics particularly Ondansetron. Treatment was delayed at times but modification of chemotherapy dose was not needed in any patient.

3.3. Recurrence rate

3.3.1. Radical surgery without systemic chemotherapy

Clinical recurrence was diagnosed after a median period of 10 months (range 8–14 months) in the first 13 patients who did not receive any adjuvant systemic chemotherapy following EPP. The recurrence pattern was aggressive and 10/13 patients died within 5 weeks (range 3 weeks to 6 months) following diagnosis of the recurrence.

3.3.2. Radical surgery + systemic and intrapleural chemotherapy

The median time to relapse for patients who received chemotherapy following their radical surgery was 37 months (14–42 months). There were 31 patients who recurred at 33 sites, among the 51 evaluable patients (60%). Thirty-two (88%) of the recurrences were confirmed by histological or cytological assessment [5]. Radiological imaging studies and physical examination determined the recurrence in the remaining case. The sites of the first recurrence are listed in Table 2. Recurrence was treated by the same regime of systemic intravenous chemotherapy whenever patient fitness permitted. Twenty-three of 31 patients with recurrence received up to six treatments each at monthly intervals. In six of these patients, the course of treatment had to be cut short and stopped due to excessive toxicity or disease progression during treatment. The average survival of the 17 patients who received a full course of chemotherapy for recurrence was 13 months (5–31 months)

It seemed to keep the disease, including ascites (four patients), in check for some months after treatment was completed and visible reduction of size of subcutaneous recurrent lumps were noted, but cure was never achieved.

3.4. Survival

The median length of follow-up for all 302 patients was 16 months (range 0–71 months). The median survival without any treatment was 7 months (1–19 months). Over-all survival analysis did not show any significant difference between patients who underwent EPP without adjuvant chemotherapy (13 months) when compared to patients who had a decortication/pleurectomy (14 months) (Fig. 2).

Adjuvant chemotherapy appeared to significantly influence the survival after EPP. The 1 and 3 years survival rates were 84 and 48%, respectively, and the median survival was 35 months (range 0–71 months) for patients who received chemotherapy following EPP. This compared well with survival rate of 49 and 0% at 1 and 3 years, and a median survival of 13 months (range 0–23 months) for those who did not receive systemic chemotherapy following

<table>
<thead>
<tr>
<th>Site of first recurrence</th>
<th>No of patients</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Thorax ipsilateral</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Thorax contralateral</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Liver</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Abdomen/retroperitoneal nodes</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Kidney</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Adrenals</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Brain/nervous system</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>1.5</td>
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their radical surgery ($P = 0.001$ and $0.0001$ for 1 and 3 years differences, respectively). (Fig. 3). Eighteen percent (9/51) of our patients who were treated with radical surgery followed by systemic chemotherapy have achieved more than 5 years of survival. The univariate analyses of survival in patients treated with systemic chemotherapy according to TN status and stages are shown in figures (Figs. 4 and 5). Comparison of individual T status categories showed significant difference in survival for T1 vs. T2, and also significant difference was noted for T2 vs. T3. The median survival for T1 tumour was 42.8 months. This was significantly different from the median survival of 31 months and 14 months for T2 and T3, respectively. The survival prevalence was 90 and 70% for T1 patients, and 85 and 36% for T2 patients, and 49 and 0% for T3 patients at 1 and 3 years, respectively ($P = 0.007, 0.002$, respectively).

However, in variance to others’ experience, no significant difference in survival was noted between N0 and patients who had nodal spread ($P = 0.08$ at 3 years interval). Univariate analysis of survival according to the histological type demonstrated no significant difference between either of the types. However, there was better trend of survival in favour of epithelial tumours ($P = 0.07$ at 3 years interval) rather than sarcomatous tumours. There was no difference in survival according to differences in age, sex, period of asbestos exposure and pre-operative symptoms.

4. Discussion

The management of MPM remains a subject of controversy because of incomplete understanding of its natural history and apparent resistance to standard forms of therapy. The treatment of MPM has gained importance because the disease is becoming more prevalent worldwide [3]. The perceived high operative mortality after EPP was the main reason for reluctance to operate, as early experience from Butchart et al. [9] cited hospital mortality of 31% (9 out of 29). Bamler and MaaBeen [10] found a similarly high rate of 24% (4 out of 17). Operative mortality as high as this is bound to reduce any potential therapeutic effect. Recent experience [11–13] confirms that the operative mortality of EPP although still higher than for a decortication/pleurectomy, is not dissimilar to that for a standard pneumonect-
omy in the hands of surgeons or single institutions that perform this operation regularly. In our experience, the operative mortality was 9.1% (6 out of 64) and continues to improve with only a single mortality in the last 21 patients and it is comparable with the operative mortality of standard pneumonectomy in our centre.

We did not find much difference in survival between patients who underwent decortication/pleurectomy compared to patients without any surgical intervention. It is almost impossible to achieve reasonable degree of surgical clearance without radical surgery. Although the palliative effect could not be assessed in this retrospective study, it was not impressive and it was clear that more radical intervention was required to get better results.

The long-term result after radical surgery alone proved to be poor in initial experiences. In the literature [13–17], a 1-year survival rate of 29–53% is quoted for patients who undergo radical resection alone. Survival reported after radical surgery alone is only slightly better than after palliative decortication/pleurectomy or palliative care and in our series found early aggressive recurrence in patients who were treated by radical surgery alone. Radical surgery alone in form of EPP with resection of pericardium and diaphragm without adjuvant therapy did not achieve any survival advantage over a palliative decortication/pleurectomy with maximum tumour reduction. Therefore, though the morbidity and mortality of EPP have diminished, the long-term benefit of radical surgery alone remains doubtful. Due to its lower complication rate, pleurectomy/decortication seemed to be superior to radical surgery alone and achieved some palliation in reducing pain, and is hence recommended by many authors [14–16]. We can confirm the same results as previous reports [18–19] about increased incidence of peritoneal spread and recurrence following EPP. This is because the diaphragm, which acts as a natural barrier to peritoneal dissemination, has been removed during the operation.

Various trials of systemic chemotherapeutic agents for management of MPM [20–25] have been performed over the years, but few have shown clear benefit. Most of the series have been too small in scale to accurately measure the response. Additional problems include heterogeneity of the patient population, difficulty in accurate staging in the unoperated patient, and a possibility of erroneous pathologic diagnosis. Platinum based compounds alone or in combination with anthracyclines (Epirubicin) has been proved to be effective in providing the response rates between 10 and 20% in several European studies [23–24]. The first experience of intrapleural chemotherapy was reported by Rice et al. [13] in a group of 19 patients treated with intrapleural chemotherapy following pleurectomy or EPP, however, local recurrence was very common in their group. Although the intrapleural regime avoided the systemic side effect of chemotherapy, it did not reduce the incidence of local or distant recurrence of the disease.

In agreement with previous bigger studies reported by both Rusch et al. [8,10] and Sugarbaker et al. [22,23], our results confirm that T1 and T2 patients have a much more favourable survival outcome when radical surgery and thus post-operative chemotherapy has been used. Our data also shows that T1 tumour exhibits better long-term survival outcome than T2 disease. T3 tumour has a poor prognosis even when radical surgical resection was achieved and hence, we need to identify these patients before surgery and avoid operating on them. Tumour T stage does seem to be an important selection criteria.

The negative significance of lymph node involvement on survival following EPP has been illustrated in some bigger series [25]. The negative influence of lymph node involvement in the survival of MPM following radical surgery and chemotherapy is not supported by our series. However, some other previous papers were also not able to demonstrate a worse prognosis in patients with lymph node involvement [16]. Such contrary findings may be due to smaller number of study population in our series. On clinical grounds, we find the CT scan inadequate for clearly separating lymph nodes from pleural nodules in the same area, which hinders pre-operative staging. In any case we do not consider lymph node involvement as an absolute contraindication for EPP pre-operatively if the patient is considered suitable (T1) and generally fit for surgical resection. Entering such patients into clinical trials and testing the outcome of radical surgery and chemotherapy on them would be desirable.

5. Study limitations

Our study is limited by factors, which may affect any retrospective and non-randomised analysis. Systemic chemotherapy was not offered to patients who underwent decortication/pleurectomy because complete resection was not possible but this may be worth looking into. The influence of lymph node metastasis and histopathological type of MPM may require further studies to validate these findings. We expect that patients with diffuse MPM suitable for radical resection and post-operative chemotherapy will represent only up to 25% of total MPM patients at any institution. Finally, it has to be commented that the decision between EPP and pleurectomy may not be easy in all MPM patients particularly those with good general condition, resectable tumour and lymph node metastasis (N1 or N2). The decision in these cases will be mainly based on the subjective impression of the individual surgeon and sometimes on findings on the table.

This study did not include a proper quality of life assessment of patients after their major operative procedure nor after their chemotherapy. This is needed to establish the true benefits of this regime. However, the toxicity was not overwhelming at the post-operative course and most patients seemed to enjoy a good standard of life including work and foreign holidays during their disease free period. Pain
was significant by its absence except for occasional post thoracotomy pain for which analgesics were not needed and rarely prescribed.

6. Conclusions

The question of surgery in MPM is a subject that has already been aired by many others. We have tried to find a way to separate patients who are unsuitable for any treatment from those who may benefit from a palliative procedure and those who deserve the best chance for a good outcome by being offered a radical resection (EPP) combined with adjuvant chemotherapy. Several types of adjuvant therapy are currently vying for a role in the post-operative setting such as radiotherapy, radioisotope beads, other drug regimes, immunotherapy and perhaps gene therapy. As the number of MPM patients is growing and there is increased awareness of this disease by public and medical professionals alike, we need to look closely at refinement of operative techniques and of post-operative care to make the procedure safer, thus expanding the number of potentially resectable patients with MPM. The median survival of 40.8 months for T1 disease after EPP and chemotherapy is superior to results with other forms of treatment.

Radical surgical resection is an important first step in the treatment of MPM whenever it is feasible. This should be followed by some form of adjuvant therapy as shown here. We should aim to improve on this by further trials on adjuvant therapy methods and regimes.

References

recurrence, when it occurred, was very vigorous, aggressive, and some of the patients died within weeks of recurrence occurring. In the second group of patients, we do have long-term survivors, and although 31 patients had recurrence, the recurrence was still treatable, we gave them a further course of chemotherapy, which seemed to control the disease for a short period of time; for a few months, before they died.

Dr Toomes: The treatment of mesothelioma is also a question of selection, and, as you said, Sugarbaker has selected subgroups, and in subgroups with epithelial mesothelioma with only surgical treatment, he achieves a 46% five-year survival. Do you want to comment on this?

Dr Prakash: We have not been as selective, we have not ruled out surgery for sarcomatous patients at this stage. In the future, one may want to consider that. But I think we do have sarcomatous patients surviving long term, and we felt we should not deprive them of surgical treatment.

Dr H. Aebert: (Tubingen, Germany): I have a question relating to your patients just receiving biopsy and best supportive care. Did you radiate the biopsy site, and how many local recurrences did you have?

Dr Prakash: We did not radiate the biopsy sites. The local chest wall recurrences was small, I don’t have a figure at the moment, but the number was small, and more importantly, these chest wall recurrences were neither painful nor very problematic; they didn’t ulcerate through the skin and so on like some other tumors. So we didn’t actively treat or prevent them.

Dr H. Ris: (Lausanne, Switzerland): You had 18 long-term survivors in your series. Could you please comment on the pathological pattern of this disease in these patients? And the second question, whether all patients were operated by extrapleural pneumonectomy or did you have long-term survivors in other categories?

Dr Prakash: I didn’t get your second question.

Dr Ris: The second question was, in these long-term survivors, were these all patients who were treated by extrapleural pneumonectomy?

Dr Prakash: Yes. Our long-term survivors was 9, not the figure you mentioned. I corrected myself. The long-term survival was 18%, or 9 patients, in the group with chemotherapy. And there were no special characteristics in these 9 patients that we were able to pick up; some of them did have nodal involvement and some of them were sarcomatous.

Dr D. Dougenis: (Patras, Greece): Why do you consider a contraindication to a radical extrapleural pneumonectomy the invasion of the diaphragm? Do you remove the diaphragm along with the entire lung during the procedure?

Dr Prakash: Yes, we do remove the diaphragm. We do preserve the underlying diaphragmatic peritoneum wherever possible. We feel that if the diaphragm itself has been invaded on CT findings, the chances are that the underlying peritoneum may be involved and therefore the chance of the patient doing well is less. So we don’t choose to operate on these patients at the moment.

Dr H. Toomes: What kind of material do you use for the replacement of the diaphragm?

Dr Prakash: The diaphragm is replaced by a two-way stretch Dacron material sewn all around at the level of the thoracotomy rather than the original level of the diaphragm. We use mercilene mesh loosely applied for replacing the pericardium.