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Extra-pleural pneumonectomy for malignant pleural mesothelioma: the risks of induction chemotherapy, right-sided procedures and prolonged operations☆

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Abstract

Objective: With the increasing incidence of malignant pleural mesothelioma and renewed interest in radical surgery as a therapeutic option, we have examined our experience of extra-pleural pneumonectomy, to document the incidence and management of its peri-operative complications. **Methods**: This analysis was conducted using prospectively entered data contained within the departmental database, with additional information from retrospective case note review. Details of patient selection criteria and operative modifications are included. **Results**: Over a 59-month period, extra-pleural pneumonectomy was carried out on 74 patients (66 men; 8 women; median age 57 years). Fifteen patients (20%) received cisplatin-doublet induction chemotherapy. The majority (80%) of patients had epithelial tumours and 85% of patients had disease in International Mesothelioma Interest Group stages III and IV. The 30-day post-operative mortality was 6.75% (five patients) and significant morbidity was recorded in 47 patients (63%). Major complications included those of technical origin (diaphragmatic patch dehiscence 8.1%; chylothorax 6.7%; intra-thoracic haemorrhage 6.7%; bronchopleural fistula 6.7%), cardiovascular morbidity (atrial fibrillation 17.5%; mediastinal shift with subacute tamponade 10.8%; right ventricular failure 4%; pulmonary embolus 2.7%) and respiratory morbidity (pneumonia 10.8%; acute lung injury 8.1%). Admission to intensive care was required in 19 patients (26%). Univariate analysis identified the incidence of acute lung injury and mediastinal shift to be significantly associated with induction chemotherapy ($P=0.005$ and 0.014, respectively). In addition to this, laterality of operation influenced respiratory morbidity ($P=0.018$) and admission to intensive care ($P=0.025$). Finally, prolonged operations (greater than the median) were associated with an increased risk of technical ($P=0.018$) and gastro-intestinal ($P=0.023$) complications. **Conclusions**: Extra-pleural pneumonectomy is associated with a high rate of morbidity, but an acceptable mortality rate can be achieved with increasing peri-operative experience. Surgery following induction chemotherapy requires extra vigilance for the development of post-operative respiratory complications.

Keywords: Pleural mesothelioma; Extra-pleural pneumonectomy; Morbidity; Risk factors

1. Introduction

Despite the varying options available for the management of malignant pleural mesothelioma (MPM), surgery in this disease has largely been limited to obtaining tissue diagnosis or achieving adequate pleurodesis for the control of symptomatic effusion [1]. Extra-pleural pneumonectomy (EPP) has been applied to the management of MPM with varying results over the last 30 years. In 1976, Butchart et al. [2] published the results of 29 patients who underwent EPP for diffuse MPM over a 13 year period. Despite an operative mortality of 31%, a survival advantage over conservative measures for patients with epithelial tumours was identified. Since then other series have reported operative mortality rates between 4.5 and 15%, the trend being towards improved operative survival.

Most published series have contained relatively small numbers of patients, and although crude mortality rates are presented, the incidence of major morbidity associated with EPP has been harder to evaluate. However, a recent analysis of over 300 patients who underwent EPP over a 20-year period has been published, with an overall morbidity rate (major and minor) of 60.4% [3].

We have reviewed our experience of this procedure, with particular reference to the incidence of peri-operative complications, and the modifications we have employed to

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manage them. We have also identified pre-operative risk factors that may influence the selection of patients, or post-operative management.

2. Methods

From a prospective database (for which the appropriate regional ethics committee approval has been obtained), patients who underwent EPP at our institution were identified and a retrospective review of medical records was undertaken for absent data. Complications were classified as either major or minor. A major complication was defined as one leading either to the death of a patient, or to a significant deterioration in the clinical condition of a patient, leading either to re-operation or prolongation of hospital stay. Technical complications were defined as those directly associated with the operative technique.

As part of our routine preparation for this operation, all patients were staged according to the International Mesothelioma Interest Group (IMIG) tumour, node, metastasis (TNM) system [4]. Patients of T stage 1–3 (assessed using high-resolution computed tomography, with contrast-enhanced magnetic resonance imaging for equivocal cases [5]) and N stage 0–1 (absence of mediastinal lymph node involvement is now confirmed in all cases regardless of size on cross-sectional imaging [6]) were deemed resectable. Operability was assessed according to the British Thoracic Society guidelines for pneumonectomy for lung cancer [7].

EPP has been described in detail previously [8]. At our institution we have, over time, made several modifications, both to the operative technique and to peri-operative management. The peritoneal covering of the inferior surface of the hemi-diaphragm is routinely excised en-bloc, reconstructed with a single polytetrafluoroethane (PTFE) Gortex patch (W.L. Gore and Associates, Inc.) and protected post-operatively with a large-bore nasogastric tube regularly aspirated to reduce stomach dilatation. The hemi-pericardium is routinely replaced with either Prolene mesh (Ethicon, Somerville, NJ), or more recently a fenestrated Gortex membrane (W.L. Gore and Associates, Inc.). We have successfully most recently used median sternotomy for access for right-sided procedures [9]. An oesophageal bougie is positioned intra-operatively to aid identification of the oesophagus during dissection of the mediastinal pleura. All patients receive an infusion of the serine protease inhibitor, Aprotinin (Trasylol, Bayer Corp., West Haven, CT), at a dose of 500,000 Kallikrein Inhibitor Units (70 mg) per hour, but without a loading dose, for the duration of the operative procedure. Appropriate inotropic support is instituted as required. Patients are now ventilated with nitric oxide mixed with the anaesthetic gases at a concentration of 10 parts per million (ppm), in an attempt to reduce the increase in right-ventricular afterload associated with pneumonectomy [10]. At the end of the procedure, following removal of the operative specimen and insertion of the prostheses, the bronchial stump is routinely covered with an intercostal muscle flap to reduce the incidence of bronchopleural fistula. All patients are electively extubated in the operating theatre and are transferred for further post-operative care to a dedicated thoracic surgery high dependency unit (HDU). The HDU provides an established setting, with nursing staff proficient in invasive methods of cardiovascular monitoring, the use of inotropic support and non-invasive ventilatory pressure support as required.

Table 1
Patient demographics ($n=74$)

Variable		Number (%)
Gender	Male	66 (89)
	Female	8 (11)
Operated side	Right	41 (55)
	Left	33 (45)
Histology	Epithelial	59 (80)
	Biphasic	12 (16)
	Sarcomatoid	3 (4)
Pathological IMIG stage	I	5 (7)
	II	6 (8)
	III	46 (62)
	IV	17 (23)

2.1. Statistical analysis

Statistical analysis was carried out using the software package SPSS for Windows, version 11, SPSS Inc. The incidence and significance of peri-operative morbidities was compared to clinicopathological factors using χ^2 or Fisher's exact test as appropriate.

3. Results

Over a period of 59 months, from August 1999 to July 2004, 74 patients of median age 57 years (range 39–70) underwent EPP for MPM (Table 1). Fifteen patients (20%) received cisplatin-based doublet induction chemotherapy, with gemcitabine in nine, pemetrexed in five and vinorelbine in one patient. The 30-day operative mortality was 6.75% (five patients), the causes of which are shown in Table 2. The median operating time was 3.75 (range 1.5–5.3) hours, but we have identified a trend towards a reduction in this (Fig. 1). The median length of post-operative stay was 13 (range 5–184) days. Of the 74 patients, 47 (63%) had either a major or minor peri-operative complication (Table 3), with some patients suffering more than one problem.

3.1. Technical complications

Dehisence of the diaphragmatic patch was the most common technical complication seen, occurring in 6 (8.1%) patients, most commonly associated with post-operative nausea and retching. A post-operative chylothorax was identified in five patients (6.7%), with three patients

Table 2
Causes of death for patients dying within 30 days of operation ($n=5$)

Cause of death	Number
Right ventricular failure	2
Myocardial infarction	1
Pulmonary embolism	1
Perforated oesophagus	1

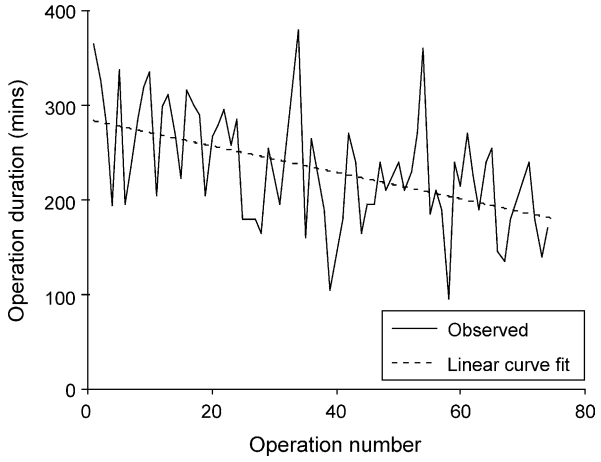

Fig. 1. Operation times for individual patients with trend-line, showing overall reduction in operating time ($P<0.001$, $R^2=0.239$).

requiring operative closure of the thoracic duct. These procedures were undertaken in the early post-operative period after failed conservative management principally because of problems relating to rapid filling of the pneumonectomy space. Five patients (6.7%) developed a bronchopleural fistula and intra-cavitary sepsis early in the post-operative period. All patients were treated with drainage and debridement of the infected space. Two patients underwent removal of the diaphragmatic and pericardial patches, in one patient this was accomplished thoracoscopically. Significant intra-thoracic haemorrhage was seen in five patients (6.7%), requiring emergent re-operation to prevent further blood loss. One patient (1.3%) required repair of a deep thoracotomy wound dehisence. The overall re-operation rate was 24% (18 patients).

Table 3
Post-operative morbidities following EPP

Complications		Number (%)
Technical	Diaphragmatic patch dehiscence	6 (8.1)
	Chylothorax	5 (6.7)
	Intra-thoracic haemorrhage	5 (6.7)
	Bronchopleural fistula/ Intracavitary sepsis	5 (6.7)
	Pericostal wound dehisence	1 (1.3)
Cardiovascular	Atrial fibrillation	13 (17.5)
	Mediastinal shift with subacute tamponade	8 (10.8)
	Acute right ventricular failure	3 (4)
	Pulmonary hypertension	3 (4)
	Pulmonary embolus	2 (2.7)
	Cardiac arrest	2 (2.7)
	Patent foramen ovale	2 (2.7)
	Haemorrhagic cerebrovascular accident	1 (1.3)
	Deep vein thrombosis	1 (1.3)
Respiratory	Pneumonia	8 (10.8)
	Acute lung injury	6 (8.1)
	Contralateral pneumothorax	1(1.3)
Gastro-intestinal	Pseudo-obstruction	2 (2.7)
	Gastric ulceration	1 (1.3)
	Perforated oesophagus	1 (1.3)
Infective	MRSA superficial wound dehiscence	1 (1.3)
	Pseudomonas septicaemia	1 (1.3)
	Systemic sepsis leading to multi-organ failure	
	Systemic sepsis leading to multi-organ failure	1 (1.3)

3.2. Cardiovascular complications

Atrial fibrillation, occurring in 13 patients (17.5%), was the most common source of morbidity. Mediastinal shift, resulting from rapid filling of the empty hemithorax and leading to subacute tamponade, occurred in 8 (10.8%) patients. Other problems included acute right ventricular failure with pulmonary hypertension (three patients, 4%), myocardial infarction (two patients, 2.7%), pulmonary embolus (two patients, 2.7%) and post-operative patent foramen ovale with right-to-left intra-cardiac shunt (two patients, 2.7%).

3.3. Respiratory complications

Culture-proven lower respiratory tract infections, or pneumonia, were seen in eight patients (10.8%) in the post-operative period. Six patients (8.1%) developed the clinical condition of acute lung injury (ALI), using criteria devised by the American–European Consensus Conference on ARDS in 1994 [11], requiring additional respiratory support.

3.4. Gastro-intestinal complications

Two patients (2.7%) developed pseudo-obstruction requiring general surgical review and culminating in colonoscopic decompression to prevent caecal perforation. One patient (1.3%) developed bleeding gastric ulceration, which was treated medically. One patient (1.3%), who developed the clinical picture of intra-cavitary infection with associated systemic sepsis, underwent a second thoracotomy to debride the EPP space, and was found to have a spontaneous oesophageal perforation.

3.5. Intensive care

There was no routine use of the intensive care unit (ICU) in the post-operative management of this cohort of patients with all patients electively transferred to a thoracic surgical high dependency unit. However, 19 patients (26%) were admitted to ICU for assistance in the management of post-operative morbidity, most commonly for mechanical ventilation. Of those patients admitted to ICU, 79% (15 patients) of them were discharged back to the ward. Tracheostomy was required in four patients. The median ICU stay of survivors was 3 (1–141) days.

3.6. Predictors of peri-operative morbidity

On univariate analysis, three pre-operative variables were identified as indicators of increased risk. Induction chemotherapy was significantly associated with ALI ($P=0.005$, χ^2) and symptomatic mediastinal shift requiring thoracocentesis ($P=0.014$). Prolonged operations (greater than the median time) were associated with an increased risk of technical ($P=0.018$) and gastro-intestinal

Table 4
Risk factors for peri-operative morbidity (χ^2 or Fishers exact test)

Variable	Morbidity	*P* value
Induction chemotherapy	Acute lung injury	0.005
	Symptomatic mediastinal shift	0.014
Right-sided procedures	Pneumonia	0.018
	Admission to ITU	0.025
Prolonged procedures (greater than median time)	Technical complications	0.018
	Gastro-intestinal complications	0.023
30-day deaths	Atrial fibrillation	0.038

complications ($P=0.023$). Thirdly, right-sided procedures were found to be significantly associated with the incidence of post-operative pneumonia ($P=0.018$), admission to ICU ($P=0.025$) and increased overall risk of peri-operative mortality ($P=0.047$) (Table 4).

In addition, the post-operative development of atrial fibrillation was significantly associated with an increased risk of 30-day mortality ($P=0.038$). Neither gender, type of operative incision, IMIG stage nor histological subtype had any significant impact on the incidence of complications.

4. Discussion

In contrast to pulmonary resection alone, very little data exist on the complications associated with EPP for malignant pleural mesothelioma. The recent report by Sugarbaker et al. [3] details a series of over 300 cases, operated on over a twenty year period, identifying the need for a unique approach to management. The most common complication in this series was atrial fibrillation (AF), seen in 44.2% of patients. In our series, the comparative figure was only 17.5% (13 patients), despite our avoidance of anti-arrhythmic prophylaxis. There is no obvious reason for this discrepancy, although the 9 l of pulsed lavage used by Sugarbaker and colleagues at the end of the procedure in an attempt to reduce the incidence of intra-cavitary infection may have a role. Indeed, patients in their series who have had pulsed intra-pleural hyperthermic chemotherapy have an 80% incidence of AF.

Our finding of increased risk of significant post-operative morbidity and mortality from right-sided procedures is in agreement with previously published series of patients undergoing pneumonectomy [12]. Furthermore, a study by Harpole et al. [13] actually includes a sub-group of 55 people undergoing EPP for MPM, which identified the association between right-sided procedures and increased risk of major morbidity.

We have noted that patients undergoing prolonged procedures tend to be at increased risk of technical complications. The most difficult, and, therefore, the most time consuming procedures are generally associated with more bulky local disease, which may not reflect the IMIG stage of the tumour. Bulky disease in the costophrenic recess (T2 tumour) may necessitate leaving only a small margin to which the diaphragmatic patch can be attached. This may lead to an increased risk of diaphragmatic patch dehiscence (a major contributor to technical complications). The 'learning curve' experience in operating time that we have identified has been shown by Sugarbaker et al. [3], to be the single most important factor in improving patient outcomes. The re-operation rate of 24% is represented largely by an aggressive interventional policy for the management of complications, and in particular, those of a technical nature.

The reasons for the development of an oesophageal perforation were not clear. There is no precedent in the published literature as a complication of this operation, but the authors are of the opinion that there are three possible mechanisms of injury. Firstly, post-operative retching and vomiting are commonly seen after this operation, marking the importance of a naso-gastric tube to ensure an empty and undilated stomach. In addition, despite the use of the oesophageal bougie it is possible for unidentified oesophageal injury to occur at the time of operation, which may take more than one form. Damage to the vascular supply of the oesophagus may occur during mediastinal pleural dissection, leading to ischaemic perforation. Finally, direct injury to the muscle layers of the oesophagus may also occur via the same mechanism, with delayed post-operative mucosal perforation.

Of the 19 patients requiring admission to the ICU, almost 80% were discharged back to the ward. A significant number of these patients were admitted for re-warming prior to extubation following prolonged procedures, or after re-operation. The four patients who died in the ICU developed failure of more than one organ system, a scenario known to be associated with a poor outcome in patients undergoing pulmonary resections [14].

The use of induction chemotherapy in MPM is not routine. In a pilot study, Weder et al. [15] evaluated the role of neoadjuvant cisplatin and gemicitabine chemotherapy prior to EPP, with optional adjuvant radiotherapy, in 19 patients. Fifteen patients in our series received cisplatin-based neoadjuvant chemotherapy, most frequently combined with gemcitabine, for a total of three cycles. Few post-operative complications were seen in the Weder study, although data available on the use of induction chemotherapy in non-small call lung cancer (NSCLC) would suggest that it is not without significant risk [16]. Although our total numbers are small, our findings would suggest that these patients are at significant risk of developing ALI in the post-operative period, most frequently seen 3–5 days after operation. Acute lung injury is known to be a major cause of mortality after lung resection [17], but the mechanism for its development is unclear. It is well documented that chemotherapy, such as cisplatin and gemcitabine, lead to pulmonary toxicity with injury to the alveolar-capillary membrane as the possible mechanism [18]. Other possible mechanisms include excessive fluid administration, impaired lymph drainage and a pan-endothelial injury induced by the surgical procedure [19] with an associated increase in endothelial permeability [20]. It is likely that no single factor will be reliably implicated and all, including the chemotherapeutic agents, will have a role.

The rapid filling of the pneumonectomy space unique to the procedure of EPP, that produces paradoxical mediastinal shift away from the operated side, leading to a shift in the mediastinum and compression of the remaining lung is

well recognised with this operation. Sugarbaker et al. [3], identifying the significance of this entity, have described the use of a flexible intra-pleural catheter, which remains in-situ for approximately 3 days post-operatively to allow removal of fluid from the operated hemi-thorax should the need arise. We have found very similar requirements in this cohort of patients and also now routinely leave an intercostal drain in position for longer than with a standard pneumonectomy. Illustrating the need for this approach, of the eight people in this series who developed paradoxical mediastinal shift, five patients had their drain removed early (two on post-operative day 1, and three on day 2). As a consequence, four required aspiration of 1–3 l (L) from the pneumonectomy space, with one patient having an intercostal drain re-inserted on the sixth post-operative day. In the remaining three patients, the drains were clamped without release on post-operative day 1, but not removed. Two went on to develop clinically apparent chylothoraces, draining volumes in excess of 2 l per day and the final patient developed an oesophago-pleural fistula, becoming progressively unwell. It is interesting to note that for the remainder of the patients in this series the median length of drain time in-situ is 2 (range 1–6) days, with a median total drainage of 1.1 (range 0.85–1.31) L. As this figure is not hugely different from those patients experiencing mediastinal shift, it may be that this clinical situation depends to a greater extent on the rapidity of the space filling, rather than the absolute volume involved. We did identify a significant association between the incidence of mediastinal shift requiring removal of fluid from the operated hemi-thorax and those patients who received induction chemotherapy. It is possible that this may be due to the pan-endothelial injury identified above, leading to leakage of tissue fluid from the large surface area left following the extra-pleural dissection.

We have instituted several peri-operative manoeuvres to simplify the procedure and improve overall outcome. There is now increasing experience regarding the use of nitric oxide in adults with pulmonary hypertension and RV dysfunction or failure, in order to reduce the pulmonary vascular resistance (PVR) and therefore, RV afterload [21,22]. Because three patients have developed acute RV failure, with or without pulmonary hypertension in this series, which has ultimately become refractory to treatment, we have instituted the use of nitric oxide, at a low dose of 10 ppm given with the mixture of anaesthetic gases for the duration of the operation. This is an attempt to reduce the rise in pulmonary artery pressure on completion of the pneumonectomy. All the patients who developed acute RV failure were not treated with nitric oxide, and since its use has begun, only one patient has developed significant pulmonary hypertension, which occurred more than 30 days post-operatively. Although there is a theoretical risk of causing further damage to the remaining lung and affecting the systemic circulation, animal studies would appear to suggest otherwise [23].

We use an intra-operative infusion of the serine protease inhibitor, Aprotinin, as it has been used for many years in cardiac surgery [24], because of its potential beneficial effects of reducing peri-operative blood loss from the large denuded surface of the operated cavity. However, additional potential benefits of Aprotinin are beginning to surface, such as the potential to interfere with tumour growth and development of metastases, principally by the inhibition of several serine proteases thought to be vitally important in tumour progression [24]. There is evidence that it may improve survival after resection of colorectal liver metastases [25].

EPP will remain an operation with an inherently high morbidity rate that may be compounded by induction chemotherapy. However, with careful pre-operative assessment and peri-operative vigilance, accompanied by aggressive intervention where required, the mortality rate can be reduced to an acceptable level, compared with the 8.1% seen in pneumonectomy for NSCLC (UK Thoracic Surgical Register 2000–2001). There is a clear learning curve associated with this operation, both in terms of the operating surgeon and the peri-operative management at all levels of the multi-disciplinary team, requiring understanding and close communication. It is the suggestion of the authors that the sporadic, isolated performance of this operation should be discouraged and that EPP should only be performed in interested centres with experience of the unique potential complications and their management.

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