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Review

Surgery for malignant pleural mesothelioma: Why, when and what?

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ABSTRACT

Malignant pleural mesothelioma is a fatal cancer developing in the pleural cavity, linked to asbestos exposure. Various therapies have been tried in the past 50 years including surgery, radiotherapy, chemotherapy, immunotherapy and more recently, targeted therapy. Radical surgery remains controversial in malignant pleural mesothelioma and two procedures have been offered in the past to obtain maximal cytoreduction: extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D). Despite growing evidence that EPP might be detrimental, many believe that radical surgery should still be part of multimodality therapy in patients with malignant pleural mesothelioma. Recent evidence suggests that P/D is well tolerated and produces low mortality and morbidity. The role of adjuvant intrapleural therapies remains to be determined and evaluated in large prospective trials. Pleurectomy/decortication does not jeopardize the chance of having chemotherapy, or chemoradiotherapy either. Many now believe that it should be the default procedure in multimodality regimens. However, this remains to be proven in a large randomized trial. Palliative surgery still has an important role to play in mesothelioma, in establishing or refining diagnosis and in controlling symptoms and improving quality of life in many patients whose life expectancy is limited. Recent progress in molecular analyses and biomarkers should help with patient selection for surgery, immunotherapy and systemic therapies in the near future.

Malignant pleural mesothelioma (MPM) remains a major cause of death in patients exposed to asbestos [1]. At present, there is no known curative treatment for MPM and the majority of patients are offered best supportive care or palliative chemotherapy [2]. With best supportive care only, the median survival following diagnosis is often less than 12 months [2,3]. The standard of care now consists of a platinum-containing chemotherapy doublet as two phase III randomized trial using pemetrexed and cisplatin or raltitrexed and cisplatin showed these combinations to offer a survival advantage and a median survival around 12 months [3,4]. Immunotherapy has been used for years in pleural mesothelioma with various effects, but seems to be active mainly in patients with very early stage disease [5–7]. Targeted therapy is emerging as an interesting therapy and the search for "drugable" targets is ongoing [8–12].

Most patients presenting with pleural mesothelioma in the Western world are in their sixth or seventh decade and often have severe co-morbidities precluding any radical treatment. Nonetheless, surgery plays an important role in those patients, helping to achieve a precise diagnosis (open or videothoracoscopic biopsy) and palliate malignant pleural effusion through talc pleurodesis, VATS pleurectomy or insertion of an indwelling pleural catheter [13]. For more than 50 years, patients with early-stage disease and good performance status have been offered radical procedures aiming at removing all tumour and in the past 30 years the concept of multi-modality therapy involving cytoreductive surgery, radiotherapy, chemotherapy has prevailed at most institutions [14,15].

Recently, Flores et al. reported that in the US, radical surgery (cancer-directed surgery) is offered to approximately 22% of patients [16]. This estimate may be lower in many European countries and in developing countries due to the lack of local expertise and reluctance/impossibility to travel to a tertiary centre.

1. Radical surgery

No other field as radical surgery for mesothelioma has attracted so much controversy in the thoracic community [17]. Two procedures have been offered to resect pleural mesotheliomas: extrapleural pneumonectomy which involves en-bloc resection of the all lung (pneumonectomy) with surrounding pleura, ipsilateral hemi-diaphragm and ipsilateral pericardium (Fig. 1), and pleurectomy which involves a resection of the pleural tissues only (Fig. 2). Although the different steps involved in EPP (en-bloc excision of pleura, lung, hemi-diaphragm and pericardium, followed by reconstruction of the diaphragm and pericardium by synthetic meshes) are well defined, it is less clear what surgeons actually perform

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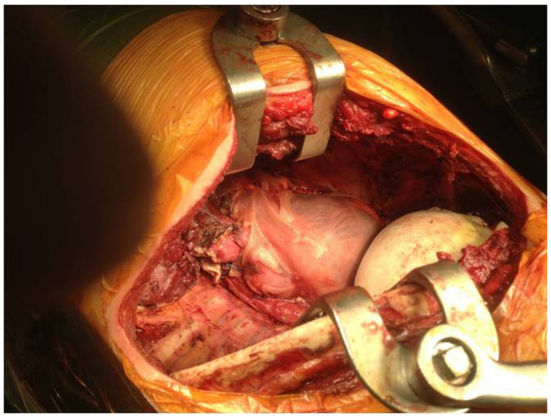

Fig. 1. Operative view, right extrapleural resection. The pericardium and diaphragm have been resected and replaced by a Vicryl and PTFE mesh, respectively.

when they do a pleurectomy. Various terms have been introduced over the years i.e. pleurectomy/decortication, radical pleurectomy, total pleurectomy, extended pleurectomy, to account for the procedure performed. Recently, the international association for the study of lung cancer (IASLC) and the international mesothelioma interest group (IMIG) have proposed uniform definitions [18]: total pleurectomy involves the removal of all pleural tissues (parietal, visceral, mediastinal and diaphragmatic pleura), the term radical or extended pleurectomy should be used when the diaphragm, pericardium and any other structure such as lung or vessel are excised as well.

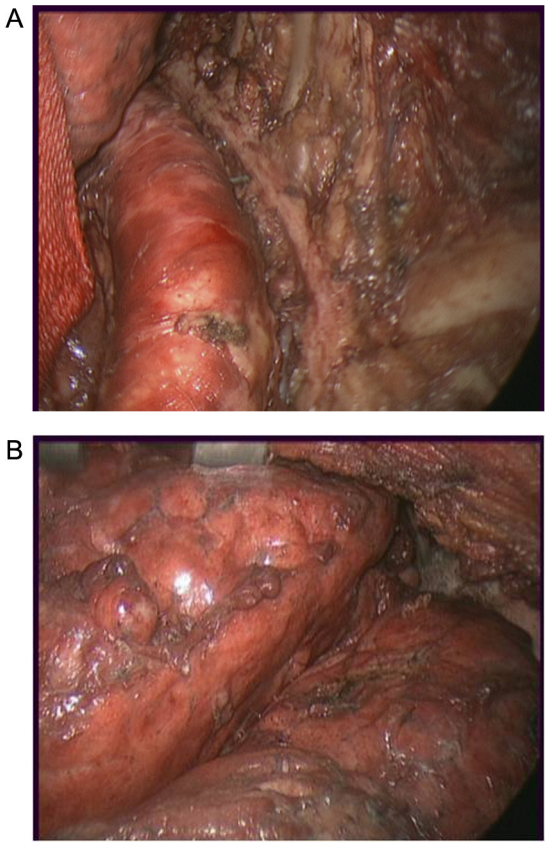

Fig. 2. Left total pleurectomy/decortication, operative views. The oblique fissure has been completely cleared (a) and the mediastinal pleura completely excised as well down to its reflexion. The descending thoracic aorta and sympathetic nerve are well visible following clearance over the posterior mediastinum (b).

1.1. Extrapleural pneumonectomy

EPP is usually performed via a large posterolateral thoracotomy but a median sternotomy has been advocated by Waller et al. for right-sided EPP [19]. Very often, a two-level thoracotomy (5th and 8th interspace) is necessary to dissect the hilum and perform the pneumonectomy, then resect the diaphragm and repair it with a mesh. At present, most surgeons use a large polytetrafluoroethylene mesh (PTFE) to replace the diaphragm. Of note, lymph node dissection is advocated during EPP and P/D in order to get adequate staging.

Several studies have shown that patients with N2 disease do not benefit greatly from EPP [15]. Therefore, assessing intrathoracic nodes before EPP is of paramount importance to exclude patients who would not benefit from such extensive surgery. Several studies have shown that malignant lymph node involvement cannot be accurately predicted from nodal uptake on positron-emission tomography (PET) scanning [20,21] or from nodal size [22], therefore cervical mediastinoscopy, endobronchial ultrasound-guided biopsy (EBUS), and endo-esophageal ultrasound-guided biospy (EUS) are to be considered to rule out N2 or N3 disease before embarking on radical surgery. As many nodal stations are out of reach for mediastinoscopy (stations 8, 9, 10) EBUS and EUS seem to be more adequate. EBUS has the advantage of offering a good exploration of the bronchial tree as well. Anterior paracardiac nodes, intercostal nodes and intercostal nodes are also out of reach for mediastinoscopy, but can be reached percutaneously sometimes, using fine needle aspiration. In any case, the N component of the TNM staging for mesothelioma is far from being perfect and was adapted from the lung cancer classification. There is no prospective validation of the actual classification and the IASLC is working on a new TNM classification based on several thousand of cases [23].

Extrapleural pneumonectomy (EPP) was first reported in the treatment of patients with pulmonary tuberculosis [24]. In 1976, Butchard et al. reported their experience with EPP in the treatment of malignant pleural mesothelioma in 29 consecutive patients: in hospital mortality was 31 percent and only 3 patients (10%) survived 2 years or longer [25]. Considering the high mortality and dismal prognosis, most surgeons stopped offering EPP for mesothelioma. Nonetheless, radical surgery continued at few tertiary referral centres and attempts at reducing the mortality, reduce local and distant relapses and improve long-term survival were made using high dose adjuvant radiotherapy and chemotherapy [26,27]. In 1999, Sugarbaker et al. reported a large series of mesothelioma patients treated by EPP, chemotherapy and adjuvant hemithoracic radiotherapy at Brigham and women hospital/Dana Farber Cancer Institute [15]. The in-hospital mortality was low and the 5-year survival was up to 46% in a selected group of patients with epithelioid subtype, clear surgical margins and N0 disease. Several groups started offering this procedure routinely in combination with induction chemotherapy and adjuvant radiotherapy [28–31] (Table 1). In the last two decades, hyperthermic intraoperative pleural cisplatin chemotherapy was introduced at specialist centres in an attempt to reduce local recurrence rate and improve survival [32]. In their most recent publication, Sugarbaker et al. reported an overall survival of 35.3 months in 72 consecutive patients with epithelioid histology, significantly better than in 31 patients who did not receive hyperthermic intrapleural chemotherapy (overall survival 22.8 months) [32].

However, evidence is still lacking and a comprehensive review published in 2005 claimed there was no evidence to support the role of EPP in mesothelioma [33]. More recently, Nowak and colleagues reported no significant difference in survival (20.4 versus 20.7 months) in 18 EPP patients and 18 non-EPP patients referred for trimodality therapy at the main tertiary referral centre in