

REVIEW ARTICLE

Surgical treatment for malignant pleural mesothelioma: extrapleural pneumonectomy, pleurectomy/decortication or extended pleurectomy?

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Summary

Malignant pleural mesothelioma (MPM) is an asbestos-related disease with a dismal prognosis. Ethic, social, legal and economic parameters are implicated in its management. It is quite clear that multimodality therapy is necessary to improve long-term results but precise treatment schemes have not yet been equivocally accepted. The extent of surgery is questioned and radical operations are highly debatable. On the other hand, debulking or cyto-reductive surgery have been also proposed within a multimodality

approach. However, the role and order of adjuvant or neoadjuvant use of chemotherapy, radiotherapy and surgery has not been established. The aim of this study was to analyze contemporary studies on the impact of different surgical approaches on outcome of patients with MPM.

Key words: asbestos exposure, extrapleural pneumonectomy, malignant mesothelioma, pleurectomy

Introduction

MPM represents a unique occupational malignancy. It has a dismal natural history with a median survival of 6 to 8 months if left untreated. It is environmentally-related, and has such an ethic, economic and social impact more than any other disease in surgery. MPM is usually presented with dyspnea, chest pain, and effusion. Over the last 40 years it has been postulated that mesothelioma is a cancer caused by the environmental carcinogens asbestos and erionite. These agents seem to interact with genetic predisposition and viral infections during carcinogenesis [1].

The peak incidence is predicted for 2030 in UK, Australia and North America, due to the asbestos use in industry until the end of 1980 [2].

Controversy exists in almost all issues of mes-

othelioma up until today. For more than 40 years scientists have argued on the role of chrysotile fibers and recently for SV40, a DNA virus that is present in animal and some human mesotheliomas.

Also, conflict exists regarding the role of surgery in the therapeutic protocols [1]. It seems that, although not yet clearly defined, a subset of patients may actually benefit from a surgery-based multimodality treatment plan. Surgery alone, however, is unlikely to oncologically sterilize the hemithorax. The goal of surgery is to remove all visible macroscopic disease. Surgical approaches to achieve a macroscopic complete resection include lung-sacrificing and lung-sparing techniques. The three surgical procedures that have

been used for the treatment or palliation of MPM are extended pleurectomy (EP), pleurectomy/de-cortication (P/D), and extrapleural pneumonectomy (EPP). Unfortunately, none of these procedures as a single modality has resulted in a significant prolongation of median survival.

The purpose of this study was to focus on the current knowledge over the treatment methods of this dismal neoplasm, based on the relevant literature data.

Methods

Literature search

A literature search using Medline was conducted from 1980 onwards, searching for articles with relevant key words such as malignant pleural mesothelioma, debulking or cyto-reductive surgery, EP, P/D, and EPP.

Appropriate additional references were found from the references of the identified papers of interest. Any relevant scientific conference proceedings or medical texts were checked when necessary.

Review of the literature

Trimodality treatment (TMT) with adjuvant chemotherapy, surgery and radiotherapy offers a curative chance in selected patients with pleural malignancies. A systematic review of 16 studies assessed the safety and efficacy of TMT in the current literature [3]. The primary endpoint was overall survival and secondary endpoints included disease-free survival, disease recurrence, perioperative morbidity and length of hospital stay. It was suggested that TMT may offer acceptable perioperative outcomes and long-term survival in selected patients that received treatment in specialized centers. Cytoreduction in early disease stage is a good prognostic factor [4] and is usually achieved by radical pleurectomy or EPP [5], although it is quite clear that a combination of radiotherapy, chemotherapy and lung-sparing operations have better outcomes over pneumonectomy [6]. Patient selection for either EPP or radical pleurectomy depends not only on the cardiopulmonary status of the patient, tumor stage and intraoperative findings, but it is also strongly influenced by the surgeon's preference, experience and philosophy [7,8].

EPP involves removal of the lung, hemi-diaphragm and the pericardium *en bloc*. This was the usual operative technique in the 1970s and is preferred in cases with lung parenchyma and fissural invasion. The concept behind this operation is its potential for a radical treatment. Selection criteria include good performance status, earlier disease stage and not more than localized involvement of the thoracic wall. However, this operation has been associated with high perioperative morbidity and mortality [9]. Pneumonectomy is a hazardous and debilitating operation. Postoperatively,

patients have severe cardiopulmonary/hemodynamic overload and fluid and electrolyte balance disorders may rapidly develop. Cardiac dysrhythmias and/or hypotension may increase the mortality rate up to 5-30%. On the other hand, it is debatable whether a complete resection (R0) can be achieved in MPM cases with any technique. The possible role of EPP in patients with N2 or sarcomatoid-type disease is also controversial [10,11].

On the other hand, P/D has been considered for elderly patients or when EPP could not leave negative margins behind.

EP is usually performed in patients with disease confined to parietal pleura and in those with poor respiratory status [12].

EP is preferred in cases where standard pleurectomy is technically inappropriate and in cases of invasion of lung parenchyma, especially in patients with poor performance status or other comorbidities [13].

It is generally accepted that local recurrence of MPM is almost inevitable and EPP and EP may control local disease better [14,15]. Although radical surgery seems to be abandoned [2], by comparing survival advantage between incomplete pleurectomy and EPP within standardized multimodality treatment protocols it was concluded that patients undergoing pleurectomy had inferior outcomes. This prompted that EPP can be used in selected patients to achieve macroscopic complete resection [16].

Recruitment into clinical trials is the proposal of a study that does not recognize any survival benefit from any form of surgery. This study concluded that there is doubt about any survival or even symptomatic benefit and those patients should be informed and encouraged to participate in clinical trials [17].

Despite its limitations, the MARS study concluded that EPP is a dangerous operation on the basis of randomization of MPM cases [18]. The objective of the MARS trial was to determine whether radical surgery after induction chemotherapy is better compared to chemotherapy alone. It revealed that survival after chemotherapy alone was better and complications were less than chemotherapy plus radical surgery. Surgery was found to offer no benefit and to even harm the patients. As a result, EPP efficacy is debated in cases with parenchymal involvement, visceral pleura invasion, or cases of tumor extension into the fissure.

P/D is considered again as acceptable alternatives in selected cases. On the contrary Zucali et al. [19] reported that the data in the MARS study does not support its conclusions and it misdirected the clinical outcomes.

Hiddinga et al. [10] reported that P/D is better than EPP, and EPP with preoperative chemotherapy was shown to be more beneficial than standard EPP. In another recent study, Nakas and Waller [20] while identifying predictors of long-term survival following radical surgery for MPM, found that there was no survival benefit of EPP over EP.

Table 1. Criteria for maximal complete resection and poor prognostic features

| <i>Criteria for maximal complete resection</i> |
|---|
| No imaging evidence of disseminated disease outside the involved hemithorax (clinical stage I-III). |
| Full of partial expansion of the underlying lung following drainage of any associated pleural effusion. |
| Adequate cardiopulmonary function such that he/she will be able to tolerate the procedure. |
| No serious comorbidity. ECOG performance status 2 or worse are generally excluded. |
| <i>Poor prognostic features</i> |
| Histology other than epithelial |
| Age > 50 years |
| Male gender |
| Platelet count > 400,000 platelets/mL |
| White blood cell count > 15,000 cells/mL |
| Bulk of solid tumor on presentation with chest wall pain at presentation |

In a recent systematic review and metaanalysis on surgical treatments of MPM it was concluded that selected patients who underwent extended P/D had lower perioperative morbidity and mortality with similar, if not superior, long-term survival compared to EPP, in the context of multi-modality therapy [21]. There are no established criteria to help the clinician decide on which patients are candidates for a trimodality approach that includes a maximal complete resection (MCR). These aggressive procedures usually concern centers with adequate expertise in these procedures and in the management of MPM. A list of criteria that we propose are seen on Table 1. In Table 2 we are discussing the studies of different centers that had an experience on TMT protocols with the respective survival and mortality data.

A multicenter retrospective analysis of 1365 consecutive patients on the impact of surgery in MPM proposed that patients with good prognostic factors had a similar survival whether they received medical therapy only, P/D, or EPP [22].

Finally, a recent study from Turkey dealing with clinical characteristics, treatment and survival outcomes from 150 patients with MPM treated from 2005 to 2012 concluded that there was no survival benefit of EEP over P/D [23].

Discussion

It is quite clear that TMT is supported by most studies [24-27]. The main concept behind treatment theories is the careful selection of patients, centers specialized on mesotheliomas and patient participation into clinical trials. Pneumonectomy is considered a dangerous operation and even if it is successfully performed, onco-sterilization of the hemithorax is debatable. P/D is considered an acceptable alternative associated with results similar to pneumonectomy. However, this is not supported by all studies. The MARS study suggests that surgery has no benefit in MPM [18].

Table 2. Trimodality studies on malignant pleural mesothelioma

| <i>First author [Ref]</i> | <i>Patients, N</i> | <i>Overall survival (months)</i> | <i>Mortality (%)</i> |
|---------------------------|--------------------|----------------------------------|----------------------|
| Okada [24] | 27 | 13 | 3.7 |
| Bille [25] | 25 | 12.8 | 4 |
| Pasello [26] | 54 | 15.5 | N/M |
| Van Schil [27] | 58 | 18.4 | 6.5 |
| Krug [28] | 77 | 16.8 | 4 |
| De Perrot [29] | 60 | 14 | 6.7 |
| Buduhan [30] | 55 | N/M | 4.3 |
| Opitz [31] | 63 | N/M | 3.2 |
| Flores [32] | 21 | 19 | 0 |
| Rea [33] | 21 | 25.5 | 0 |
| Weder [15] | 61 | 19.8 | 2.2 |
| Weder [34] | 19 | 23 | 0 |

N/M: not mentioned

It is certain that most studies are obscured and have multiple limitations [28-31]. The numbers of patients are small and studies are retrospectively analysed. This disease has a rapid dismal progression and there is no consensus on its proper treatment. Multimodality treatment combines all acceptable types of therapies we have in our hands today in any order, usually according to personal and local preferences, so that conclusions are not easily extracted. Several specialties are implicated in the patients' treatment. Surgical techniques, radiotherapy models and adjuvant/neoadjuvant chemotherapy protocols must all be considered under the same context and estimated for their efficacy prospectively [32-34].

Future therapeutic techniques are currently under investigation. Hyperthermic intrapleural chemotherapy, immunotherapy, gene therapy and photodynamic therapy are being evaluated, al-

though no randomized comparisons are available yet. Pleural carcinogenesis is better understood with the recent discovery of BAP1 susceptibility gene.

Conclusion

We conclude that the review of the literature

on malignant pleural mesothelioma cannot lead to safe recommendations and it lacks convincing evidence to support treatment practices. We feel that trimodality treatment protocols and inclusion into prospective trials may lead to better understanding of the nature of this malignancy, giving hope for more efficient treatments in the future.

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