

# Radical surgery for malignant pleural mesothelioma: have we identified the appropriate selection tools?

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## Introduction

The extensive utilization of asbestos in the previous century in industrialized countries, the rapid surge of asbestos use in developing countries and the omnipresence of asbestos containing materials in most man-made environments continue to contribute to the constantly increasing epidemic of malignant pleural mesothelioma (MPM) (1-3). Chronic inflammation elicited by inhaled asbestos fibers is considered the principal etiologic factor for this almost universally lethal malignancy originating in the pleura. It is assumed that 20-60 years (median around 40 years) of chronic inflammation is needed before this disease manifests itself (4). The direct consequence of this long latency period is that MPM is most frequently diagnosed at an older age (5).

MPM is usually confined to one hemithorax at the time of diagnosis, but the disease has a strong tendency to spread and involve the entire pleura and interlobular space. Infiltration into adjacent structures is characteristic of advanced MPM and despite attempts to completely resect the affected pleura, MPM will recur in most cases.

## Radical surgery

Notwithstanding the dismal overall prognosis of MPM, there is a subgroup of MPM patients in whom the disease shows a less aggressive course and prolonged survival. An early report revealing that radical surgical treatment for MPM may be followed by prolonged survival appeared in 1959 (6). A 43 year-old female, who underwent a right pleuropneumonectomy for what was finally diagnosed as MPM, survived for more than 6 years. Butchart and colleagues reported the first series of MPM patients who underwent pleuropneumonectomy, a procedure currently referred to as extrapleural pneumonectomy (EPP) (7). Observations from

this series, consisting of 29 MPM patients who underwent radical surgical treatment (EPP) and 17 MPM patients who received non-surgical treatment, were sufficient to suggest a potentially curative role for EPP. These observations further led to the proposal of an algorithm for individualization of treatment of MPM on the basis of age, performance status, stage and histological subtype, as well as a staging system. Moreover, a number of contentious issues concerning surgery in MPM were discussed in this paper, including the impediments to achieving complete tumour clearance, the risk of seeding tumour in the chest wall and the high (hospital) mortality associated with EPP. The hospital mortality in Butchart's series was around 30% and this high figure and the difficulties in achieving complete tumour clearance led to a fierce debate.

In an overview article published 13 years later Butchart lists a number of factors that complicate the interpretation of surgical reports on MPM, including a frequent lack of information about preoperative performance status, lack of staging information, selection bias, lack of precise histological subtyping, varied surgical techniques and the lack of information concerning use of (neo)-adjuvant therapy (8). It seems reasonable to add the expertise of the surgeon and his team to this list, as data from retro- and prospective studies reveal that certain institutions were able to limit the surgical morbidity and mortality of EPP (9). Mortality rates of 6% or less were documented in a number of reports in which EPP formed a part of multimodality treatment (10-16). Multivariate analyses suggested that EPP was associated with prolonged survival, especially when the radical surgery was part of a multimodality treatment program (17). While it could be argued that the studies mentioned above might have suffered from selection bias, it is worth noting that results obtained in one center were reproducible in another. During the last 10 years, the

surgical oncological community has devoted considerable time to discussions concerning the role of radical surgery in the treatment of MPM, including, the use of uniform definitions of surgical techniques (18), comparisons between EPP and pleurectomy and decortication (P/D) (19), the lack of randomized controlled clinical trials (20,21) and the need to include quality of life measures in in surgical trials for MPM (22).

A study to test the feasibility of randomizing MPM patients between EPP and no EPP following induction chemotherapy was initiated in 2005 (23). Recruiting patients for this study was considered difficult and a feasibility study with the objective of randomizing 50 patients in one year to gauge the potential recruitment rate was organized. Patient accrual indeed turned out to be difficult and 2 years were needed to randomly assign 50 patients from 12 participating centers to the two study arms (23). The interpretation of the results of this multicenter feasibility study is complicated by the facts that the induction was not standardized and that protocol deviations occurred in a significant percentage of patients. The perioperative mortality in the EPP arm amounted to 18% and contributed to the poor overall survival in the EPP arm, which turned out to be inferior to the survival in the no-EPP arm. The authors concluded that radical surgery in the form of EPP within trimodality therapy might have harmed patients. It is obvious that the teams involved in this multicentre study were unable to equal the standards set by other single or multicenter teams (12,15,16,21), making it difficult to generalize their conclusion - that EPP is potentially harmful - to centres outside those participating in the UK study (24).

In recent years, several studies have pointed to a relationship between surgical volume/expertise and the outcomes of surgical treatment. This relationship is prominent in the surgical treatment of lung cancer (25) and it is tempting to use this relation as an explanation for the better outcomes of surgery and combined modality therapy for MPM in experienced (high-volume) centers. A recent retrospective single institution study describing 18 years of EPP practice confirmed that more experience (higher patient numbers) and better outcomes (perioperative morbidity and overall survival) were associated and provides support for this explanation (17). The assumption that experienced surgeons, in high volume centres, might be in a better position to adequately select patients for multimodality therapy (on the basis of prognostic factors and co-morbidity) may be used as an additional argument.

### Prognostic factors and patient selection

The prognostic value of histologic subtype became apparent in one of the first MPM cohorts published and this finding has been consistently confirmed in later studies (26,27). As well tumor grade has been proposed as a prognostic factor for MPM and recent studies exploring calretinin and aquaporin 1 suggest that tumour differentiation is associated with survival (28-30). The importance of mediastinal lymph node involvement for the prognosis of MPM was recognized in the 1990s and has been used to propose a modification of the Butchart staging system (27). Shortly thereafter a new staging system was proposed by the International Mesothelioma Interest Group (IMIG) (31). A staging project (IMIG/IASLC) is underway to collect a (surgical) dataset of sufficient size to validate the TNM elements of this system. The progress in staging of MPM has been negatively influenced by the low incidence of the disease and also by the fact that the IMIG staging system is based on post-resection parameters. The debate about the value of staging in MPM is ongoing and some discrepancies have been noticed between the clinical and pathologic staging, emphasizing the importance of the ongoing project activities of IMIG and IASLC (32-34).

Mediastinoscopy has been advocated as a valuable staging procedure for patients eligible for radical treatment approaches. A thorough preoperative staging approach with bilateral thoracoscopy, mediastinoscopy and laparoscopy revealed that a significant proportion (26%) of MPM patients were ineligible for radical treatment (35,36).

Other factors with prognostic importance were identified by retrospective pooling of data from European Organization for Research and Treatment of Cancer (EORTC) studies in MPM patients and included poor performance status, high white blood cell count, an uncertain histologic diagnosis and male gender (37). A similar exercise carried out by the Cancer and Leukemia Group B (CALGB) revealed that elevated platelet counts, elevated serum LDH levels and the presence of chest pain were all associated with poor prognosis and further confirmed that younger age, good performance status and epithelial histology were associated with a more favorable prognosis (38). Scoring systems based on EORTC and CALGB data were independently validated and multivariate analyses showed that histologic subtype, hemoglobin level, leukocytosis and thrombocytosis remained independent prognostic factors.

The Neutrophil-to-Lymphocyte Ratio (NLR), a measure of systemic inflammation, was found to provide more

accurate prognostic information than elevated leukocyte and thrombocyte counts and was able to separate MPM patients who underwent EPP or received standard chemotherapy into different prognostic categories (29). In one study, normalization of NLR in patients receiving chemotherapy was found to be clearly associated with prognosis (39). It is interesting to speculate whether NLR is purely host related as MPM cells produce significant amounts of myeloid cell stimulating factors. Numbers of tumor-infiltrating myeloid cells and monocytes have also been found to be associated with survival of MPM patients (40), pointing to an important host-tumour interaction. The NLR may be described as an 'inflammatory performance status' and, after recent independent validations, this simple and inexpensive test is well on its way to becoming a valuable tool to select MPM patients (41-43). In addition PET scanning has been recognized as a potential tool to separate MPM patients into categories of poor and more favorable prognosis. A study from Western Australia suggested that total glycolytic volume in non-sarcomatous mesothelioma provided more important prognostic information than the anatomic extent of the tumor (44). Considering the limited number of established prognostic factors for MPM the real challenge will be to prospectively validate the prognostic value of NLR and PET in MPM.

### The way forward

Before discussing the future, it seems appropriate to repeat the carefully drafted conclusion in Van Schil's paper on trimodality therapy for MPM:

*Although a trimodality treatment consisting of induction chemotherapy followed by extrapleural resection and postoperative radiotherapy seems feasible in selected patients with early stage mesothelioma, the results of the present study do not warrant its use outside selected institutions with high level of expertise and, preferably, in prospective clinical trials exploring ways to improve its acceptance rate and overall success (21).*

It is clear that multimodality therapy for MPM should be offered only to carefully selected patients and it might be prudent to add that individual modalities should be weighted for their efficacy and morbidity. For example the proposed use of P/D as an alternative to EPP must take into account that the efficacy of the induction regimen, in combination with a less radical surgical procedure, is critical and it seems justified that radical P/D only be considered after a significant response to chemotherapy. Assessing the response to chemotherapy is notoriously difficult and as this

is considered an important element in judging a patient's eligibility for EPP, it seems appropriate to include PET scans and serial measurements of soluble mesothelin in the pre-operative work-up (45).

Locoregional (intracavitary) administration of chemotherapy remains an attractive approach for MPM as higher doses of chemotherapy can be delivered with less systemic toxicity (46-48). While results of pilot studies that combined intracavitary chemotherapy with surgery in MPM were not encouraging (49), promising results obtained with this combination in peritoneal mesothelioma justify further research in MPM (50).

The place of radical surgery in MPM and especially the morbidity and mortality associated with EPP continue to be subjects of controversy (51-54). Before expressing an opinion for or against EPP, it is important to remember how multimodality therapy for MPM has developed (55) and to accept that the debate about EPP will not be solved by renewed efforts to get an answer from a randomized study. In a time in which the oncological community is confronted with increasing numbers of subgroups within malignant diseases it is now becoming a challenge to explore alternatives (surrogates) to randomization. One of the reasons for randomization is to balance host-related and tumour related prognostic factors. If it were possible to select a specific subgroup of patients using (a set of) excellent prognostic factors, and to reproduce treatment outcomes in independent groups of patients selected by the use of the same factors, might be in better position to compare treatment options.

A dominant factor in the multimodality therapy for MPM remains the expertise of the surgeon and his or her team. The collective literature on expertise and treatment outcome allows no other conclusion other than that it is reasonable to encourage referral of MPM patients to centres with expertise. Another step forward could be made by the prospective collection of data from patients undergoing radical multimodality treatment as is being done for patients with peritoneal mesothelioma (56). The IMIG/IASLC staging project would greatly benefit from such an exercise and when combined with high-quality biobanking it would assist in collecting the materials necessary to sequence the MPM genome, a project of the TCGA/ICGC (cancergenome.nih.gov).

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