

Surgery for malignant pleural mesothelioma: an international guidelines review

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Abstract: Currently there is no universally accepted surgical therapy for malignant pleural mesothelioma (MPM). The goal of surgery in this dismal disease is a macroscopic complete resection (MCR) and there are two types of intervention with a curative intent. At one side, there is the extrapleural pneumonectomy (EPP) which consists in an en-bloc resection of the lung, pleura, pericardium and diaphragm and at the other side, there is pleurectomy/decortication (P/D) a lung-sparing surgery. Initially, EPP was considered the only surgical option with a curative aim, but during the decades P/D have acquired a role of increasing importance in MPM therapy. Several randomized prospective trials are required to establish the best strategy in the treatment of pleural mesothelioma. Although which is the best surgical option remains unclear, the International Mesothelioma Interest Group (IMIG), recently have stated that the type of surgery depends on clinical factors and on individual surgical judgment and expertise. Moreover, according to the current evidence, the surgery should be performed in high-volume centres within multimodality protocols. The aim of this study is to examine the currently available international guidelines in the surgical diagnosis and treatment of MPM.

Keywords: Pleural mesothelioma; surgery; guidelines; multimodality treatment; review

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Introduction

Malignant pleural mesothelioma (MPM) is a rare and sorrowful disease arising from the mesothelial cells of the parietal pleura. Its incidence is related to asbestos exposure with a long latency period which can even be up to 40 years, the number of deaths from MPM in Europe is expected to have peak in 2020–2025 (1,2). The optimal treatment for mesothelioma remains under debate; thus a multimodal setting is generally used, but none of the available therapies, both alone or combined, are able to ensure good long-term

survival (3).

Throughout the years different surgical approaches have been proposed (3), but a great debate around the role of surgery is currently ongoing. In case of resectable MPM (*Table 1*), during the last decade, the extrapleural pneumonectomy (EPP) was widely performed, but recently pleurectomy and decortication (P/D) and extended pleurectomy and decortication (EPD) have obtained an increasing number of consents (4).

Currently, several national and international guidelines

Table 1 VIII TNM clinical classification

Descriptor	Definition
T—primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor involves ipsilateral parietal or visceral pleura only, with or without involvement of visceral, mediastinal or diaphragmatic pleura
T2	Tumor involves the ipsilateral pleura (parietal or visceral pleura), with a least one of the following: Invasion of diaphragmatic muscle Invasion of lung parenchyma
T3	Tumor involves ipsilateral pleura (parietal or visceral pleura), with a least one of the following: Invasion of endothoracic fascia Invasion into mediastinal fat Solitary focus of tumor invading soft tissue of the chest wall Non-transmural involvement of the pericardium
T4	Tumor involves ipsilateral pleura (parietal or visceral pleura), with a least one of the following: Chest wall, with or without associated rib destruction (diffuse or multifocal) Peritoneum (via direct transdiaphragmatic extension) Contralateral pleura Mediastinal organs (oesophagus, trachea, heart, great vessels) Vertebra, neuroforamen, spinal cord Internal surface of the pericardium (transmural invasion with or without a pericardial effusion)
N—regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to ipsilateral intrathoracic lymph nodes (includes ipsilateral bronchopulmonary, hilar, subcarinal, paratracheal, aortopulmonary, paraesophageal, peridiaphragmatic, pericardial fat pad, intercostal and internal mammary nodes)
N2	Metastases to contralateral intrathoracic lymph nodes Metastases to ipsilateral or contralateral supraclavicular lymph nodes
M—distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

are available on the diagnosis and surgical treatment of MPM. Within these guidelines, several topics remain controversial, and even in case of consensus, the evidence is frequently lacking.

Methods

A systematic research on the guidelines on MPM has been conducted. To identify the articles available in the literature, MEDLINE database was used and accessed through PubMed on August 2017.

The inclusion criteria used were national and international guidelines, clear recommendations based on levels of evidence (LE) or grades of recommendation, the availability of a full text version in English and a publication date within the past ten years.

Results

After searching MEDLINE and PubMed and applying the above-mentioned inclusion criteria the included guidelines were those of the British Thoracic Society 2007 (BTS) (5), the European Respiratory Society and European Society of Thoracic Surgeons 2010 (ERS-ESTS) (6), Australian Asbestos Disease Research Institute 2013 (AUSTRALIAN) (7), European Society for Medical Oncology 2015 (ESMO) (8), Italian Society of Medical Oncology 2016 (AIOM) (9) and National Comprehensive Cancer Network 2017 (NCCN) (10).

BTS guidelines 2007 (5)

According to the BTS guidelines the role of surgery in MPM is very uncertain because there are no randomized trials to establish the role of radical surgery. The authors identified two surgical options: the EPP, more radical, and a cytoreductive/debulking surgery.

The EPP consists in en-bloc resection of the visceral and parietal pleura with the lung, pericardium and diaphragm. Considering the high mortality (operative mortality 4–9%) and morbidity (postoperative complications occur in over 60% of patients) of this intervention, it must be proposed to very selected patients. A rigorous preoperative assessment of cardiorespiratory function and an accurate staging with CT scan, PET scan and mediastinoscopy must be conducted: only T1–3, N0–1, M0 fit patients may be eligible for EPP. Unless a randomized trial, anyway, the EPP cannot be

recommended as a treatment of choice.

The less radical approach consists in the removal of as much as possible of the tumour, preserving lung, pericardium and diaphragm. This approach, performed by Mini-invasive technique or thoracotomy, may offer a better control of the symptoms with less morbidity. Furthermore, the second type of surgery has not yet been tested with randomized trial (at the time of BTS guidelines publication), then according to the panel its role is uncertain.

All patients must be informed about the risks of the procedures and the possibility of a multimodality therapy (chemotherapy and radiotherapy should be proceeded or followed surgery to improve the survival rate) to improve their survival: the greater benefits are provided by a trimodality treatment.

Lastly surgery should be centralized in high volume centres.

ERS/ESTS guidelines 2010 (6)

In the ERS/ESTS guidelines, surgery acquired a role both in diagnosis and in treatment of malignant mesothelioma. The panel in fact recommends that a cytological suspicion of MPM is followed by a tissue confirmation (Grade 1B). For diagnostic investigation, a deep and large piece of parietal pleura (preferably including fat and/or muscle) obtained with thoracoscopy biopsy, should be preferred (Grade 1A); it is recommended to take a sample of both abnormal and normal pleura (Grade 1C).

Regarding surgical treatment of MPM, the group distinguishes a radical surgery (EPP) and a symptoms control surgery [pleurectomy/decortication (P/D)].

The authors highlight the limited evidences about the efficacy of radical surgery: all procedures should be considered R1 and the EPP must be performed in specialized centres, in clinical trials and as a part of multimodality treatment.

The debulking decortication/pleurectomy consists in macroscopic but incomplete tumour resection finalized to relieve a trapped lung, removing visceral pleura, to reduce chest wall pain and to decrease the restrictive ventilatory deficit, removing parietal pleura. This type of surgery should not be proposed in a curative intent, but may be considered in symptomatic patients, who cannot benefit from chemical pleurodesis, to obtain symptoms control (Grade 2C). If possible, VATS approach should be preferred (Grade 1C).

AUSTRALIAN 2013 (7)

The role of surgery for MPM involves diagnostic procedures, debulking procedures and extensive cytoreductive operations.

According to Australian guidelines the thoracoscopy is not only the gold standard for a conclusive pathological diagnosis, but it also permits efficient drainage of pleural effusion (Grade A). In the management of patients affected by MPM, with symptomatic pleural effusion, VATS is a really useful technique to achieve a successful pleurodesis and to improve symptoms control (Grade B).

P/D is a not well-defined procedure: some surgeons use P/D referring to extensive operation for resection of visceral and parietal pleura; others use this term to describe a debulking/palliative procedure. In case of failure of thoracoscopic pleurodesis, palliative P/D should be used for symptoms control (Grade C). The role of P/D with radical purpose has not yet been shown in randomized trial.

The EPP consists in a more aggressive surgical procedure and it is believed to be, by some specialists, a more radical operation allowing better macroscopic tumour resection. Because of the high perioperative mortality and morbidity, the EPP should be executed in high volume surgical centres (Grade B).

Surgery, including P/D and EPP, should be proposed only to patients with favourable staging, histology and good performance status (Grade A). In absence of randomized trials, it is impossible to say which surgery procedure offers more benefits in term of survival, but the extensive cytoreductive surgery should be considered only as a part of a multimodality treatment (Grade B).

ESMO 2015 (8)

Surgery has an important role in diagnosis, staging and therapy of malignant mesothelioma.

Regarding the diagnosis, a large tissue sample, obtained using VATS, is preferred for pathological and molecular analyses (II, A), it is also crucial for proper patients staging (II, A).

VATS can also be used for palliation: in case of pleural effusion a talc poudrage is useful to control symptoms (II, A).

Finally, the aim of surgery with a radical intent (EPP or P/D) is to remove as much tumour as possible, to obtain macroscopic resection (III, C). The radical surgery should be inserted in a multimodality treatment plan, preferably as part of a study (II, A).

Italian Association of Medical Oncology Guidelines (AIOM) 2016 (9)

According to Italian society of medical oncology, surgery has a role in diagnosis and treatment of malignant mesothelioma. When is possible multiple biopsies of both abnormal and normal pleura, including underlying tissues, should be obtained using thoracoscopy.

Patients with resectable disease (stage I–II and selected N0–stage III) should be managed by a multidisciplinary team, including pneumologists, surgeons, oncologists (medical and radiation) and radiologists, indicating the best treatment strategy. In case of doubt about nodal status, mediastinoscopy or EBUS/EUS are recommended to assess the correct N stage.

EPP and extended P/D are the procedures with curative intent which should be performed in selected patients, with good performance status and cardiopulmonary reserve. Despite the absence of randomized trials makes difficult to determinate which is the best procedure, several studies suggest that P/D has similar survival rate than EPP, but a lower rate of complications and mortality. Radical surgical procedures should be executed only in high volume and referral thoracic centres.

The multidisciplinary team should define the best multimodality approach for each individual case, patients should receive surgical resection (P/D or EPP), adjuvant radiation therapy, and neoadjuvant/adjuvant chemotherapy.

Surgery is also useful for management of pleural effusion: talc poudrage should be used to decrease spill, dyspnea and chest pain in patients who tolerate general anaesthesia. This procedure is also recommended in patients who are candidates for EPP or P/D, because pleural adhesion minimizes the tumour dissemination and simplifies the extrapleural dissection.

NCCN guidelines version 2.2017 (10)

The aim of surgery for MPM is cytoreductive, removing all visible and palpable tumour.

Surgery should be dedicated to select patients with good performance status, with epithelioid/mixed histology if a complete gross cytoreduction can be obtained.

Surgery should be dismissed if a macroscopic complete resection (MCR) is not possible (stage \neq I–III, N2 disease), unless if the total of the disease can be removed with a minimal impact on morbidity and advantages for the

postoperative management. Only surgeons with expertise in MPM should indicate and should perform the surgical resections.

The NCCN panel believes that EPP and P/D are both effective surgical options that should be considered in select patients in the context of multimodal treatment. It is not clear which surgical procedure can ensure better oncologic results, however neither P/D nor EPP can't guarantee an R0 resection. In case of early stage (stage I, N0–1) with epithelioid histology P/D should be considered the first choice of treatment.

Surgery is not recommended for stage IV MPM or sarcomatoid histology. In case of N2 disease or mixed histology surgical operation should be indicated only in high volume centres or in the context of clinical trials.

Pleurodesis and debulking P/D are palliative surgical procedures used to limit pleural effusion and to relieve pain. VATS has a palliative role (e.g., pleurodesis), but it is not accepted to perform the P/D.

Discussion

As of today, there is no international agreement regarding surgical treatment of mesothelioma with curative intent.

Oppositely the role that surgery has in the treatment of solid tumours, for MPM all surgical strategies would not be radical, but cytoreductive (11). MCR should be considered the goal of MPM surgery, which is generally used in a multidisciplinary plan of therapies.

There are two types of curative-intent surgical procedures: P/D and EPP.

The EPP is a broadly standardized operation with en-bloc resection of parietal and visceral pleura, underlying lung, pericardium and diaphragm. On the other hand the correct meaning of P/D is still confused; because of the term P/D is applied to variety of different procedures, in 2011 the International Study of Lung Cancer (IASLC) and International Mesothelioma Interest Group (IMIG) proposed a classification into three different categories: (I) partial pleurectomy (PP), a cytoreductive procedure used for diagnostic or palliative intent, without the purpose of a MCR; (II) P/D, a complete resection of parietal and visceral pleura; (III) extended P/D (EPD), parietal and visceral pleurectomy with additional resection of pericardium and/or diaphragm (12).

A great debate around the best surgical option is still ongoing and discrepancies regarding recommendations for

EPP and P/D exist obviously. On the one hand EPP seems to be more radical than P/D (13,14), on the other hand P/D appears to have lower mortality and morbidity rate (15,16). Because of the absence of randomized trials comparing long term survival and results of P/D and EPP, which is the best surgical procedure remains clouded.

The BTS and ERS/ESTS guidelines declare that radical surgery should be addressed only to selected patients, as a part of a multimodal treatment algorithm and in specialized high-volume centres. According to panels, because of the role of surgery remains uncertain, this treatment should be used only in clinical trials. Both BTS and ERS/ESTS distinguish a radical surgery (EPP) and a symptoms control surgery (P/D), the groups do not recognize P/D as a procedure with curative purpose, but only obtaining symptoms control. Recently, several studies have established the role of P/D with a curative intent, therefore these outdated guidelines should probably be edited.

The European Society of Medical Oncology and the Italian consensus conference on mesothelioma state that also P/D has a role in radical treatment of mesothelioma. According to Italian guidelines P/D is advantageous for patients with early-stage disease and EPP achieves satisfactory local control of MPM. The ESMO recommend entrusting the management of patients to a multidisciplinary team with suitable experience which should guarantee a personalized tri-modality therapy plan.

The Australian guidelines believe both EPP and P/D as radical surgery and recommend to offer such procedures only to patients with favourable staging, histology and good performance status and should be considered only as a part of a multimodality treatment.

Finally, NCCN guidelines state that surgical procedures should be utilised only for patients with good performance status and with stage I–III MPM. In case of early stage (stage I, N0–1) with epithelioid histology P/D should be considered the first choice of treatment.

Taken all this information together it is clear that no worldwide accepted surgical intervention for mesothelioma exists. The sole point on which the guidelines agree is that the surgery should be executed by skill surgeons in high-volume centres and should be considered only in a multimodality treatment plan for selected patients.

The absence of randomized trial comparing P/D and EPP leaves open the question about which is the best surgical choice for MPM resectable patients.

EPP is an aggressive approach associated with high

mortality and morbidity rate (17). Cao *et al.* (18) in a systematic review on EPP reported a mortality rate of 0–11.8% and morbidity rate of 22–82%. The median overall survival (OS) diversified from 9.4–27.5 months and the 1-, 2- and 5-year survival rates from 36–83%, 5–59% and 0–24% respectively. The retrospective analysis on IASLC database (19) reported a median OS of 40 months after EPP for early stage MPM.

The role of EPP is widely discussed after the publication of MARS trial, a prospective randomized study which compared outcomes of patients who were randomly assigned to EPP or to chemotherapy alone (20). The trial exposed that EPP within tri-modality therapy tendered no survival benefits and could be detrimental for treated patients.

P/D is notionally considered to be less radical than EPP, but several studies reported an equal or even better survival results compared to EPP (15,21). Preservation of the underlying lung seems to guarantee a lower mortality and morbidity rate: Cao *et al.* reported a perioperative mortality of 2.9% (*vs.* 6.8% of EPP) and morbidity of 27.9% (*vs.* 62% of EPP) (15), Flores showed a mortality and morbidity rate of 4% (*vs.* 7% of EPP) and 6.4% (*vs.* 10% of EPP) respectively (22). Several authors also insisted on the importance of a case-by-case patient's characteristics evaluation: the EPP and P/D should not be considered as alternative approaches (22,23) and P/D could be used in a greater number of patients because of its lower mortality and morbidity rate, with similar long-term survival rate (24).

Many authors highlighted that patients treated with P/D have the possibility for more additional therapies in case of recurrence compared to whom were treated with EPP, with a longer survival (25–27). Moreover, the quality of life (QoL) appeared to be better after P/D over EPP (28,29). Because of local recurrence is one of the most important problems arising after surgery, which occurs in 60% of cases approximately (22), recently a wide range of additional intraoperative treatment has been proposed with the aim to reduce the risk of relapse.

Friedberg suggested the use of intracavitary photodynamic therapy (PDT) after P/D or EPP (30), a recent review considered intrapleural PDT as a feasible procedure with minimum toxicities, but randomized trials are required to define the benefits of this technique (31).

The use hyperthermic intraoperative lavage with povidone-iodine solution or with chemotherapy agents (e.g., cisplatin, doxorubicin + cisplatin) seemed to give good results without additional toxicities (32–35).

Palliative surgery

Generally, mesothelioma is diagnosed in advanced stage, when a MCR with curative intent is not possible. In this phase of disease, the surgery acquires an important role for symptoms control, VATS pleurodesis or PP appeared to be effective procedures to manage recurrent pleural effusion or entrapped lung (6,8,36). Palliative surgery should be executed by VATS to decrease the longer postoperative recovery and the likely detrimental effects of thoracotomy (37). The MESOVATS trial, a randomized study likening VATS pleurectomy *vs.* talc pleurodesis (via thoracoscopy or via chest drain-talc slurry), has shown that VATS-PP did not improve survival and talc pleurodesis should be preferred due to the fewer complications and the shorter hospital stay (38).

Conclusions

Although there is no clear evidence about the role of surgery in mesothelioma, IMIG settled that: (I) MCR and control of micrometastatic disease play a vital role in the multimodality therapy of MPM, as is the case for other solid malignancies; (II) surgical cytoreduction is indicated when MCR is deemed achievable; (III) the type of surgery (EPP or P/D) depends on clinical factors and on individual surgical judgment and expertise; (IV) all patients with the diagnosis of MPM should be initially evaluated in a multidisciplinary setting, including medical oncology, radiation oncology, and surgery; (V) the histological subtype should be identified by tissue biopsy before initiation of therapy (39).

According to the current evidences, the surgery should be performed in high-volume centres within multimodality protocols and the best surgical option must be tailored to the patient.

Currently there is no universally accepted surgical therapy for MPM. Initially P/D was considered only palliative, but during the decades its role was redefined and this type of surgery gained an important position as a radical surgery. Recent studies have shown that survival time after EPP and P/D is similar, while mortality and morbidity are higher post EPP (24,40,41).

Moreover, patients treated with P/D appear to have more chances for additional therapies after surgery, also in case of recurrence. Therefore, survival after recurrence seems to be better in patients initially treated with P/D (25,27).

Nowadays multimodality treatment is considered the cornerstone of care in MPM and surgery should be

considered an important part of this strategy. A surgical approach which is less mortal and morbid appears to ensure better QoL and greater adherence to adjuvant therapies in treated patients.

In this complex scenario is clear that further studies and a constant revision of guidelines are mandatory to establish the best treatment for this dismal disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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