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REVIEW ARTICLE

The role of surgery in the management of malignant pleural mesothelioma

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Summary

Malignant pleural mesothelioma (MPM) is a relatively rare multifocal pleural tumor with low metastatic potential. Surgery can be used in MPM for diagnostic and therapeutic purposes. Thoracoscopy is a useful tool to obtain tissue biopsy to establish a definitive diagnosis and to perform talc poudrage of the pleural cavity in order to prevent reaccumulation of fluid. Cytoreductive procedures, such as pleurectomy/decortication (PD) and extrapleural pneumonectomy (EPP) are also used in multimodal treatment protocols.

The available evidence until now suggests that EPP offers better palliation of dyspnea and orthopnea due to a trapped lung and ventilation perfusion mismatch and better adjuvant radiation therapy planning when compared to PD. Better local disease control and obvious survival benefit by using EPP instead of PD are at the moment unproven. However, EPP is connected with high mortality and morbidity rates, especially if performed in centers without expertise with this complex procedure. EPP and thoracoscopic parietal pleurectomy are now tested in two ongoing prospective randomized trials for their efficacy in the treatment of this disease. In the absence of any controlled randomized trial, EPP should be considered as part of the treatment of MPM only within the context of a prospective randomized trial or in special centers with expertise in the procedure and always within a tri-modal or four-modal treatment protocol, including also chemotherapy, radiotherapy, intrapleural immunochemotherapy and laser photodynamic therapy.

Key words: cytoreductive surgery, extrapleural pneumonectomy, malignant pleural mesothelioma, pleural tumors, pleurectomy/decortication, video-assisted thoracoscopy

Introduction

Malignant pleural mesothelioma (MPM) is an uncommon malignancy with unique characteristics, which is difficult to approach and to properly manage [1]. MPM is a multifocal tumor which invades all the mesothelial surfaces within the involved hemithorax (visceral, parietal, mediastinal and diaphragmatic pleura). MPM respects the tissue planes and it is confined within the pleural envelop until a relatively advanced stage, where the tumor spreads to infiltrate the surrounding structures (mediastinal organs, chest wall, diaphragm) [1,2]. MPM has 3 distinct histologic subtypes, which are the epithelial, the sarcomatoid and the mixed or biphasic. The epithelial subtype has longer survival when compared to other subtypes [1-3].

MPM is relatively resistant to chemotherapy and radiotherapy and there is lack of a standard therapy worldwide [1,4]. In addition, it is not easy, even with the newest imaging modalities, to accurately stage the disease and to monitor the results of treatment [4-6]. Lack of randomized trials concerning the results of surgical treatment creates confusion over the optimal treatment of this disease.

Two staging systems are currently in use to stage MPM: the Brigham staging system (1993) and the International Mesothelioma Interest Group staging system (1995) (Table 1 and 2) [5]. Although staging has little use for the medical management of the disease, it has extreme value for any curative surgical manipulation [1]. Many of the available studies on the surgical management of MPM vary as to which staging system

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Table 1. The Brigham system for staging MPM

Stage	*Description*
I	Disease confined within the capsule of the parietal pleura, involving only ipsilateral pleura, lung, pericardium, diaphragm, or chest wall disease limited to previous biopsy sites
II	All of stage I with positive intrathoracic lymph nodes (N1 and N2)
III	Local extension of disease into chest wall or mediastinum or heart or peritoneum through the diaphragm; With or without extrathoracic or contralateral (N3) lymph node involvement
IV	Distant metastatic disease

was used and discrepancies between the various staging systems used in the past result in non-uniformity of reporting [4].

MPM is well related to asbestos exposure, but the mechanism of carcinogenesis is not fully understood [1-5]. Despite the use of asbestos is prohibited and avoided in the European Union and the United States, an increase in MPM victims is expected during the next two decades from previous exposure of humans to asbestos, 20-40 years ago [1].

The role of surgery in the management of MPM still remains controversial and the available evidence will be summarized.

Indications for surgery in MPM management

Surgery has 4 main indications in the management of mesothelioma:

a) To establish a definitive diagnosis.

b) To palliate the devastating symptom of dyspnea that is connected with recurrent pleural effusions.

c) To accurately stage the disease before surgical treatment.

d) To offer cytoreductive and radical procedures within the multimodal treatment protocols currently in use.

A. Establishing a definitive diagnosis

In most cases cytology of the pleural fluid is not able to establish the diagnosis of MPM and cannot contribute to the differential diagnosis from adenocarcinomas spreading to the pleura [1,5-7]. The definitive diagnosis of MPM requires almost always pleural biopsy [5-8]. Video-assisted thoracoscopy (VATS) is the most useful diagnostic tool to obtain the appropriate pleural

Table 2. The International Mesothelioma Interest Group system for staging diffuse MPM

Stage	*Definition*
T1	T1a: Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura: no involvement of visceral pleura
	T1b: Tumor involving the ipsilateral parietal pleura, mediastinal and diaphragmatic pleura; scattered foci of tumor involving also the visceral pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura)
	Involvement of diaphragmatic muscle
	Confluent visceral pleural tumor (including fissures) or extension of the tumor into the underlying lung parenchyma
T3	Describes locally advanced but potentially resectable tumor
	Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral) with at least one of the following features:
	Involvement of the endothoracic fascia
	Extension into the mediastinal fat
	Solitary, completely resectable focus of tumor extending into soft tissues of the chest wall
	Nontransmural involvement of the pericardium
T4	Describes locally technically unresectable tumor
	Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral) with at least one of the following features:
	Diffuse extension of multifocal masses of tumor in the chest wall, with or without associated rib destruction
	Direct transdiaphragmatic extension of the tumor to the peritoneum
	Direct extension of the tumor to the contralateral pleura
	Direct extension of the tumor to one or more mediastinal organs
	Direct extension of the tumor into the spine
	Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion, or tumor involving the pericardium
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes
Mx	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastasis present

Stage grouping: Stage I: Ia: T1aN0M0, Ib: T1bN0M0; Stage II: T2N0M0; Stage III: Any T3M0, Any N1M0, Any N2M0; Stage IV: Any T4, Any N3, Any M1

specimen for histologic and immunohistochemical examination [5-7]. Thoracoscopy allows the operator to completely drain the pleural effusion, to inspect the whole pleural cavity and to make an estimation of the extent of the disease within the involved hemithorax. In addition, the operator can perform talc pleurodesis in order to stop recurrence of the effusion [5-7]. Talc pleurodesis is not recommended in cases where the macroscopic aspect of the pleura is not indicative of a malignant lesion [7]. The only major hazard of thoracoscopy is seeding of the chest wall with tumor cells and the development of chest wall implants [5,9]. The recent development of uniportal VATS techniques offers additional advantage by limiting the chest wall ports to one, limiting that way the sites of possible chest wall seeding.

VATS procedures are superior to any other blind, percutaneous needle biopsy (i.e. Abrams needle), which fail in many instances to establish the diagnosis (diagnostic yield of about 30%), resulting that way in delay on diagnosis and treatment [5-7].

In some advanced cases, where the tumor consumes more of the hemithorax and fuses the lung to the chest wall, the definitive diagnosis can be made by mini thoracotomy, resection of a small piece of one rib and then direct biopsy of the underlying parietal pleura / tumor [5,7].

B. Palliation of dyspnea due to recurrent pleural effusion

Most of MPM victims (60-80%) present with symptoms associated with a large pleural effusion, such as breathlessness and aggravated dyspnea on exertion [1,5,6]. Pleural effusion tends rapidly to re-accumulate after simple drainage. Performing a permanent pleurodesis is of great importance for the patient because he will become free of symptoms and will avoid repeated admissions for thoracocentesis. Repeated thoracocentesis has in addition the potential danger to induce painful chest wall implants [6,7].

Permanent pleurodesis can be achieved by 3 ways:

1) by chest tube insertion, evacuation of the effusion and instillation of sclerosing agents within the pleural cavity through the chest tube. The commonly used sclerosing agents are slurry talc (4 g), tetracycline (1 g) and bleomycin (60-90 mg). The success rate is higher for slurry talc pleurodesis (70-100%) vs. bleomycin or tetracycline pleurodesis (60-85%) [9,10].

2) by thoracoscopic talc poudrage (4 g of sterile talc), which has the higher success rate (>90%) [9-11].

3) by performing open or thoracoscopic parietal pleurectomy.

In cases of lung entrapment by the neoplastic peel covering most of the visceral pleura surface, the surgeon can implant a permanent tunnelled pleural catheter (Pleur-X pleural catheter system, Denver Biomedical, Colorado) that allows continuous drainage of the effusion within a plastic vacuum bottle, through a one-way valve mechanism. Spontaneous pleurodesis is reported to be achieved in about 50% of patients with this system within a few (4-6) weeks. The system enables physicians to manage patients in a home setting [7,12].

MPM behavior is similar to that of soft tissue sarcomas and any "hole" made in the chest wall to insert chest tubes or a port for VATS or a needle for thoracocentesis / pleural biopsy can be the site of a chest wall implant in the near future [4-6]. External radiation should be applied in any chest wall incision made for diagnostic or therapeutic purposes according to British Thoracic Society guidelines for the management of mesothelioma [6]. Three randomized controlled trials and 4 retrospective series are available on the topic of prophylactic drain site radiotherapy in mesothelioma with inconsistent results (Table 3) [13-20]. The value of uniportal VATS techniques is highlighted by eliminating the sites of possible chest wall seeding.

Table 3. Published series on radiotherapy to mesothelioma drain sites

Year of publication	*First author [Ref. no.]*	*Study design*	*No. of included patients*	*RT group Chest wall implants (%)*	*No RT group Chest wall implants (%)*
1995	Boutin [14]	RCT	40	0	40
1995	Low [15]	RS	20	0	N/A
2004	Bydder [16]	RCT	43	7	10
2004	Cellerin [17]	RS	33	22	48
2005	Pinto [18]	RS	85	N/A	0
2006	West [19]	RS	37	5	N/A
2007	O'Rourke [20]	RCT	61	23	10

RCT: randomized controlled trial, RS: retrospective series, RT: radiotherapy, N/A: non applicable

C. Accurate pre-invasive staging of the disease

Accurate staging of the disease within a multimodal approach including cytoreductive or radical surgical procedures cannot be made by imaging modalities alone. PET-CT scan is inaccurate for the evaluation of transdiaphragmatic extension of the tumor within the abdomen and mediastinal lymph node metastasis [4,7,21,22]. Higher SUV rates in the primary tumor are associated with increased rate of nodal metastasis and poorer survival rates [7,21]. However, the final diagnosis of possible nodal metastasis and/or transdiaphragmatic extension of the tumor will be made only with invasive techniques [4,7,21,22].

Aggressive invasive pre-treatment staging of the disease includes cervical mediastinoscopy to rule out invasion of ipsilateral (N2) or contralateral (N3) mediastinal lymph nodes, laparoscopy and peritoneal lavage to look up for transdiaphragmatic extension of the tumor within the abdomen or silent peritoneal metastasis and contralateral VATS exploration to exclude involvement of the contralateral pleura [23,24]. However, the French Speaking Society for Chest Medicine does not recommend aggressive staging with laparoscopy and contralateral VATS and recommends mediastinoscopy only in patients in whom CT scan or PET-CT scan suggest invasion of mediastinal lymph nodes [9]. The topic of aggressive invasive staging before multimodal treatment including radical surgery still remains debatable. Indeed, cervical mediastinoscopy to exclude N2 or N3 disease should always be performed before radical surgery, because nodal metastasis has a serious negative impact on survival after radical surgery [5,7,25,26].

D. Palliative, cytoreductive and radical surgical procedures for MPM treatment

Three surgical techniques are available for the surgical treatment of MPM: parietal pleurectomy (PP), pleurectomy-decortication (PD) and extrapleural pneumonectomy (EPP).

Open or thoracoscopic parietal pleurectomy is almost always a palliative technique to achieve pleurodesis and tumor debulking in cases with parietal pleural deposits and minimal or no obvious visceral pleural involvement [27]. PP is a relatively safe procedure (mortality rate <2%), but the same result (permanent pleurodesis) can be reached with simpler and less traumatic techniques, such as VATS talc poudrage. Complications of pleurectomy include prolonged air leak, hemorrhage, pneumonia and subcutaneous emphysema, and, rarely, empyema and vocal cord paralysis [27].

Pleurectomy and decortication is a debulking (cytoreductive) procedure that is also referred to as "limited surgical management" [6,28,29]. PD is not a well defined operation, because its description is variable in the surgical literature. The term PD is used to describe one of the following operations:

a) parietal pleurectomy and resection of the major visceral pleura deposits [30].

b) parietal pleurectomy and full lung "decortication" which is described as the resection of parietal pleura and visceral decortication, including lung fissures. The operation is described also as "subtotal PD" [23]. Decortication is only partially possible in mesothelioma and only when the tumor can be peeled off, which is not always the case without producing extensive air leaks (Figure 1) [31].

c) parietal pleurectomy and full lung decortication plus resection of the hemidiaphragm and pericardium and replacement of both structures with synthetic materials, an operation reported as "radical PD" or "total PD" [32].

The proper indications to proceed with PD in MPM are not clear and the ideal candidate to undergo PD is not known. The procedure could be applied in patients with diminished performance status or in multimorbid patients who cannot tolerate an extrapleural pneumonectomy. PD could also be applied in patients with locally advanced disease (i.e. with mediastinal lymph node invasion or invasion beyond the pleural envelop) where EPP is not indicated [5,29-33]. Results of PD in treating MPM in most of the published series are presented in Table 4 [29,32,34-44]. Cytoreduction obtained with PD has acceptable mortality rates (2.2-8.3%), while the median survival ranges in different series between 9 and 18.3 months. Morbidity rates are reported to range between 3.7 and 50% [45]. The commonest complications of PD are prolonged air leak

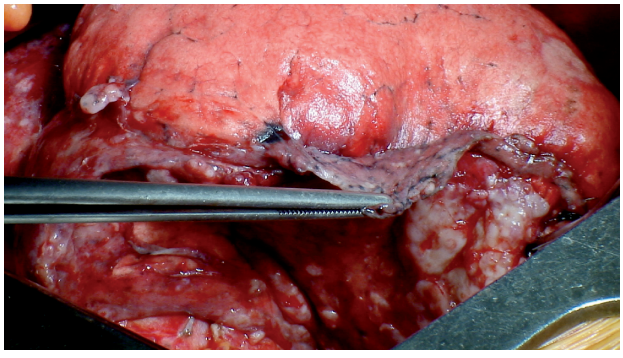

Figure 1. Pleurectomy/decortication of the left lung for malignant pleural mesothelioma. The decorticated lung expands well. Multiple deposits in the visceral pleura of the non-decorticated yet surface of the lung (from AHEPA University Hospital, Department of Cardiothoracic Surgery).

Table 4. Results of pleurectomy/decortication for malignant pleural mesothelioma, with or without the addition of adjuvant therapy, in most of the published series

First author, year of publication [Ref. no.]	*Patients and treatment*	*Mortality (%)*	*Morbidity (%)*	*Median survival (months)*
Rusch, 1994 [34]	27 PD + CT	3.7	44	18.3
Lee, 1995 [35]	15 PD + CT	0	13	11.5
Sauter, 1995 [36]	13 PD + CT	N/A	N/A	9.0
Colleoni, 1996 [37]	20 PD + CT	N/A	15	11.5
Alberts, 1988 [38]	26 PD	N/A	3.7	10.9
Achatzy, 1989 [39]	46 PD	N/A	4.3	10.1
	72 subtotal PD	N/A	11.1	10.1
Ball, 1990 [40]	13PD	N/A	N/A	17.0
Brancatisano, 1991 [41]	45 subtotal PD	2.2	16	16.0
Soysal, 1997 [42]	100 total & subtotal PD	1	22	17.0
Ceresoli, 2001 [43]	38 PD	N/A	N/A	12.5
	16 PD + CT	N/A	N/A	14.0
Lee, 2002 [44]	32 PD	N/A	6.2	18.1
Phillips, 2003 [29]	15 PD	6.7	20	14.0
Martin-Ukar, 2005 [32]	12 PD ± RT, CT	8.3	50	16.0

CT: chemotherapy, RT: radiotherapy, PD: pleurectomy/decortication, N/A: non applicable

(40%), empyema and atrial dysrhythmias. PD is less technically demanding than EPP and therefore it can be performed in most centers [4].

Contrary to PD, *extrapleural pneumonectomy or pleuro-pneumonectomy* is a well defined operation involving *en bloc* resection of the lung and pleura through the extrapleural plane of dissection and resection and reconstruction by using synthetic materials of the hemidiaphragm and pericardium plus resection of any previous biopsy scar(s). Good results of EPP within a multimodal approach of the disease were reported for the first time by Sugarbaker et al. in 1999 [25]. The median survival had reached 51 months and the reported 5-year survival was 46% in a subset of patients with stage I disease, epithelial histology and negative resection margins [25]. The question was if EPP for MPM is a really radical resection with no residual disease (R0 resection) and if negative resection margins can be obtained at the end of the operation. The answer was given by Sugarbaker in 2007 who stated that "the goal of primary surgery for MPM is to achieve macroscopic complete resection" and consequently EPP is definitely considered today to be a "radical" cytoreductive procedure (R1 resection) [46].

The ideal candidate to undergo EPP is the good risk for major surgery patient according to age (less than 75 years old and ideally less than 60 years old), performance status (Karnofsky score >70) and preoperative evaluation with pulmonary function tests (FEV_1 >2 L), liver and renal function tests, Doppler echocardiography (EF >45% and absence of pulmonary hypertension), stress Doppler echocardiography, lung perfusion scan and arterial blood gases determination (pO_2 >65 mm Hg on breathing room air and pCO_2 < 45 mm Hg) [5,6,47]. Epithelial histology of the tumor and stage I disease (Brigham staging system) are prerequired conditions to perform EPP in most centers [6,48]. The question to be answered is how much this good selection of patients contributes to good results of radical surgery with EPP.

EPP is a major procedure that adds significant risk to the patient. Mortality rates vary from 3.7% in centers with large experience with the procedure to 50% in older series and inexperienced centers. The morbidity rates vary from 25 to 60%, including complications related to pneumonectomy and specific complications related to the procedure itself (Table 5) [47,49,50]. EPP on the right side and transfusion of more than 4 units of packed red blood cells intraoperatively are significant risk factors for major complications [50].

Failure of surgery for MPM

Recurrence of MPM after surgery can be distinguished between local recurrence, observed within the operated hemithorax, and distant recurrence, observed within the abdomen or the contralateral hemithorax [51]. Metastasis to other organs is a rare event in the course of the disease [30]. Local recurrence is considered preventable by using EPP instead of PD and by using high-dose adjuvant radiation therapy (45-60 Gy), which is impossible to apply in the presence of the lung as in PD [1,4,30,51].

Table 5. Complications observed after extrapleural pneumonectomy for malignant pleural mesothelioma according to Sugarbaker et al [49].

Complication	*Rate (%)*
Atrial fibrillation	44.0
Prolonged tracheal intubation	7.9
Deep venous thrombosis	6.7
Vocal cord paralysis	6.7
Technical complications: pericardial or diaphragmatic patch failure and postoperative bleeding	6.1
ARDS	3.6
Cardiac tamponade	3.5
Cardiac arrest	3.0
Constrictive cardiac physiology (inflammatory pericarditis)	2.7
Renal failure	2.7
Thoracic empyema	2.5
Myocardial infarction	1.5
Pulmonary embolism	1.5
Bronchopleural fistula	<1.0
Chylothorax	<1.0

ARDS: acute respiratory distress syndrome

Performing pleurodesis at the time of thoracoscopic pleural biopsy is considered to prevent local recurrences and recurrences within the abdomen after EPP, because the tumor will be eliminated within the firmly adherent pleural surfaces and consequently, it will be resected *en bloc* with the lung without handling with the contaminated with malignant cells pleural space during surgery [7].

Comments

Little evidence is available for the role of surgery in treating MPM. Maziac et al. [45] in their systematic review conclude that "even if surgery is very aggressive, patients usually succumb to their disease within 2 years" [45]. Treasure et al. state that, in the absence of evidence, a doctor with a particular point of view should not deny active treatment in a patient with lethal cancer and should not also put a patient through extreme treatments [52].

Recently published trials using multimodality treatment protocols including chemotherapy, radiotherapy, intrapleural immunochemotherapy and surgery (EPP or PD) detected only small gains in survival (median survival between 19 and 26 months) and symptoms control by using these well intentioned radical treatments (Table 6) [53-57]. On the other hand, these radical treatments are connected with increased morbidity (52.4-62.4%) [54-57]. In addition, one should keep in mind that radical treatments for MPM and the morbidity associated with them will occupy the first 3 months after the establishment of diagnosis, which are the best 3 months of the remaining life of the patient with a fatal disease [58].

The Institute for Cancer Research in the United Kingdom runs from 2005 a prospective randomized trial named "Mesothelioma And Radical Surgery" (MARS trial) to delineate the role of EPP in the treatment of MPM. Patients who will enter the trial protocol will receive 3 cycles of induction chemotherapy before their randomization in one of the two arms of the study. In the first arm patients will undergo EPP and will receive adjuvant radiation therapy in the operated

Table 6. Main results of recently published prospective studies using multimodality (trimodality and four-modality) treatment protocols

First author, year of publication [Ref. no.]	*No. of included patients*	*Stage/type of operation*	*Chemotherapy*	*Postoperative radiation*	*Median survival (months)*	*Morbidity (%)*
Weder, 2007 [53]	61	T1-3, N0-2/EPP	cisplatin+gemcitabine	High-risk areas, 45-60 Gy	19.8	N/A
Lucchi, 2007 [54]	49	II-III/PD	intrapleural IL-2 cisplatin + gemcitabine + s.c. IL-2	Targeting scars and residual disease 30 Gy	26.0	No grade IV toxicity
Rea, 2007 [55]	21	I-III / EPP	cisplatin+gemcitabine	Hemithoracic 45 Gy	25.5	52.4
Flores, 2006 [56]	21	T3-4, N0-2/EPP	cisplatin+gemcitabine	Hemithoracic 54 Gy	19.0	No grade IV toxicity
Opitz, 2006 [57]	72	T1-3, N0-2 / EPP	cisplatin+gemcitabine or cisplatin+pemetrexed	Optional (75% treated)	23.0	62.0

IL-2: interleukin 2, EEP: extrapleural pneumonectomy, PD: pleurectomy/decortication, N/A: non applicable

hemithorax. In the second arm patients will undergo any other form of treatment such as chemotherapy, radiotherapy and less major than EPP surgery. The pilot study enrolling 50 patients is expected to be completed until the end of 2008. If the results of the pilot study are encouraging, the study will expand to enroll a total of 700 patients worldwide. The main end points of the MARS trial are the possible benefits of radical surgery (EPP) on survival and quality of life [7,52].

Another controlled randomized trial (the Meso-VATS trial) which compares the effectiveness of VATS pleurectomy vs. chest tube talc pleurodesis in controlling recurrent pleural effusion in MPM victims is ongoing in the United Kingdom (Institute for Cancer Research). The trial will recruit 196 patients in two groups and enrollment of patients will stop at the end of 2009 [6].

The unpublished recent personal experience of the first of the 3 co-authors of the present review article has demonstrated that the management of 13 MPM patients with VATS talc pleurodesis plus port-site radiotherapy and chemotherapy has resulted in a median survival of 14 months and quite good quality of life for the first 10-12 months after the diagnosis. Prolonged median survival (19.4 months) is also reported by Aelony and Yao in their case-series (2005) by thoracoscopic talc poudrage alone or in combination with radiotherapy or chemotherapy [59].

Intraoperative laser photodynamic therapy (PDT) is another surgical technique for local disease control and prevention of local recurrences after radical or cytoreductive surgery. PDT is a local treatment for a disease with high tendency for local recurrence but low metastatic potential [60]. PDT is a promising technique for the "sterilization" of the pleural cavity after surgery [60,61]. Some technical problems need to be solved in the near future concerning the application of intracavitary (intrapleural) PDT [60,61]. Two future interesting options are: first, the minimally invasive surgical management of the disease by performing VATS PD and intraoperative PDT; and second, the intraoperative addition of PDT after EPP performed for early-stage disease [60]. A lot of research work is currently under progress in this topic.

The available evidence until now suggests that EPP offers better palliation of dyspnea and orthopnea due to a trapped lung and ventilation perfusion mismatch and better adjuvant radiation therapy planning when compared to PD. Better local control of the disease and obvious survival benefit by using EPP instead of PD are at the moment unproven considerations [30, 45,58].

The available evidence for the current role of surgery in the management of MPM is summarized as follows:

1. Uniportal thoracoscopy is the best way to establish a definitive diagnosis and to achieve long-lasting pleurodesis.

2. Cytoreductive procedures, and especially EPP, should be offered in good risk patients within a multimodal therapeutic approach. The decision should always be made by a multidisciplinary team.

3. Invasive staging with mediastinoscopy and possibly with laparoscopy is a necessary step before proceeding with EPP.

4. EPP should be performed only in stage I disease according to Brigham staging system and only in centers with expertise in this complex procedure.

References

1. Robinson WBS, Musk AW, Lake RA. Malignant mesothelioma. Lancet 2005; 336: 397-408.
2. Bueno R, Gordon GJ. Genetics of malignant pleural mesothelioma: molecular markers and biologic targets. Thorac Surg Clin 2004; 14: 461-468.
3. Zellos L, Christiani DC. Epidemiology, biologic behavior and natural history of mesothelioma. Thorac Surg Clin 2004; 14: 469-477.
4. Cersoli GL, Gridelli C, Santoro R. Multidisciplinary treatment of malignant pleural mesothelioma. The Oncologist 2007; 12: 850-863.
5. Paul S, Neragi-Miandoab S, Jaklitsch MT. Preoperative assessment and therapeutic options for patients with malignant pleural mesothelioma. Thorac Surg Clin 2004; 14: 505-516.
6. Truong MT, Marom EM, Erasmus JJ. Preoperative evaluation of patients with malignant pleural mesothelioma: Role of integrated CT-PET imaging. J Thoracic Imaging 2006; 21: 146-153.
7. BTS statement on malignant mesothelioma in the UK, 2007. British Thoracic Society Standards of Care Committee. Thorax 2007: 62 (Suppl 2): ii1-ii19.
8. Stojsic J, Spasic Z, Velinovic M et al. Diagnostic procedures for malignant pleural mesothelioma: our experience. J BUON 2004; 9: 423-426.
9. Scherpereel A, French Speaking Society for Chest Medicine for management of malignant pleural mesothelioma. Resp Med 2007; 101: 1265-1276.
10. Foroulis C, Kotoulas C, Konstantinou M, Lioulias A. The management of malignant pleural effusions: talc pleurodesis versus bleomycin pleurodesis. J BUON 2001; 6: 397-400.
11. Shaw P, Agrawal R. Pleurodesis for malignant pleural effusions. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002916. DOI: 10.1002/14651858.CD002916.pub2
12. Brubacher S, Gobel BH. Use of the Pleurx Pleural Catheter for the management of malignant pleural effusions. Clin J Oncol Nurs 2003; 7: 35-38.
13. Muirhead R, O'Rourke N. Drain site radiotherapy in malignant pleural mesothelioma: a wasted resource. Eur Resp J 2007; 30: 1021.

14. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with malignant pleural mesothelioma. A randomized trial of local radiotherapy. Chest 1995; 108: 754-758.
15. Low EM, Khoury GG, Matthews EW, Neville E. Prevention of tumour seeding following thoracoscopy in mesothelioma by prophylactic radiotherapy. Clin Oncol (R Coll Radiol) 1995; 7: 317-318.
16. Bydder S, Phillips M, Joseph DJ et al. A randomised trial of single-dose radiotherapy to prevent procedure tract metastasis by malignant mesothelioma. Br J Cancer 2004; 91: 9-10.
17. Cellerin L, Garry P, Mahe MA, Chailleux E. Malignant pleural mesothelioma: radiotherapy for the prevention of seeding nodules. Rev Mal Respir 2004; 21: 53-58.
18. Pinto C, Sperandi F, Marino A, Mutri V, Martoni A. Is prophylactic radiotherapy necessary as prevention of tumor seeding following thoracoscopy in malignant pleural mesothelioma (MPM)? Lung Cancer 2005; 49 (Suppl 2): S227 (abstr).
19. West SD, Foord T, Davies RJ. Needle-track metastases and prophylactic radiotherapy for malignant mesothelioma. Respir Med 2006; 100:1037-1040.
20. O'Rourke N, Garcia JC, Paul J, Lawless C, McMenemin R, Hill J. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. Radiother Oncol 2007; 84: 18-22.
21. Flores RM. The role of PET in the surgical management of malignant pleural mesothelioma. Lung Cancer 2005; 49 (Suppl 1): S27-S32.
22. van Meerbeeck JP, Boyer M. Consensus report: pre-treatment minimal staging and treatment of potentially resectable malignant pleural mesothelioma. Lung Cancer 2005; 49 (Suppl 1): S123-S127.
23. Rice DC, Erasmus JJ, Stevens CW et al. Extended surgical staging for potentially resectable malignant pleural mesothelioma. Ann Thorac Surg 2005; 80: 1988-1993.
24. Alvarez JM, Musk W, Robins P, Price R, Byrne MJ. Importance of mediastinoscopy, bilateral thoracoscopy, and laparoscopy in correct staging of malignant mesothelioma before extrapleural pneumonectomy. J Thorac Cardiovasc Surg 2005; 130: 905-906.
25. Sugarbaker DJ, Flores RM, Jaklitsch MT et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999; 117: 54-65.
26. de Perrot M, Uy K, Anraku M et al. Impact of lymph node metastasis on outcome after extrapleural pneumonectomy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2007; 133: 111-116.
27. Sterman DH, Kaiser LR, Albelda SM. Advances in the treatment of malignant pleural mesothelioma. Chest 1999; 16: 504-520.
28. Cowan SW, Pechet TT. Pleurectomy and decortication for malignant mesothelioma. Thorac Surg Clin 2004; 14: 517-521.
29. Philips PG, Asimakopoulos G, Mainwand O. Malignant pleural mesothelioma: outcome of limited surgical management. Inter Cardiovasc Thorac Surg 2003; 2: 30-34.
30. Cameron RB. Extrapleural pneumonectomy is the preferred surgical management in the multimodality therapy of pleural mesothelioma: Con argument. Ann Surg Oncol 2007; 14: 1249-1253.
31. Moghissi K. Pleural neoplasms. In: Moghissi K, Thorpe JAC, Giulli F (Eds): Moghissi's Essentials of Thoracic and Cardiovascular surgery. Elsevier Science B.V., Amsterdam – Netherlands, 2003, pp 205-210.
32. Martin-Ukar AE, Nakas A, Edwards JG, Waller DA. Case-control study between extrapleural pneumonectomy and radical pleurectomy/decortication for pathological N2 malignant pleural mesothelioma. Eur J Cardiothorac Surg 2007; 31: 765-771.
33. Neragi-Miandoab S. Multimodality approach in management of malignant pleural mesothelioma. Eur J Cardiothorac Surg 2006; 29: 14-19.
34. Rusch V, Saltz L, Venkatraman E et al. A phase II trial of pleurectomy/decortication followed by intrapleural and systemic chemotherapy for malignant pleural mesothelioma. J Clin Oncol 1994; 12: 1156-1163.
35. Lee JD, Perez S, Wang HJ, Figlin RA, Holmes EC. Intrapleural chemotherapy for patients with incompletely resected malignant mesothelioma: the UCLA experience. J Surg Oncol 1995; 60: 262-267.
36. Sauter ER, Langer C, Coia LR, Goldberg M, Keller SM. Optimal management of malignant mesothelioma after subtotal pleurectomy: revisiting the role of intrapleural chemotherapy and postoperative radiation. J Surg Oncol 1995; 60: 100-105.
37. Colleoni M, Sartori F, Calabro F et al. Surgery followed by intracavitary plus systemic chemotherapy in malignant pleural mesothelioma. Tumori 1996; 82: 53-56.
38. Alberts AS, Falkson F, Goehdals L, Vorobiof DA, Van Der Merwe CA. Malignant pleural mesothelioma: a disease unaffected by current therapeutic maneuvers. J Clin Oncol 1988; 6: 527-535.
39. Achatzy R, Beba W, Ritschhler R et al. The diagnosis, therapy and prognosis of diffuse malignant mesothelioma. Eur J Cardiothorac Surg 1989; 3: 445-447.
40. Ball DL, Cruickshank DG. The treatment of malignant mesothelioma of the pleura: review of five year experience, with special reference to radiotherapy. Am J Clin Oncol 1990; 13: 4-9.
41. Brancatisano RP, Joseph MG, McCaughan BC. Pleurectomy for mesothelioma. Med J Austria 1991; 154: 455-458.
42. Soysal O, Karaoglanoglu N, Demiracan S et al. Pleurectomy/decortication for palliation in malignant pleural mesothelioma: results of surgery. Eur J Cardiothorac Surg 1997; 11: 210-213.
43. Ceresoli GL, Locati LD, Ferreri AJ et al. Therapeutic outcome according to histologic subtype in 121 patients with malignant pleural mesothelioma. Lung Cancer 2001; 34: 279-287.
44. Lee TT, Everett DL, Shu HK et al. Radical pleurectomy/decortication and intraoperative radiotherapy followed by conformal radiation with or without chemotherapy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2002; 124: 1183-1189.
45. Maziak DE, Gagliardi A, Haynes AE, Mackay JA, Evans WK. Surgical management of malignant pleural mesothelioma: a systematic review and evidence summary. Lung Cancer 2005; 48: 157-169.
46. Sugarbaker DJ. Macroscopic complete resection: the goal of primary surgery in multimodality therapy for pleural mesothelioma. J Thorac Oncol 2007; 1: 175-176.
47. Chang MY, Sugarbaker DJ. Extrapleural pneumonectomy for diffuse malignant pleural mesothelioma: techniques and complications. Thorac Surg Clin 2004; 14: 523-530.

48. Miller Dl. Extrapleural pneumonectomy. www.ctsnet.org/sections/clinicalresources/thoracic/expert_tech-7.html
49. Sugarbaker DJ, Jaklitsch MT, Bueno R et al. Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies. J Thorac Cardiovasc Surg 2004; 128: 138-146.
50. de Perrot M, McRae K, Anraku M et al. Risk factors for major complications after extrapleural pneumonectomy for malignant pleural mesothelioma. Ann Thorac Surg 2008; 85: 1206-1210.
51. Janne PA, Baldini EH. Patterns of failure following surgical resection for malignant pleural mesothelioma. Thorac Surg Clin 2004; 14: 567-573.
52. Treasure T, Tan C, Lang-Lazdunski L, Waller D. The MARS trial: mesothelioma and radical surgery. Interact Cardiovasc Thorac Surg 2006; 5: 58-59.
53. Weder W, Stahel RA, Bernhard J et al. On behalf of the Swiss group for clinical cancer research. Multicenter trial on neoadjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. Ann Oncol 2007; 18: 1196-1202.
54. Lucchi M, Chella A, Melfi F et al. A phase II study of intrapleural immuno-chemotherapy, pleurectomy/decortication, radiotherapy, systemic chemotherapy and long-term subcutaneous IL-2 in stage II-III malignant pleural mesothelioma. Eur J Cardiothorac Surg 2007; 31: 529-535.
55. Rea F, Marulli G, Bortolotti L et al. Induction chemotherapy, extrapleural pneumonectomy (EPP) and adjuvant hemi-thoracic radiation in malignant pleural mesothelioma (MPM): feasibility and results. Lung Cancer 2007; 57: 89-95.
56. Flores RM, Krug LM, Rosenweig KE et al. Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma. J Thorac Oncol 2006; 1: 289-295.
57. Opitz I, Kestenholz P, Lardinois D et al. Incidence and management of complications after neoadjuvant chemotherapy followed by extrapleural pneumonectomy for malignant pleural mesothelioma. Eur J Cardiothorac Surg 2006; 29: 579-584.
58. Treasure T, Sedranyan A. Pleural mesothelioma: little evidence, still time to do trials. Lancet 2004; 364: 1183-1185.
59. Aelony Y, Yao JE. Prolonged survival after talc poudrage for malignant pleural mesothelioma: case series. Respirology 2005; 10: 649-655.
60. Moghissi K, Dixon K. Photodynamic therapy in the management of malignant pleural mesothelioma: A review. Photodiag Photodyn Ther 2005; 2: 135-147.
61. Ris HB. Photodynamic therapy as an adjunct to surgery for malignant pleural mesothelioma. Lung Cancer 2005; 49 (Suppl 1): S65-S68.