Chapter 7

Recent Advances in Surgical Techniques for Multimodality Treatment of Malignant Pleural Mesothelioma

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Additional information is available at the end of the chapter

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1. Introduction

Malignant mesothelioma is a tumour which arises from mesothelial or possibly more primitive sub-mesothelial cells. It occurs most commonly in the pleura, but also in the peritoneum and rarely in the pericardium or tunica vaginalis testis [1]. The vast majority of cases (almost 80%) arise from the pleural mesothelium, and of these, most (60-70%) are associated with asbestos exposure [2]. The first clear evidence of a causal link between asbestos exposure and primary malignant tumours of the mesothelium was the observation by Wagner et al. (1960) of 33 cases of pleural mesothelioma in the Northwest Cape Province of South Africa, 28 in individuals who had lived close to the crocidolite mines, mostly as children [3]. Subsequent studies, especially work by Selikoff and associates (1965) and Whitwell and Rawcliffe (1971) in the United States, confirmed that asbestos exposure was the major risk factor for malignant pleural mesothelioma [4–6]. The epidemiology of malignant pleural mesothelioma is now well understood, but its biological behavior remains an enigma and the treatment of this cancer is still controversial.

2. Incidence

The incidence of malignant pleural mesothelioma was increasing and reached a peak in the years 2000-2005 in the United States, because of the large number of individuals who were exposed to asbestos during the 1930s to 1960s in asbestos mines and asbestos-related industries, before the causal relationship between asbestos and malignant pleural mesothelioma was

recognized [7]. The recent decline in incidence is attributable to declining asbestos exposure, and this trend is expected to continue [2]. On the other hand, asbestos use in Western Europe remained high until 1980, and substantial quantities are still used in several European countries. Peto et al. suggested that for the period 1995–2029 the number of men dying from mesothelioma in Western Europe each year will almost double over the next 20 years, from 5,000 in 1998 to about 9,000 around 2018, and then decline, with a total of about a quarter of a million deaths over the next 35 years [8]. The highest risk will be suffered by men born around 1945–50, of whom about 1 in 150 will die of mesothelioma. These projections are based on the fit of a simple age and birth cohort model to male pleural cancer mortality from 1970 to 1989 for six countries (Britain, France, Germany, Italy, The Netherlands and Switzerland) which together account for three-quarters of the population of Western Europe [8]. According to Surveillance, Epidemiology and End Results (SEER) Program data, the incidence of malignant mesothelioma in the United States is estimated to be between 1-2/million in states with minimal exposure to mineral fibers and 10-15/million in states where large amounts of asbestos were used [9]. The latest data available show that malignant mesothelioma is responsible for approximately 3,000 deaths per year in the United States and an additional 5,000 deaths in Western Europe [10], [11]. The latency period, which is the interval between first exposure and the development of malignant mesothelioma, ranges from about 25 to 71 years and appears to be influenced by the amount of exposure, because workers in trades with higher amounts of exposure may experience shorter latencies compared to those exposed to lower amount of asbestos [11], [12]. It is of crucial importance for the Thoracic Surgeons to be fully informed about malignant pleural mesothelioma in order to reach the correct diagnosis and recommend the appropriate treatment when dealing with it.

3. Epidemiology

The main risk factor in developing malignant mesothelioma is asbestos exposure [13]. Asbestos refers collectively to a group of naturally occurring hydrated mineral silicate fibers that include two major forms: serpentine, represented by chrysotile (white asbestos); and the amphiboles, including crocidolite (blue asbestos), amosite (brown asbestos), anthophyllite, actinolite and tremolite [13], [14]. Crocidolite fibers are regarded as the most oncogenic type of asbestos because they are long and thin, and are believed to persist longer in the pleura, but the exact way in which asbestos induces the development of malignant mesothelioma is still not well understood [13], [14]. Inflammation appears to play a critical role as following asbestos exposure in vivo, recruitment of mononuclear phagocytes (which differentiate into macrophages that in turn phagocytize asbestos) was observed, resulting in the release of tumour necrosis factor-alpha (TNF-a) by the phagocytes and mesothelial cells [14]. Exposure to asbestos can also lead to the accumulation of DNA damage in mesothelial cells through interaction with reactive nitrogen and oxygen species, which coupled to the activation of the NF-kB pathway by TNF-a perpetuates the survival of the DNA-damaged mesothelial cells [14–16].

Crocidolite asbestos is found only in South Africa and Western Australia but has been exported all over the world for various industrial uses [17]. Chrysotile accounts for 97% of worldwide

asbestos production and has been mined principally in Russia, Canada (Quebec Province), South Africa, Italy, and Cyprus [17]. Chrysotile itself is not thought to cause malignant pleural mesothelioma but is often contaminated with amphibole fibers, such as tremolite or amosite [18], [19]. However, the issue of chrysotile as a cause of malignant mesothelioma remains still controversial [17–19].

Individuals can be exposed to asbestos in many situations because of its widespread use [17], [20]. However, the areas of the world that have a high incidence of malignant pleural mesothelioma are those with asbestos mines and countries that have shipyards, insulation, construction, and automobile industries that use large amounts of asbestos [17], [21–23].Regarding tobacco use, there is no evidence that smoking increases the risk of development of malignant mesothelioma [1], [24]. On the other hand, past radiotherapy is considered as a risk factor from case series [1], [25].

4. Biological behavior

The right pleural cavity is more commonly involved than the left. In the early stages of the disease, the tumour often appears as multiple nodules on the surface of the visceral and parietal pleurae [1]. Occasionally, a localized pleural mass may develop but more often the nodules coalesce to form a sheet of tumour which surrounds the lung, extends along the fissures and may invade the underlying parenchyma [1]. Pericardial and diaphragmatic invasion are common. Bronchial invasion, usually by spread from the pleura near the hilum, is uncommon and may lead to diagnostic confusion if tumour is visible at bronchoscopy [26]. At post-mortem examination, distant metastases are common, occurring in about two-thirds of the cases with sarcomatoid type and one-third of the patients with the epithelioid and mixed types [26].

Diffuse malignant mesothelioma is divided into three main histological types: epithelioid which is most common, sarcomatoid and mixed or biphasic. The epithelial variety displays several patterns including tubulopapillary and glandular [1]. Histochemical and immunohistochemical stains assist in differentiating epithelioid mesothelioma from adenocarcinoma, the most common and difficult differential diagnosis [27].

A small number of localized serosal/subserosal neoplasms with histopathologic, histochemical, immunohistochemical, and ultrastructural features identical to those of diffuse malignant mesothelioma have been described and given the designation ''localized malignant mesothelioma'' [28]. Crotty et al first described a series of 6 localized malignant mesotheliomas in 1994 [28]. Localized malignant mesotheliomas are extremely rare solitary circumscribed nodular tumors, attached either in a sessile or pedunculated manner to the surface of the pleura [29]. Most localized malignant mesotheliomas present as incidental findings or with nonspecific symptoms. Epithelial-type localized malignant mesotheliomas predominate, and very few tumors are purely sarcomatous [29]. However, as opposed to ordinary diffuse malignant mesotheliomas where epithelial forms have a better prognosis than sarcomatous forms and biphasic forms are intermediate, histologic subtype does not correlate with survival [29]. Tumor size also does not appear to affect the clinical course [28]. Because of the vastly different

treatment and prognosis, it is crucial to separate localized malignant mesotheliomas from diffuse malignant mesotheliomas. Diffuse malignant mesotheliomas always show gross and/or microscopic evidence of widespread tumor on the serosal surface, as individual tumor nodules, or as a rind around viscera or as tumor caking [29]. Recurrent spread of localized malignant mesothelioma in the manner of diffuse malignant mesothelioma has been reported [30]. The crucial feature of localized malignant mesothelioma is that many cases can apparently be cured by surgical excision [29]. Localized malignant mesotheliomas should be separated from diffuse malignant mesotheliomas because of their localized presentation, quite different biologic behavior, and far better prognosis.

5. Clinical presentation

The majority of cases occur in men, reflecting their greater frequency of occupational asbestos exposure. A careful occupational history should be taken when mesothelioma is suspected or confirmed [1]. Median age at presentation is in the seventh decade but the disease may occur at any age [31]. During the early stages of disease, dyspnea is the predominant symptom and is related to the presence of an effusion. When the effusion is drained, patients are asymptomatic [17], [32]. As the tumor grows, patients develop ill-defined, mild, but continuous chest discomfort. Dyspnea may actually improve during this phase of the disease because, with tumor growth, the pleural surfaces fuse and the effusion resolves [17], [33]. Only when the disease becomes locally advanced does the patient develop severe chest pain, which is related to tumor infiltration of the chest wall and intercostal nerves [17], [33]. This is accompanied by a sense of chest tightness and dyspnea caused by entrapment of the lung by tumor [17]. There may be anorexia, weight loss and general malaise. Profuse sweats, particularly at night, often occur [1]. In the final stages of disease, dyspnea and chest pain become severe and unremitting [17]. These symptoms are related to encasement of the chest wall, lung, and mediastinum, and are occasionally associated with mediastinal shift and compression of the contralateral lung [17], [32]. Subcutaneous nodules may develop, particularly at sites of previous pleural aspiration or biopsy [1]. Other late features may include superior vena caval obstruction, pericardial tamponade due to malignant effusion or pericardial constriction due to tumour invasion of the pericardium [1], [32]. The tumour may spread to the abdominal cavity causing ascites. Mesothelioma may metastasize widely to all areas including the contralateral pleura and lung, intra- and extra-thoracic lymph nodes, liver, bone and brain [1], [26].

6. The role of biomarkers in early detection of malignant pleural mesothelioma and in predicting patients' response after therapy and outcome

Because of mesothelioma's nonspecific presenting symptoms, patients often suffer a substantial diagnostic delay, resulting in a more advanced disease at diagnosis [34]. At present, the only

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instruments for screening and diagnosis are based on radiological tests, posing evident economic and radio-protectionist problems [35]. An adequate screening program and subsequent earlier detection might improve patient outcome [36]. Current guidelines on mesothelioma management do, however, not advocate the use of screening and recommend that the efficacy of any screening tool should be further evaluated in high-risk populations [37]. Soluble mesothelin (SM) and megakaryocyte potentiating factor (MPF) are serum biomarkers of mesothelioma [38], [39]. Mesothelin is a 40 kDa cell surface glycophosphatidylinositol- anchored protein expressed at a low level by normal mesothelial cells in the pleura, peritoneum, and pericardium. It is highly expressed in pancreatic cancer, ovarian cancer, mesotheliomas, and some other cancers [40]. Hollevoet et al. showed that the longitudinal behavior of SM and MPF in controls indicates that a biomarker-based screening approach can benefit from the incorporation of serial measurements and individual-specific screening rules, adjusted for age and glomerular filtration rate (GFR) in their prospective longitudinal cohort study in asbestos-exposed individuals [34]. Large-scale validation remains nevertheless mandatory to elucidate whether such an approach can improve the early detection of mesothelioma [34].

Other authors are evaluating different combination of biological indicators as screening and early diagnosis markers, such as plasma osteopontin (pOPN) and serum soluble mesothelin-related peptides (SMRP) [35]. OPN is a glycoprotein overexpressed in several human neoplasms such as lung, breast, and colon cancer [41]. OPN modulates cell-matrix interactions; high levels correlate with tumor invasion, progression, and metastasis [35]. Serum OPN (sOPN) levels in patients with malignant pleural mesothelioma have been reported to be higher than in healthy subjects [42], [43]. Cristaudo et al. showed for the first time that combined SMRP and pOPN measurements can increase both sensitivity and specificity, in diagnosis of epithelioid malignant pleural mesothelioma, in terms of combined risk index [35].

Biomarkers are also urgently needed for the selection of patients likely to benefit from multimodality therapy regimens while preventing aggressive but futile treatment interventions in ineligibles [37], [44]. Serum C-reactive protein (CRP) is known as a widely available routine marker for diagnosis and follow-up of patients affected by various inflammatory diseases [45]. Recently, a negative prognostic value has been assigned to elevated serum CRP levels in several malignant diseases including breast, ovarian, renal, and lung cancer [45–49]. The results of Ghanim et al. suggest that multimodality regimens including radical resection increase survival selectively in malignant pleural mesothelioma patients with normal pre-treatment serum CRP levels, in their retrospective multicenter analysis [50].

The last few years there is an increased focus on markers of resistance, which can be used to predict treatment efficacy and thereby guide treatment decisions. Cisplatin and carboplatin work by binding to the DNA forming adducts that lead to intra- or interstrand cross-links. The formation of these DNA cross-links inhibits the cell from replicating and drives it toward apoptosis. This proapoptotic signal can be counteracted by the cells' intrinsic ability to recognize and repair the DNA damage. Nucleotide excision repair is a highly conserved pathway that maintains DNA integrity by removing helix-distorting cross-links. This pathway seems to be a key element in mediating resistance toward platinum compounds. There are three important steps in this pathway. First, the DNA damage is recognized then excised, and

finally, the excised area is resynthesized. Excision repair cross-complementation group 1 enzyme (ERCC1) plays a rate-limiting step in this process by forming a complex with xeroderma pigmentosum complementation group F that excises the damaged DNA [51–54]. Two studies have recently addressed the possible predictive and prognostic role of ERCC1 in malignant pleural mesothelioma [51]. In an observational study by Righi et al., immunohistochemistry was used to detect ERCC1 in a cohort of 45 malignant pleural mesotheliomas treated with different platinum-based therapies (cisplatin-pemetrexed or carboplatin-pemetrexed in different regimens) [55]. In this series, there was no association between ERCC1 status and treatment response, but the authors did find high ERCC1 levels to be associated with a better prognosis regardless of the chemotherapy regimen used [51], [55]. Zucali et al. also used immunohistochemistry to detect ERCC1 in a retrospective cohort of 67 malignant pleural mesotheliomas treated with a combination of pemetrexed and carboplatin [56]. These authors found no association between ERCC1 protein status and clinical outcome in terms of disease control, progression-free survival and overall survival [51], [56]. The retrospective study of Zimling et al. in malignant pleural mesothelioma patients treated with cisplatin/vinorelbine suggests that low ERCC1 expression, evaluated by immunohistochemistry, may predict longer progression-free survival, a result that warrants further validation [51].

7. Staging

Because of the lack of a universally accepted staging system, the International Mesothelioma Interest Group (IMIG) developed an internationally accepted staging system that was based on the available data correlating clinical and pathologic extent of disease with outcome [57]. The IMIG staging system has become universally accepted and adopted by the UICC and the AJCC. [17] This is based upon a TNM (tumour, node, metastasis) system (Tables 1 and 2) [57]. Information regarding the degree of visceral and parietal pleural involvement often requires the use of diagnostic thoracoscopy by means of VATS (Video Assisted Thoracic Surgery). Chest CT may also be helpful.

Cervical mediastinoscopy as a pre-operative invasive mediastinal staging tool remains still a debating issue. The high rate of false negative results or the presence of disease in lymph nodes inaccessible by mediastinoscopy, are the main reasons for its limited role in the staging algorithm [58]. Pilling et al. suggested the use of cervical mediastinoscopy as a selection tool in order to identify the patients who would benefit most from extrapleural pneumonectomy as nodal size on CT is an unreliable marker of malignancy [59]. Lately, it has been proposed that cervical mediastinoscopy should be used as routine method of prognostic staging in all patients undergoing radical surgery for malignant pleural mesothelioma [60].

Positron emission tomography (PET) scan has a crucial role in thoracic oncology due to its impact on diagnosis, staging and prognosis [61]. PET is useful diagnostic tool to identify and stage malignant pleural mesothelioma and differentiate it from benign pleural disease. Its impact in the prediction of survival, determination of mortality risk and detection of metastases and recurrent disease is considered valuable. However, the combination of PET-CT can produce superior diagnostic results than PET alone [62].

T1	T1a Tumour limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura. No involvement of the visceral pleura
	T1b Tumour involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura. Scattered foci of tumour also involving the visceral pleura
T2	Tumour involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features: Involvement of diaphragmatic muscle Confluent visceral pleural tumour (including the fissures) or extension of tumour from visceral pleura into the underlying pulmonary parenchyma
T3	Describes locally advanced but potentially resectable tumour. Tumour 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 tumour extending into the soft tissues of the chest wall Non-transmural involvement of the pericardium
T4	Describes locally advanced technically unresectable tumour. Tumour involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral) with at least one of the following features: Diffuse extension or multifocal masses of tumour in the chest wall with or without associated rib destruction Direct transdiaphragmatic extension of tumour to the peritoneum Direct extension of tumour to the contralateral pleura Direct extension of tumour to one or more mediastinal organs Direct extension of tumour into the spine Tumour extending through to the internal surface of the pericardium with or without a pericardial effusion, or tumour involving the myocardium
N	Lymph nodes
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 the 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
M	Metastases
MX	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Table 1. New International Staging System for Malignant Pleural Mesothelioma (IMIG): TNM staging (Rusch VW).

Stage	Description
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

Table 2. New International Staging System for Malignant Pleural Mesothelioma (IMIG): Clinical staging (Rusch VW).

8. Surgical treatment

Malignant pleural mesothelioma is a disease that is difficult to be cured. But efforts made, combining various medical specialties such as thoracic surgery, oncology, radiotherapy and pulmonology, to the greatest possible therapeutic approach. In this chapter, the goal is, through the review of contemporary literature, to highlight the modern surgical strategy for treatment of malignant pleural mesothelioma.

Based on the clinical staging of disease and histological type, the treatment strategy should be decided. Specifically, for clinical stage I-III or epithelioid or mixed histology type, the proposed treatment is surgical or combined, whereas for clinical stage IV or sarcomatoid histology type, chemotherapy is suggested [63].

In case that surgical treatment has been chosen, the patient should undergo a careful preoperative evaluation, that includes the following selection criteria [64]:

- Performance status 0 – 1
- Predicted postoperative FEV1 > 1.0 L
- Room air PaO2 > 65 mmHg
- Room air PaCO2 < 45 mmHg

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- Ejection fraction > 40%
- Mean pulmonary artery pressure < 30 mmHg

The aim of surgical treatment is to achieve the maximum cytoreduction and radical resection of macroscopic lesions of the disease and includes the following approaches [65]:

- Extrapleural pneumonectomy
- Pleurectomy - Decortication
- Pleurectomy - Decortication and Hyperthermic Pleural ChemoPerfusion / Photodynamic Therapy

9. Extrapleural pneumonectomy

The extrapleural pneumonectomy involves radical excision of the entire lung, en block with the parietal pleura, including the ipsilateral hemidiaphragm and pericardium and radical mediastinal lymph node dissection. The main goal of this surgical technique is to achieve complete exclusion of macroscopic disease [66].

The surgical technique is usually applied with posterolateral thoracotomy. In case of previous incisions (probably for biopsy), all scars should be excluded in order to avoid spreading the disease. Entry into the thoracic cavity is usually made through the sixth intercostal space. To achieve good surgical field, the sixth rib may be excised or a second thoracotomy must be performed below in order to facilitate better resection and reconstruction of the hemidiaphragm. After division of the intercostal space, an extrapleural plan is created separating the parietal pleura from endothoracic fascia, carefully, without entering the pleural cavity. Usually we begin with blunt and sharp dissection caudal-to-cephalad. Particular attention is required during the preparation of parietal pleura to the anatomical area of internal mammary vessels, azygos vein, aorta, esophagus, superior vena cava, inferior vena cava and mediastinum. The pericardium is opened and explored for possible metastases and eventually is resected. The hemidiaphragm is resected with very careful dissection from the peritoneum, without entering the peritoneal cavity. Then a complete mediastinal lymphadenectomy is carried out and ligation of major thoracic duct. Finally in order to complete pneumonectomy, pulmonary artery and veins as well as the main bronchus are ligated. The deficit of the pericardium is restored by placing bovine pericardium, while hemidiaphragm defect restored with synthetic mesh. Finally place a chest tube, followed by closure of the wound in accordance with the anatomical structures' class [64], [67].

The complications of this surgical procedure are represented in the table 3 below:

Common Complications	Unommon Complications
Hemothorax	Bronchopulmonary fistula
Atrial arrhythmias	Patch dehiscence
Cardiac tamponade	Empyema
Cardiac hernia	ARDS
Chylothorax	Pneumonia
Abdominal organs herniation	Septicemia
Postpneumonectomy	Vocal cord palsy
pulmonary edema	Horner's syndrome

Table 3. Complications of extrapleural pneumonectomy

Results obtained from the most recent studies show that the rate of perioperative complications ranges in 50 - 68 %, while the mean overall survival of patients receiving combination therapy which includes extrapleural pneumonectomy ranges 12,8 - 29,1 months (table 4) [68–74].

Surgical Technique	Study Group	Publication Year	Patient Population	Median Overall Survival (months)	Complications (%)
EPP	Bille et al	2012	25	12,8	68
EPP	Rena et al	2012	19	20	62
EPP	Nakas et al	2012	99	14,7	68
EPP	Buduhan et al	2009	46	24	
EPP	Hasani et al	2009	18	20,4	
EPP	Krug et al	2009	54	29,1	
EPP	Yan et al	2009	70	20	50

Table 4. Recent studies of extrapleural pneumonectomy (EPP) for the surgical treatment of mesothioma.

10. Pleurectomy - Decortication

Pleurectomy and decortication involves the surgical treatment with performance of dissection of parietal pleura from endothoracic fascia, diaphragm and mediastinum (including the pulmonary fissures down to the pulmonary artery and pleural reflections) and decortication of visceral pleura (visceral pleura is peeled away from the lung like the stripping away of a rind), with preservation of lung parenchyma (fig 1). The resection of the parietal and visceral pleura can be partial, radical or extensive (when included excision of the pericardium and / or hemidiaphragm) [75].

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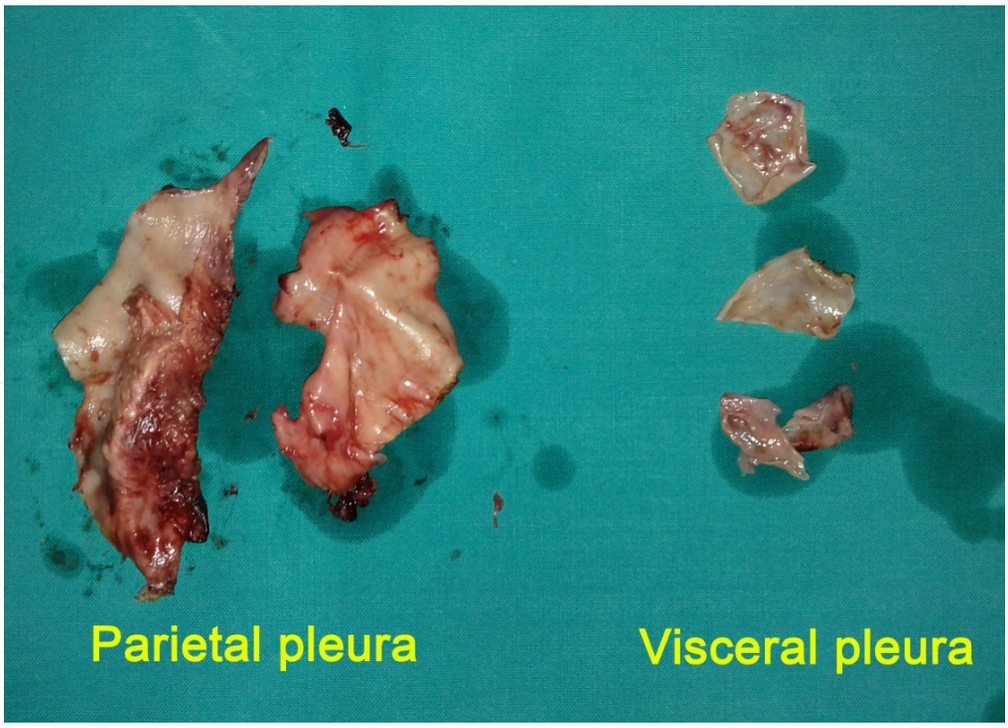

Figure 1. Parietal and visceral pleura after pleurectomy – decortication.

This surgical procedure is usually performed by posterolateral thoracotomy at the level of the sixth or seventh intercostal space. After opening the selected intercostal space, prepare the parietal pleura in all directions. We should mobilize the parietal pleura to dislodge it from the visceral pleura, where there are adhesions. In next step, visceral pleura is peeled gently away from the lung surface including the interlobar fissures, avoiding produce tears to the underlying lung. After the decortication, may proceed to parietal pleurectomy, carefully, preventing the injury of the brachial plexus, the vagus nerve, the subclavian artery and the sympathetic chain, the esophagus, the thoracic duct, the phrenic and recurrent nerves and hilar blood vessels. Finally place two chest tubes, followed by closure of the wound [67].

The complications of the procedure is primarily bleeding from the detachment of parietal pleura and the many air leaks from the detachment of visceral pleura. In recent studies, the complication rate fluctuates between 24 - 43 %, while the mean overall survival of patients with multimodality treatment including pleurectomy - decortication ranges 13,5 - 25 months (table 5).

Surgical Technique	Study Group	Publication Year	Patient Population	Median Overall Survival (months)	Complications (%)
P/D	Rena et al	2012	20	25	24
P/D	Nakas et al	2012	67	13,4	43

Table 5. Recent studies of pleurectomy - decortication (P/D) for the surgical treatment of mesothioma.

11. Pleurectomy - Decortication and hyperthermic pleural chemoperfusion / photodynamic therapy

The later and modern surgical therapy for the treatment of malignant mesothelioma is the combination of radical resection of parietal and visceral pleura (pleurectomy – decortication), by applying hyperthermic pleural lavage (40–41°C), using aqueous solution containing chemical agents such as povidone iodine or chemotherapeutic substances [76].

A newer and more advanced method is the combination of radical resection of parietal and visceral pleura (pleurectomy – decortication), followed by continuous (30min) chemoperfusion supported by extracorporeal circulation machine, for washing the pleural cavity with hyperthermic (40–41°C), aqueous solution containing chemotherapeutic substances (used also for systemic chemotherapy) [77].

Specifically after pleurectomy – decortication, place two chest tubes in the pleural cavity, ensuring that each is directed anteriorly and top and the other posteriorly and to diaphragm nearby. Usually, the first tube tube need for inflow and the second for outflow. The tubes are connected to a specific extracorporeal circulation machine and create a closed flow circuit, through which the hyperthermic solution circulate and washes the pleural cavity (fig 2-4).

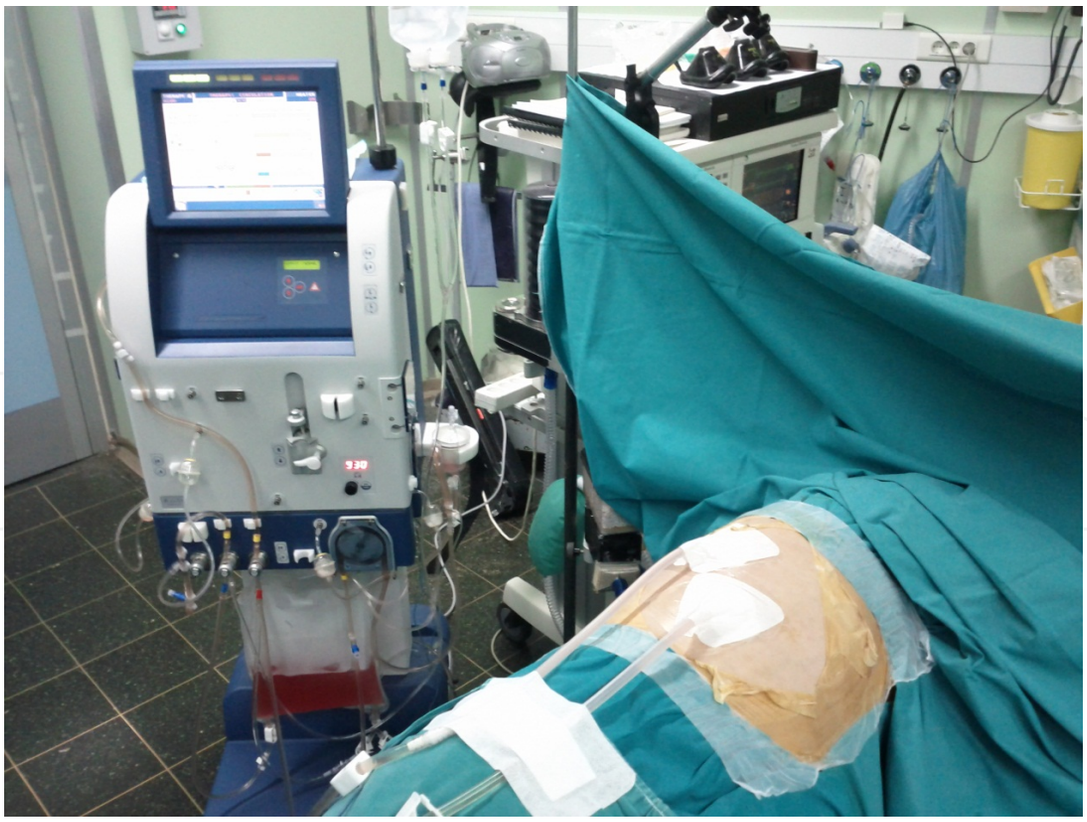

Figure 2. The patient is connected to the extracorporeal circulation circuit in order to apply hyperthermic pleural chemoperfusion.

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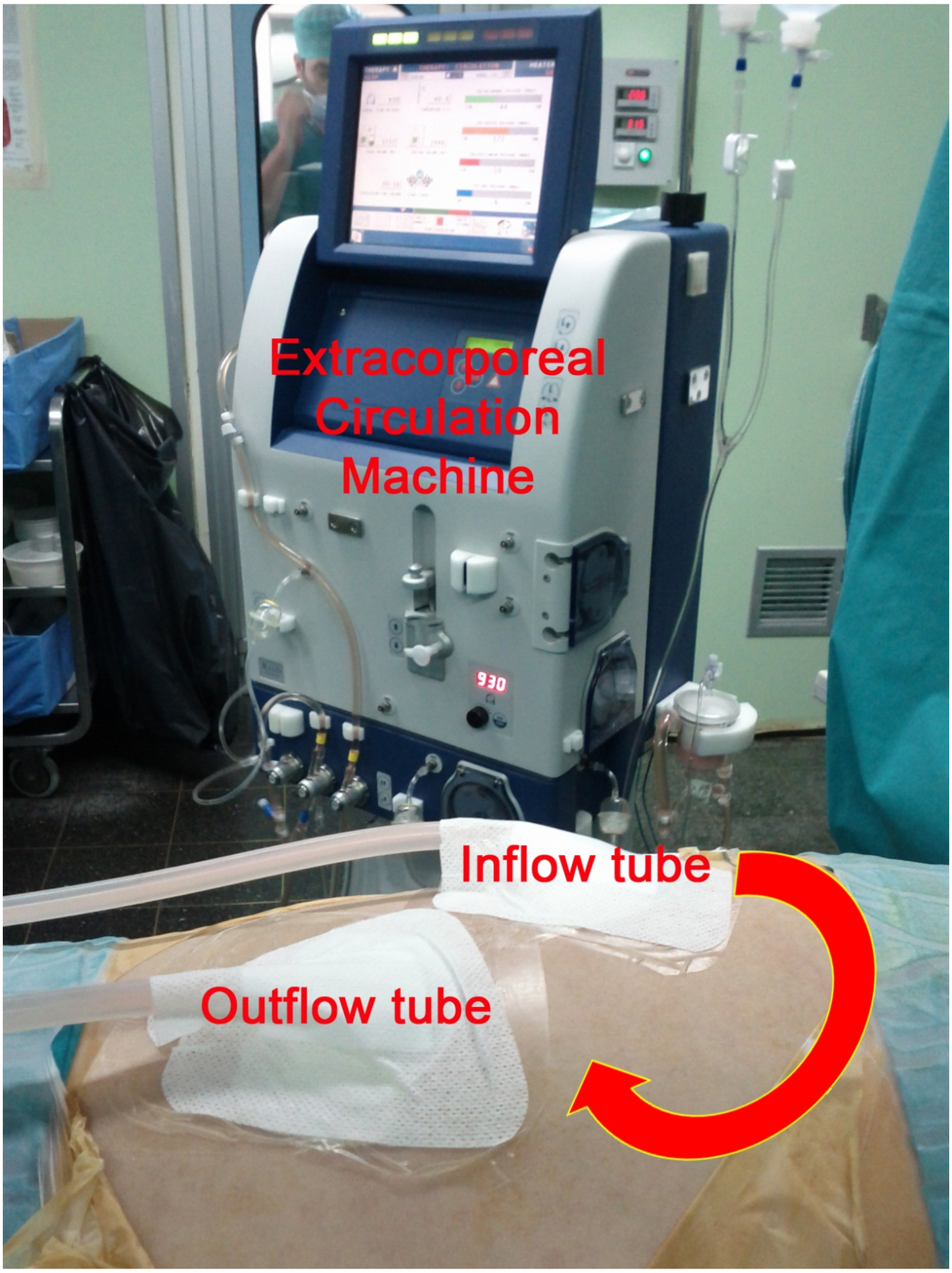

Figure 3. The arrow shows the direction flow of the hyperthermic solution inside the thoracic cavity.

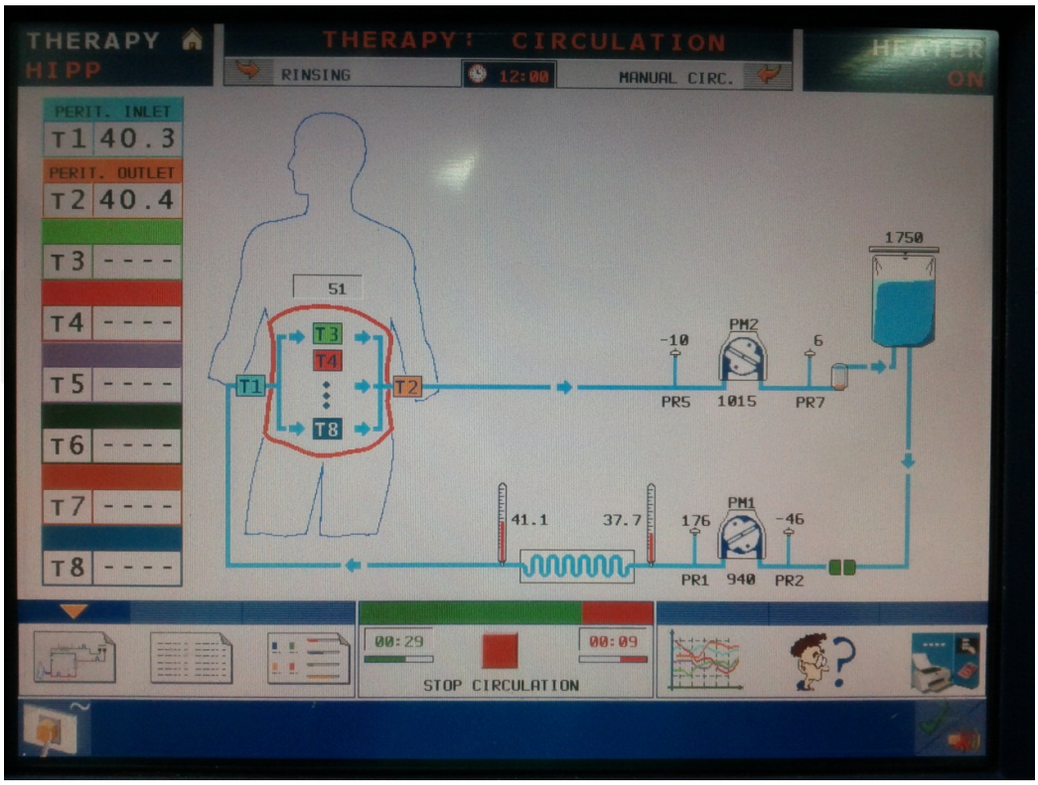

Figure 4. The screen of extracorporeal circulation machine showing in real time all parameters related to the procedure (temperature, flow-rate, time).

Hyperthermic pleural chemoperfusion can be combined with extrapleural pneumonectomy or with pleurectomy – decortication. Two recent studies suggest that the combination of hyperthermic pleural chemoperfusion after pleurectomy – decortication has a better median survival rate (23 VS 20 months) and fewer complications (27,7 VS 66 %) than the combination of hyperthermic pleural chemoperfusion after extrapleural pneumonectomy (table 6), [78], [79].

Surgical Technique	Study Group	Publication Year	Patient Population	Median Overall Survival (months)	Complications (%)
P/D and hyperthermic pleural lavage with povidone-iodine	Lang Lazdunski et al	2012	54	23	27,7
EPP and hyperthermic cisplatin perfusion	Zellos et al	2009	29	20	66

Table 6. Recent studies of extrapleural pneumonectomy (EPP) or pleurectomy - decortication (P/D) in combination with hyperthermic pleural chemoperfusion for the surgical treatment of mesothioma.

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Futhermore, hypertermic intra-thoracic chemotherapy (HITHOC) can be used even in inoperable patients with clinical stage III-IV, with very good results, mean survival rate 30 months, because it increases the process of apoptosis [80].

Also the radical resection of parietal and visceral pleura (pleurectomy – decortication) can be combined with the application of intracavitary photodynamic therapy [81]. The latest, relevant studies are very few and come from the same center. They show very good median survival rate (25 - 31,8 months) and few complications (table 7) [82], [83].

Surgical Technique	Study Group	Publication Year	Patient Population	Median Overall Survival (months)
P/D - PDT	Friedberg et al	2012	38	31,8
P/D - PDT	Friedberg et al	2011	14	25

Table 7. Recent studies of pleurectomy - decortication (P/D) in combination with intracavitary photodynamic therapy (PDT) for the surgical treatment of mesothioma.

The main goal of all these combined techniques is the elimination of possible microscopic residual disease.

12. Discussion

Unfortunately, there are not too many recent studies to demonstrate clearly the most appropriate and effective surgical therapy in the treatment of malignant pleural mesothelioma. The latest studies regarding surgical treatment of malignant mesothelioma are presented in table 8.

However, some recent studies have tried to answer the question. Apparently, extrapleural pneumonectomy has achieved greater surgically induced cytoreduction and this method was the first surgical approach for many years [84]. Also, studies show that extrapleural pneumonectomy, when is not complicated, can have a significant and rapid, positive effect on resolution of symptoms and improve the quality of life in patients with malignant pleural mesothelioma [85]. It is claimed that co-removal of pericardium and hemidiaphragm should not be applicable to extrapleural pneumonectomy, because this fact increases very much the postoperative complications and the risk of disease seeding, without significantly increase in mean survival [86].

However, current studies, that compare extrapleural pneumonectomy and pleurectomy – decortication, showed that extrapleural pneumonectomy had more and larger postoperative complications with worse quality of life, disease recurrence was delayed a little longer, while the median survival did not show a statistically significant difference [69] [70] [87] [88]. Even more, recent studies demonstrated that patients with pleurectomy – decortication were

superior therapeutically to extrapleural pneumonectomy because these patients were able to undergo even second-line chemotherapy [78].

Surgical Technique	Study Group	Publication Year	Patient Population	Radiotherapy	Systematic Chemotherapy	Median Overall Survival (months)	Complications (%)
EPP	Bille et al	2012	25	yes	yes	12,8	68
EPP	Rena et al	2012	19	yes	yes	20	62
EPP	Nakas et al	2012	99	yes	yes	14,7	68
P/D	Rena et al	2012	20	yes	yes	25	24
P/D	Nakas et al	2012	67	yes	yes	13,4	43
P/D and hyperthermic pleural lavage with povidone-iodine	Lang Lazdunski et al	2012	54	yes	yes	23	27,7
P/D PDT	Friedberg et al	2012	38	yes	yes	31,8	
MEPP	Friedberg et al	2011	14			8,4	
P/D PDT	Friedberg et al	2011	14	yes	yes	25	
EPP	Buduhan et al	2009	46	yes	yes	24	
EPP	Hasani et al	2009	18	yes	yes	20,4	
EPP	Krug et al	2009	54	yes	yes	29,1	
EPP and hyperthermic cisplatin perfusion	Zellos et al	2009	29			20	66
EPP	Yan et al	2009	70	yes	yes	20	50

Table 8. All recent studies of extrapleural pneumonectomy (EPP) or pleurectomy - decortication (P/D) or/and combination with hyperthermic pleural chemoperfusion or/and intracavitary photodynamic therapy (PDT) for the surgical treatment of mesothelioma

The results from the application of thoracic cavity lavage with hyperthermic solution and povidone iodide after pleurectomy – decortication, are promising and with fewer complications compared to extrapleural pneumonectomy [76]. In a small series of patients that chemotherapy perfusion was performed with cisplatin (100-150 mg / m) at 42 ° C for 1 h, very good results were observed. Specifically, the mean survival rate was 18 months (in combination with radiotherapy and chemotherapy), without serious perioperative complications [89].

In our department, the last three years, we have tried chemotherapy perfusion with pemetrexed (500 mg) at 42 ° C for 30 min, after pleurectomy – decortication in seven patients. Their overall treatment included radiotherapy and systemic chemotherapy (carboplatin and

pemetrexed). The follow-up of patients continues until today and the results are very encouraging. Worth to mention the case of a patient who has completed three years after the start of treatment and continues with a very good performance status. Hopefully soon, after completion of these patients study (http://clinicaltrials.gov/ct2/show/NCT01409551), the final results will be published [77].

Photodynamic therapy is a therapeutic method based on the result of the reaction of a compound containing porphyrin to the effect of visible light. The result of this reaction is the direct cellular damage and the initiation of cell apoptosis [66]. A study showed that for unclear reasons, the mean overall survival of patients who have undergone pleurectomy – decortication plus photodynamic therapy, is much larger than the group of patients who received extrapleural pneumonectomy plus photodynamic therapy (8,4 VS 25 months) [83]. Reported that the combination of pleurectomy – decortication plus photodynamic therapy has comparatively much greater mean overall survival. Perhaps, this is potentially related to preservation of the lung or some photodynamic therapy -induced effect, or both [90].

Xenograft experiments has shown that low doses of photodynamic therapy can lead to a selective and strong uptake of a circulating macromolecular chemotherapeutic drug in human malignant mesothelioma xenografts, but not in normal tissue [91].

In a recent experimental study in pigs, showed that the use of cold-plasma coagulation may help in the treatment of mesothelioma. With this technique we can predetermine the depth of tissue damage (thermo necrosis) from the surface of the lung with the selection of the appropriate dose of energy [92].

13. Conclusion

As for any other type of cancer, the treatment options for malignant pleural mesothelioma include chemotherapy, irradiation, surgery, immunotherapy or some combination of these modalities. The choice of treatment is influenced by factors like the extensive nature of this tumor, its proximity to intrathoracic organs and the general medical condition of these patients who are usually older and often have underlying diseases. Most patients due to a lack of large prospective clinical trials are treated in a highly individualized manner. Most reported studies can at best be classified as phase I type. There are very few properly structured phase II studies and no phase III studies at all.

The limitations of chemotherapy and radiotherapy have made surgery an important part of multimodality treatment for MPM. Trimodality therapy has recently emerged as a new treatment strategy to improve prognosis. To improve resectability rate and local control, induction chemotherapy is combined with aggressive surgery and post-operative radiotherapy. Pemetrexed has been shown to be among the most active agents and is currently used in induction trials.

Operations for MPM can be divided into two categories – those performed for palliation and those performed with curative intent. Video-assisted thoracic surgery (VATS) with talc

pleurodesis is an effective way to control pleural effusions in patients who are not candidates for further surgical resection. Thoracotomy and partial pleurectomy is necessary only in situations in which the pleural effusion has loculated and cannot be evacuated by VATS. The operations performed with curative intent are extrapleural pneumonectomy (EPP) and pleurectomy – decortication (PD). Surgical treatment can be combined with hyperthermic pleural chemoperfusion or intrapleural photodynamic therapy.

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References

[1] R. M. Rudd, "Malignant mesothelioma.," *British medical bulletin*, vol. 93, pp. 105–23, Jan. 2010.

[2] B. Price and A. Ware, "Time trend of mesothelioma incidence in the United States and projection of future cases: an update based on SEER data for 1973 through 2005.," *Critical reviews in toxicology*, vol. 39, no. 7, pp. 576–88, Jan. 2009.

[3] J. C. Wagner, C. A. Sleggs, And P. Marchand, "Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province.," *British journal of industrial medicine*, vol. 17, pp. 260–71, Oct. 1960.

[4] I. J. Selikoff, J. Churg, And E. C. Hammond, "Relation Between Exposure To Asbestos And Mesothelioma.," *The New England journal of medicine*, vol. 272, pp. 560–5, Mar. 1965.

[5] W. E. Smith, L. Miller, J. Churg, And I. J. Selikoff, "Mesotheliomas In Hamsters Following Intrapleural Injection Of Asbestos.," *Journal of the Mount Sinai Hospital, New York*, vol. 32, pp. 1–8.

[6] F. Whitwell and R. M. Rawcliffe, "Diffuse malignant pleural mesothelioma and asbestos exposure.," *Thorax*, vol. 26, no. 1, pp. 6–22, Jan. 1971.

[7] M. T. Milano and H. Zhang, "Malignant pleural mesothelioma: a population-based study of survival.," *Journal of thoracic oncology®: official publication of the International Association for the Study of Lung Cancer*, vol. 5, no. 11, pp. 1841–8, Nov. 2010.

[8] J. Peto, A. Decarli, C. La Vecchia, F. Levi, and E. Negri, "The European mesothelioma epidemic.," *British journal of cancer*, vol. 79, no. 3–4, pp. 666–72, Feb. 1999.

[9] S. Altekruse, C. Kosary, M. Krapcho, N. Neyman, R. Aminou, W. Waldron, J. Ruhl, N. Howlader, Z. Tatalovich, H. Cho, A. Mariotto, M. Eisner, D. Lewis, K. Cronin, H. Chen, E. Feuer, D. Stinchcomb, and B. Edwards, "SEER cancer statistics review, 1975–2007," *National Cancer Institute*, 2010. [Online]. Available: http://seer.cancer.gov/csr/1975_2007/.

[10] R. Ismail-Khan, L. A. Robinson, C. C. Williams, C. R. Garrett, G. Bepler, and G. R. Simon, "Malignant pleural mesothelioma: a comprehensive review.," *Cancer control®: journal of the Moffitt Cancer Center*, vol. 13, no. 4, pp. 255–63, Oct. 2006.

[11] M. Carbone, B. H. Ly, R. F. Dodson, I. Pagano, P. T. Morris, U. A. Dogan, A. F. Gazdar, H. I. Pass, and H. Yang, "Malignant mesothelioma: facts, myths, and hypotheses.," *Journal of cellular physiology*, vol. 227, no. 1, pp. 44–58, Jan. 2012.

[12] C. Bianchi, L. Giarelli, G. Grandi, A. Brollo, L. Ramani, and C. Zuch, "Latency periods in asbestos-related mesothelioma of the pleura.," *European journal of cancer prevention®: the official journal of the European Cancer Prevention Organisation (ECP)*, vol. 6, no. 2, pp. 162–6, Apr. 1997.

[13] H. Yang, J. R. Testa, and M. Carbone, "Mesothelioma epidemiology, carcinogenesis, and pathogenesis.," *Current treatment options in oncology*, vol. 9, no. 2–3, pp. 147–57, Jun. 2008.

[14] S. C.-H. Kao, G. Reid, K. Lee, J. Vardy, S. Clarke, and N. van Zandwijk, "Malignant mesothelioma.," *Internal medicine journal*, vol. 40, no. 11, pp. 742–50, Nov. 2010.

[15] H. Yang, M. Bocchetta, B. Kroczynska, A. G. Elmishad, Y. Chen, Z. Liu, C. Bubici, B. T. Mossman, H. I. Pass, J. R. Testa, G. Franzoso, and M. Carbone, "TNF-alpha inhibits asbestos-induced cytotoxicity via a NF-kappaB-dependent pathway, a possible mechanism for asbestos-induced oncogenesis.," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 27, pp. 10397–402, Jul. 2006.

[16] A. Shukla, M. Gulumian, T. K. Hei, D. Kamp, Q. Rahman, and B. T. Mossman, "Multiple roles of oxidants in the pathogenesis of asbestos-induced diseases.," *Free radical biology & medicine*, vol. 34, no. 9, pp. 1117–29, May 2003.

[17] T. Shields, J. LoCicero, R. Ponn, and V. Rusch, *General Thoracic Surgery*, 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2005.

[18] A. Churg and L. DePaoli, "Environmental pleural plaques in residents of a Quebec chrysotile mining town.," *Chest*, vol. 94, no. 1, pp. 58–60, Jul. 1988.

[19] J. C. McDonald, B. Armstrong, B. Case, D. Doell, W. T. McCaughey, A. D. McDonald, and P. Sébastien, "Mesothelioma and asbestos fiber type. Evidence from lung tissue analyses.," *Cancer*, vol. 63, no. 8, pp. 1544–7, Apr. 1989.

[20] M. Huncharek, "Changing risk groups for malignant mesothelioma.," *Cancer*, vol. 69, no. 11, pp. 2704–11, Jun. 1992.

[21] M. Andersson and J. H. Olsen, "Trend and distribution of mesothelioma in Denmark.," *British journal of cancer*, vol. 51, no. 5, pp. 699–705, May 1985.

[22] H. S. Malker, J. K. McLaughlin, B. K. Malker, B. J. Stone, J. A. Weiner, J. L. Erickson, and W. J. Blot, "Occupational risks for pleural mesothelioma in Sweden, 1961-79.," *Journal of the National Cancer Institute*, vol. 74, no. 1, pp. 61–6, Jan. 1985.

[23] A. D. McDonald and J. C. McDonald, "Malignant mesothelioma in North America.," *Cancer*, vol. 46, no. 7, pp. 1650–6, Oct. 1980.

[24] R. Doll and J. Peto, *Asbestos: Effects on Health of Exposure to Asbestos*. London: HMSO, 1985.

[25] A. Cavazza, L. B. Travis, W. D. Travis, J. T. Wolfe, M. L. Foo, D. J. Gillespie, N. Weidner, and T. V. Colby, "Post-irradiation malignant mesothelioma.," *Cancer*, vol. 77, no. 7, pp. 1379–85, Apr. 1996.

[26] M. R. Law, M. E. Hodson, and B. E. Heard, "Malignant mesothelioma of the pleura: relation between histological type and clinical behaviour.," *Thorax*, vol. 37, no. 11, pp. 810–5, Nov. 1982.

[27] British Thoracic Society Standards of Care Committee, "Statement on malignant mesothelioma in the United Kingdom," *Thorax*, vol. 56, no. 4, pp. 250–65, Apr. 2007.

[28] T. B. Crotty, J. L. Myers, A. L. Katzenstein, H. D. Tazelaar, S. J. Swensen, and A. Churg, "Localized malignant mesothelioma. A clinicopathologic and flow cytometric study.," *The American journal of surgical pathology*, vol. 18, no. 4, pp. 357–63, Apr. 1994.

[29] T. C. Allen, P. T. Cagle, A. M. Churg, T. V. Colby, A. R. Gibbs, S. P. Hammar, J. M. Corson, M. M. Grimes, N. G. Ordonez, V. Roggli, W. D. Travis, and M. R. Wick, "Localized malignant mesothelioma.," *The American journal of surgical pathology*, vol. 29, no. 7, pp. 866–73, Jul. 2005.

[30] H. F. Ojeda, K. Mech, and W. J. Hicken, "Localized malignant mesothelioma: a case report.," *The American surgeon*, vol. 64, no. 9, pp. 881–5, Sep. 1998.

[31] D. H. Yates, B. Corrin, P. N. Stidolph, and K. Browne, "Malignant mesothelioma in south east England: clinicopathological experience of 272 cases.," *Thorax*, vol. 52, no. 6, pp. 507–12, Jun. 1997.

[32] P. C. Elmes and J. C. Simpson, "The clinical aspects of mesothelioma.," *The Quarterly journal of medicine*, vol. 45, no. 179, pp. 427–49, Jul. 1976.

[33] P. Ruffie, R. Feld, S. Minkin, Y. Cormier, A. Boutan-Laroze, R. Ginsberg, J. Ayoub, F. A. Shepherd, W. K. Evans, and A. Figueredo, "Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients.," *Journal of clinical oncology®: official journal of the American Society of Clinical Oncology*, vol. 7, no. 8, pp. 1157–68, Aug. 1989.

[34] K. Hollevoet, J. Van Cleemput, J. Thimpont, P. De Vuyst, L. Bosquée, K. Nackaerts, P. Germonpré, S. Vansteelandt, Y. Kishi, J. R. Delanghe, and J. P. van Meerbeeck, "Seri-

http://dx.doi.org/10.5772/53397

al measurements of mesothelioma serum biomarkers in asbestos-exposed individuals: a prospective longitudinal cohort study.," *Journal of thoracic oncology®: official publication of the International Association for the Study of Lung Cancer*, vol. 6, no. 5, pp. 889–95, May 2011.

[35] A. Cristaudo, A. Bonotti, S. Simonini, A. Vivaldi, G. Guglielmi, N. Ambrosino, A. Chella, M. Lucchi, A. Mussi, and R. Foddis, "Combined serum mesothelin and plasma osteopontin measurements in malignant pleural mesothelioma.," *Journal of thoracic oncology®: official publication of the International Association for the Study of Lung Cancer*, vol. 6, no. 9, pp. 1587–93, Sep. 2011.

[36] H. I. Pass and M. Carbone, "Current status of screening for malignant pleural mesothelioma.," *Seminars in thoracic and cardiovascular surgery*, vol. 21, no. 2, pp. 97–104, Jan. 2009.

[37] W. W. E. R. S. S. of T. S. T. F. 2010;35(3):479-495. Scherpereel A, Astoul P, Baas P, Berghmans T, Clayson H, de Vuyst P, Dienemann H, Galateau-Salle F, Hennequin C, Hillerdal G, Le Péchoux C, Mutti L,Pairon JC, Stahel R, van Houtte P, van Meerbeeck J, Waller D, "Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma.," *Eur Respir J*, vol. 35, no. 3, pp. 479–495, 2010.

[38] B. W. S. Robinson, J. Creaney, R. Lake, A. Nowak, A. W. Musk, N. de Klerk, P. Winzell, K. E. Hellstrom, and I. Hellstrom, "Mesothelin-family proteins and diagnosis of mesothelioma.," *Lancet*, vol. 362, no. 9396, pp. 1612–6, Nov. 2003.

[39] K. Iwahori, T. Osaki, S. Serada, M. Fujimoto, H. Suzuki, Y. Kishi, A. Yokoyama, H. Hamada, Y. Fujii, K. Yamaguchi, T. Hirashima, K. Matsui, I. Tachibana, Y. Nakamura, I. Kawase, and T. Naka, "Megakaryocyte potentiating factor as a tumor marker of malignant pleural mesothelioma: evaluation in comparison with mesothelin.," *Lung cancer (Amsterdam, Netherlands)*, vol. 62, no. 1, pp. 45–54, Oct. 2008.

[40] K. Chang and I. Pastan, "Molecular cloning of mesothelin, a differentiation antigen present on mesothelium, mesotheliomas, and ovarian cancers.," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 1, pp. 136–40, Jan. 1996.

[41] N. S. Fedarko, A. Jain, A. Karadag, M. R. Van Eman, and L. W. Fisher, "Elevated serum bone sialoprotein and osteopontin in colon, breast, prostate, and lung cancer.," *Clinical cancer research®: an official journal of the American Association for Cancer Research*, vol. 7, no. 12, pp. 4060–6, Dec. 2001.

[42] H. I. Pass, D. Lott, F. Lonardo, M. Harbut, Z. Liu, N. Tang, M. Carbone, C. Webb, and A. Wali, "Asbestos exposure, pleural mesothelioma, and serum osteopontin levels.," *The New England journal of medicine*, vol. 353, no. 15, pp. 1564–73, Oct. 2005.

[43] B.-D. Grigoriu, A. Scherpereel, P. Devos, B. Chahine, M. Letourneux, P. Lebailly, M. Grégoire, H. Porte, M.-C. Copin, and P. Lassalle, "Utility of osteopontin and serum

mesothelin in malignant pleural mesothelioma diagnosis and prognosis assessment.," *Clinical cancer research®: an official journal of the American Association for Cancer Research*, vol. 13, no. 10, pp. 2928–35, May 2007.

[44] F. E. E. G. W. G. Stahel RA, Weder W, LievensY, "Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.," *Ann Onco*, vol. 21, no. November (suppl 5), pp. 126–128, 2010.

[45] C.-S. Wang and C.-F. Sun, "C-reactive protein and malignancy: clinico-pathological association and therapeutic implication.," *Chang Gung medical journal*, vol. 32, no. 5, pp. 471–82.

[46] B. L. Pierce, R. Ballard-Barbash, L. Bernstein, R. N. Baumgartner, M. L. Neuhouser, M. H. Wener, K. B. Baumgartner, F. D. Gilliland, B. E. Sorensen, A. McTiernan, and C. M. Ulrich, "Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients.," *Journal of clinical oncology®: official journal of the American Society of Clinical Oncology*, vol. 27, no. 21, pp. 3437–44, Jul. 2009.

[47] L. A. Hefler, N. Concin, G. Hofstetter, C. Marth, A. Mustea, J. Sehouli, R. Zeillinger, H. Leipold, H. Lass, C. Grimm, C. B. Tempfer, and A. Reinthaller, "Serum C-reactive protein as independent prognostic variable in patients with ovarian cancer.," *Clinical cancer research®: an official journal of the American Association for Cancer Research*, vol. 14, no. 3, pp. 710–4, Feb. 2008.

[48] C. O'Dowd, L. A. McRae, D. C. McMillan, A. Kirk, and R. Milroy, "Elevated preoperative C-reactive protein predicts poor cancer specific survival in patients undergoing resection for non-small cell lung cancer.," *Journal of thoracic oncology®: official publication of the International Association for the Study of Lung Cancer*, vol. 5, no. 7, pp. 988–92, Jul. 2010.

[49] S. P. K. Jagdev, W. Gregory, N. S. Vasudev, P. Harnden, S. Sim, D. Thompson, J. Cartledge, P. J. Selby, and R. E. Banks, "Improving the accuracy of pre-operative survival prediction in renal cell carcinoma with C-reactive protein.," *British journal of cancer*, vol. 103, no. 11, pp. 1649–56, Nov. 2010.

[50] B. Ghanim, M. A. Hoda, M.-P. Winter, T. Klikovits, A. Alimohammadi, B. Hegedus, B. Dome, M. Grusch, M. Arns, P. Schenk, W. Pohl, C. Zielinski, M. Filipits, W. Klepetko, and W. Berger, "Pretreatment serum C-reactive protein levels predict benefit from multimodality treatment including radical surgery in malignant pleural mesothelioma: a retrospective multicenter analysis.," *Annals of surgery*, vol. 256, no. 2, pp. 357–62, Aug. 2012.

[51] Z. G. Zimling, J. B. Sørensen, T. A. Gerds, C. Bech, C. B. Andersen, and E. Santoni-Rugiu, "Low ERCC1 expression in malignant pleural mesotheliomas treated with cisplatin and vinorelbine predicts prolonged progression-free survival.," *Journal of thoracic oncology®: official publication of the International Association for the Study of Lung Cancer*, vol. 7, no. 1, pp. 249–56, Jan. 2012.

[52] L. P. Martin, T. C. Hamilton, and R. J. Schilder, "Platinum resistance: the role of DNA repair pathways.," *Clinical cancer research®: an official journal of the American Association for Cancer Research*, vol. 14, no. 5, pp. 1291–5, Mar. 2008.

[53] Z. H. Siddik, "Cisplatin: mode of cytotoxic action and molecular basis of resistance.," *Oncogene*, vol. 22, no. 47, pp. 7265–79, Oct. 2003.

[54] H. Smeets, L. Bachinski, M. Coerwinkel, J. Schepens, J. Hoeijmakers, M. van Duin, K. H. Grzeschik, C. A. Weber, P. de Jong, and M. J. Siciliano, "A long-range restriction map of the human chromosome 19q13 region: close physical linkage between CKMM and the ERCC1 and ERCC2 genes.," *American journal of human genetics*, vol. 46, no. 3, pp. 492–501, Mar. 1990.

[55] L. Righi, M. G. Papotti, P. Ceppi, A. Billè, E. Bacillo, L. Molinaro, E. Ruffini, G. V. Scagliotti, and G. Selvaggi, "Thymidylate synthase but not excision repair cross-complementation group 1 tumor expression predicts outcome in patients with malignant pleural mesothelioma treated with pemetrexed-based chemotherapy.," *Journal of clinical oncology®: official journal of the American Society of Clinical Oncology*, vol. 28, no. 9, pp. 1534–9, Mar. 2010.

[56] P. A. Zucali, E. Giovannetti, A. Destro, M. Mencoboni, G. L. Ceresoli, L. Gianoncelli, E. Lorenzi, F. De Vincenzo, M. Simonelli, M. Perrino, A. Bruzzone, E. Thunnissen, G. Tunesi, L. Giordano, M. Roncalli, G. J. Peters, and A. Santoro, "Thymidylate synthase and excision repair cross-complementing group-1 as predictors of responsiveness in mesothelioma patients treated with pemetrexed/carboplatin.," *Clinical cancer research®: an official journal of the American Association for Cancer Research*, vol. 17, no. 8, pp. 2581–90, Apr. 2011.

[57] V. W. Rusch, "A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group.," *Chest*, vol. 108, no. 4, pp. 1122–8, Oct. 1995.

[58] M. de Perrot, K. Uy, M. Anraku, M. S. Tsao, G. Darling, T. K. Waddell, A. F. Pierre, A. Bezjak, S. Keshavjee, and M. R. Johnston, "Impact of lymph node metastasis on outcome after extrapleural pneumonectomy for malignant pleural mesothelioma.," *The Journal of thoracic and cardiovascular surgery*, vol. 133, no. 1, pp. 111–6, Jan. 2007.

[59] J. E. Pilling, D. J. Stewart, A. E. Martin-Ucar, S. Muller, K. J. O'Byrne, and D. A. Waller, "The case for routine cervical mediastinoscopy prior to radical surgery for malignant pleural mesothelioma.," *European journal of cardio-thoracic surgery®: official journal of the European Association for Cardio-thoracic Surgery*, vol. 25, no. 4, pp. 497–501, Apr. 2004.

[60] A. Nakas, D. Waller, K. Lau, C. Richards, and S. Muller, "The new case for cervical mediastinoscopy in selection for radical surgery for malignant pleural mesothelioma.," *European journal of cardio-thoracic surgery®: official journal of the European Association for Cardio-thoracic Surgery*, vol. 42, no. 1, pp. 72–6, Jul. 2012.

[61] L. Duranti, F. Leo, and U. Pastorino, "PET scan contribution in chest tumor management: a systematic review for thoracic surgeons.," *Tumori*, vol. 98, no. 2, pp. 175–84.

[62] S. Sharif, I. Zahid, T. Routledge, and M. Scarci, "Does positron emission tomography offer prognostic information in malignant pleural mesothelioma?," *Interactive cardiovascular and thoracic surgery*, vol. 12, no. 5, pp. 806–11, May 2011.

[63] Y. S. Ettinger DS, Akerley W, Borghaei H, Chang A, Cheney RT, Chirieac LR, D'Amico TA, Demmy TL, Ganti AK, Govindan R, Grannis FW, Horn L, Jahan TM, Jahanzeb M, Kessinger A, Komaki R, Kong FM, Kris MG, Krug LM, Lennes IT, Loo BW, Martins R, O'Malley J, Osarogia, "Malignant pleural mesothelioma - Clinical Practice Guidelines in Oncology," *JNCCN–Journal of the National Comprehensive Cancer Network*, vol. 10, no. 1, pp. 26–41, 2012.

[64] D. L.Miller, "Extrapleural Pneumonectomy," 2009. [Online]. Available: http://www.ctsnet.org/sections/clinicalresources/thoracic/expert_tech-7.html.

[65] D. Rice, V. Rusch, and H. Pass, "Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the International Association for the Study," *Journal of Thoracic …*, vol. 6, no. 8, pp. 1304–1312, 2011.

[66] F. E. Mott, "Mesothelioma: a review.," *The Ochsner journal*, vol. 12, no. 1, pp. 70–9, Jan. 2012.

[67] L. M. Argote-Greene, M. Y. Chang, and D. J. Sugarbaker, "Extrapleural pneumonectomy for malignant pleural mesothelioma," *Multimedia Manual of Cardio-Thoracic Surgery*, vol. 2005, no. 0628, Jan. 2005.

[68] A. Bille, E. Belcher, H. Raubenheimer, D. Landau, P. Cane, J. Spicer, and L. Lang-Lazdunski, "Induction chemotherapy, extrapleural pneumonectomy, and adjuvant radiotherapy for malignant pleural mesothelioma: experience of Guy's and St Thomas' hospitals.," *General thoracic and cardiovascular surgery*, vol. 60, no. 5, pp. 289–96, May 2012.

[69] O. Rena and C. Casadio, "Extrapleural pneumonectomy for early stage malignant pleural mesothelioma: a harmful procedure.," *Lung cancer (Amsterdam, Netherlands)*, vol. 77, no. 1, pp. 151–5, Jul. 2012.

[70] A. Nakas, E. von Meyenfeldt, K. Lau, S. Muller, and D. Waller, "Long-term survival after lung-sparing total pleurectomy for locally advanced (International Mesothelioma Interest Group Stage T3-T4) non-sarcomatoid malignant pleural mesothelioma.," *European journal of cardio-thoracic surgery©: official journal of the European Association for Cardio-thoracic Surgery*, vol. 41, no. 5, pp. 1031–6, May 2012.

[71] G. Buduhan, S. Menon, R. Aye, B. Louie, V. Mehta, and E. Vallières, "Trimodality therapy for malignant pleural mesothelioma.," *The Annals of thoracic surgery*, vol. 88, no. 3, pp. 870–5; discussion 876, Sep. 2009.

[72] A. Hasani, J. M. Alvarez, J. M. Wyatt, S. Bydder, M. Millward, M. Byrne, A. W. B. Musk, and A. K. Nowak, "Outcome for patients with malignant pleural mesothelioma referred for Trimodality therapy in Western Australia.," *Journal of thoracic oncology®: official publication of the International Association for the Study of Lung Cancer*, vol. 4, no. 8, pp. 1010–6, Aug. 2009.

[73] L. M. Krug, H. I. Pass, V. W. Rusch, H. L. Kindler, D. J. Sugarbaker, K. E. Rosenzweig, R. Flores, J. S. Friedberg, K. Pisters, M. Monberg, C. K. Obasaju, and N. J. Vogelzang, "Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma.," *Journal of clinical oncology®: official journal of the American Society of Clinical Oncology*, vol. 27, no. 18, pp. 3007–13, Jun. 2009.

[74] T. D. Yan, M. Boyer, M. M. Tin, D. Wong, C. Kennedy, J. McLean, P. G. Bannon, and B. C. McCaughan, "Extrapleural pneumonectomy for malignant pleural mesothelioma: outcomes of treatment and prognostic factors.," *The Journal of thoracic and cardiovascular surgery*, vol. 138, no. 3, pp. 619–24, Sep. 2009.

[75] "Surgical Choices: Pleurectomy With Decortication," 2012. [Online]. Available: http://www.mesothel.com/asbestos-cancer/mesothelioma/surgery/pleurectomy-decortication/pd.htm.

[76] L. Lang-Lazdunski, A. Bille, E. Belcher, P. Cane, D. Landau, J. Steele, H. Taylor, and J. Spicer, "Pleurectomy/decortication, hyperthermic pleural lavage with povidone-iodine followed by adjuvant chemotherapy in patients with malignant pleural mesothelioma.," *Journal of thoracic oncology®: official publication of the International Association for the Study of Lung Cancer*, vol. 6, no. 10, pp. 1746–52, Oct. 2011.

[77] N. Barbetakis, C. Asteriou, A. Kleontas, C. Karvelas, I. Boukovinas, E. Stergiou, M. Lalountas, K. Avgitidis, and C. Tsilikas, "Cytoreductive surgery in combination with hyperthermic pleural chemoperfusion with pemetrexed for the treatment of malignant pleural mesothilioma.," Hellenic Journal of Surgery, vol. 82, no. 6, Supl. I, pp. 420-423, Dec. 2010.

[78] L. Lang-Lazdunski, A. Bille, R. Lal, P. Cane, E. McLean, D. Landau, J. Steele, and J. Spicer, "Pleurectomy/decortication is superior to extrapleural pneumonectomy in the multimodality management of patients with malignant pleural mesothelioma.," *Journal of thoracic oncology®: official publication of the International Association for the Study of Lung Cancer*, vol. 7, no. 4, pp. 737–43, Apr. 2012.

[79] L. Zellos, W. G. Richards, L. Capalbo, M. T. Jaklitsch, L. R. Chirieac, B. E. Johnson, R. Bueno, and D. J. Sugarbaker, "A phase I study of extrapleural pneumonectomy and intracavitary intraoperative hyperthermic cisplatin with amifostine cytoprotection for malignant pleural mesothelioma.," *The Journal of thoracic and cardiovascular surgery*, vol. 137, no. 2, pp. 453–8, Feb. 2009.

[80] Y. Matsuzaki, M. Tomita, T. Shimizu, M. Hara, T. Ayabe, and T. Onitsuka, "Induction of apoptosis by intrapleural perfusion hyperthermo-chemotherapy for malig-

nant pleural mesothelioma.," *Annals of thoracic and cardiovascular surgery®: official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia*, vol. 14, no. 3, pp. 161–5, Jun. 2008.

[81] J. S. Friedberg, "Photodynamic therapy as an innovative treatment for malignant pleural mesothelioma.," *Seminars in thoracic and cardiovascular surgery*, vol. 21, no. 2, pp. 177–87, Jan. 2009.

[82] J. S. Friedberg, "Photodynamic therapy for malignant pleural mesothelioma: the future of treatment?," *Expert review of respiratory medicine*, vol. 5, no. 1, pp. 49–63, Feb. 2011.

[83] J. S. Friedberg, R. Mick, M. Culligan, J. Stevenson, A. Fernandes, D. Smith, E. Glatstein, S. M. Hahn, and K. Cengel, "Photodynamic therapy and the evolution of a lung-sparing surgical treatment for mesothelioma.," *The Annals of thoracic surgery*, vol. 91, no. 6, pp. 1738–45, Jun. 2011.

[84] S. Su, "Mesothelioma: path to multimodality treatment.," *Seminars in thoracic and cardiovascular surgery*, vol. 21, no. 2, pp. 125–31, Jan. 2009.

[85] V. Ambrogi, A. Baldi, O. Schillaci, and MineoTommaso Claudio, "Clinical Impact of Extrapleural Pneumonectomy for Malignant Pleural Mesothelioma," *Annals of Surgical Oncology*, vol. 19, no. July 2011, pp. 1692–1699, 2011.

[86] P. Bonnette, "Pleural mesothelioma: where are we with radical surgery and multimodal treatment?," *Revue de pneumologie clinique*, vol. 67, no. 4, pp. 184–90, Sep. 2011.

[87] G. Dimitrakakis, T. BinEsmael, A. Szafranek, and P. a. O'Keefe, "ERRATUM for a missing eComment 'Malignant pleural mesothelioma: a therapeutic challenge'," *Interactive CardioVascular and Thoracic Surgery*, vol. 13, no. 6, pp. 691–692, Dec. 2011.

[88] T. Treasure, L. Lang-Lazdunski, D. Waller, J. M. Bliss, C. Tan, J. Entwisle, M. Snee, M. O'Brien, G. Thomas, S. Senan, K. O'Byrne, L. S. Kilburn, J. Spicer, D. Landau, J. Edwards, G. Coombes, L. Darlison, and J. Peto, "Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study.," *The lancet oncology*, vol. 12, no. 8, pp. 763–72, Aug. 2011.

[89] M. Ried, T. Potzger, N. Braune, R. Neu, Y. Zausig, B. Schalke, C. Diez, and H.-S. Hofmann, "Cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion for malignant pleural tumours: perioperative management and clinical experience.," *European journal of cardio-thoracic surgery®: official journal of the European Association for Cardio-thoracic Surgery*, Aug. 2012.

[90] J. S. Friedberg, M. J. Culligan, R. Mick, J. Stevenson, S. M. Hahn, D. H. Sterman, S. Punekar, E. Glatstein, and K. Cengel, "Radical Pleurectomy and Intraoperative Photodynamic Therapy for Malignant Pleural Mesothelioma," in *Forty-seventh Annual*

Meeting of The Society of Thoracic Surgeons, 2011, vol. 93, no. 5, pp. 1658–65; discussion 1665–7.

[91] Y. Wang, J. Y. Perentes, S. C. Schäfer, M. Gonzalez, E. Debefve, H.-A. Lehr, H. van den Bergh, and T. Krueger, "Photodynamic drug delivery enhancement in tumours does not depend on leukocyte-endothelial interaction in a human mesothelioma xenograft model.," *European journal of cardio-thoracic surgery©: official journal of the European Association for Cardio-thoracic Surgery*, vol. 42, no. 2, pp. 348–54, Aug. 2012.

[92] M. Hoffmann, A. Ulrich, E. Schloericke, S. Limmer, J. K. Habermann, H. Wolken, H.-P. Bruch, and P. Kujath, "The application of cold-plasma coagulation on the visceral pleura results in a predictable depth of necrosis without fistula generation.," *Interactive cardiovascular and thoracic surgery*, vol. 14, no. 3, pp. 239–43, Mar. 2012.

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