Surgical Therapy of Mesothelioma 7

David Rice

Abstract The treatment of malignant pleural mesothelioma is controversial, particularly regarding the role of surgery. Though well accepted as a diagnostic modality, surgery is also frequently used to establish stage, provide palliation, and perhaps most controversially, to offer cytoreduction with the putative goal of delaying tumor progression and prolonging survival. Pleurectomy/decortication (PD) can achieve macroscopic complete resection; however, the ability to deliver effective postoperative radiation treatment is limited because of the risk of lung toxicity. Accordingly, it has been associated with higher rates of local recurrence compared to extrapleural pneumonectomy (EPP). Extrapleural pneumonectomy generally offers a more complete cytoreduction compared to PD but at the cost of increased morbidity and mortality. Adjuvant hemithoracic radiation is feasible following EPP and in most series local recurrence rates are lower after EPP than PD. There are no convincing data, however, to show that one procedure is superior to the other in terms of survival. Furthermore, no randomized data currently exist that demonstrate a survival benefit to any form of surgical cytoreduction over systemic treatment and supportive care. If cytoreductive surgery does have a beneficial effect on long-term survival, it will most likely be realized in patients with epithelioid tumors without nodal metastases.

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7.1 Introduction

With the exception of the use of thoracoscopy for diagnosis, indications for surgery in mesothelioma are controversial. Due to the rarity of disease there are no randomized surgical studies on which to base objective treatment decisions, and most of what constitutes current guidelines has been based on single center retrospective studies or phase I/II trials with limited numbers of patients. This chapter will examine the role of surgery for diagnosis, staging, palliation, and therapy for MPM. In understanding the current surgical literature for this disease, the reader is reminded that comparisons between reported series are difficult. Factors that highly influence the outcome such as tumor stage and histology

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are not only often difficult to accurately define in an individual patient but are often variably documented in published reports. Furthermore, indications for selection of patients to undergo a given procedure are often poorly explained (if at all) and this inevitably leads to bias when comparisons are performed between different series.

7.2 Natural History

The natural history of mesothelioma is for the tumor to progress locally causing dyspnea, by either lung entrapment or compression from effusion leading to atelectasis and shunting, and pain from chest wall invasion. Death usually occurs within 6–12 months from initial diagnosis. Though autopsy studies reveal that metastases occur in 50–75% of cases, most are clinically occult and are not the cause of death. The majority of patients with MPM are diagnosed when the tumor is at an advanced stage. Many untreated patients with early stage disease (American Joint Commission on Cancer (AJCC) Stage I) will probably survive significantly longer than 12 months. Ruffie et al reported median survival of 6.8 months from date of diagnosis until death in 176 untreated patients from 9 Canadian centers from 1969 to 1984 [55]. Two more recent trials, however, serve as useful contemporary benchmarks for outcome in untreated patients. Merritt et al. reported a median survival of 7.1 months in 101 consecutive patients with MPM treated at two tertiary referral centers in Ontario [40]. Symptom management alone was performed. Patients were not clinically staged, and a relatively large proportion (57%) had non-epithelioid tumors, which are known to have worse outcome. Another trial performed by the Medical Research Council of Great Britain randomized 409 patients to chemotherapy or active symptom control which included use of steroids, appetite stimulants, bronchodilators, or palliative radiotherapy [44]. Epithelioid tumors occurred in 74% of patients and 79% were AJCC stage III or IV, proportions that are consistent with most clinical series. Median survival calculated from the date of randomization (median 60 days from date of diagnosis) was 7.6 months, and 1-year survival was 29%. Chemotherapy did not have a survival benefit over active symptom control; however, pemetrexed, the current standard chemotherapeutic agent was not included in the drug regimen. Two recent prospective randomized trials using modern platinum/antifolate doublet regimens showed median survival of 11.4 months and 12.1 months, respectively, in non-resectable patients [75, 78]. The median survival for untreated patients is therefore probably between 7 and 10 months from the date of diagnosis and with chemotherapy may extend to 12–13 months, but will be influenced by initial stage and tumor histology. Though these studies provide a rough benchmark on which to base survival comparisons with surgical series. One must remember that subjects in most surgical series are usually a highly select group of good performance status patients. The natural history of MPM in such patients is still poorly defined.

7.3 Diagnosis

7.3.1 Video-Assisted Thoracoscopy

The benefit of video-assisted thoracoscopic surgery (VATS) for the diagnosis of MPM is that it is a safe, simple, widely available, and highly accurate diagnostic procedure. VATS allows large tissue samples to be obtained from multiple areas of the thoracic cavity, an important consideration since there is considerable tumor heterogeneity within individual mesothelioma tumors. In fact it has been shown that

sarcomatoid elements within a mesothelioma are not uniformly distributed within the tumor and that the greater the number of separate biopsies that are taken, the higher the likelihood of diagnosing biphasic (or mixed) histologic subtype [5]. As patients with non-epithelioid tumors have significantly worse outcome after cytoreductive surgery than those with epithelioid tumors do, prior knowledge of cell type can greatly influence subsequent therapy. VATS is generally best performed through a single 1–1.5 cm incision placed on the lateral chest wall in line of a potential future thoracotomy. The rationale for this is that MPM can occasionally track along thoracostomy incisions, thus limiting the number of incisions that is beneficial and placement in a region that can be completely excised at the time of future cytoreductive surgery facilitates complete resection without having to perform additional excision of multiple thoracostomy sites. A single 1.5 cm incision will usually allow for placement of a 5 mm angled thoracoscope and an endoscopic biopsy forceps through a soft thoracostomy port. Alternatively, a thoracoscope with a working channel can be used. A single chest drain can subsequently be placed through the same incision, though it is useful to close the fascia and subcutaneous tissue around the chest drain to limit postoperative leakage of pleural fluid. VATS can identify whether tumor involves the visceral pleura as well as the parietal pleura (IMIG/AJCC stage IB) but is otherwise fairly limited as a staging modality. VATS lymphadenectomy is to be avoided as a staging procedure as the interruption of tissue planes may hamper subsequent cytoreductive surgery and it is prone to false positivity due to contamination of specimens from the surrounding tumor. VATS is most easily performed in patients where a large effusive component exists. In this setting, port placement can be easily determined by correlation with axial imaging. In cases where there is significant parietal tumor bulk, it is often best to locate an underlying pocket of fluid first with an 18 gauge spinal needle. Occasionally, tumor burden is such that VATS is impossible and in these instances a small 2 cm incision (again, placed in line with a potential thoracotomy incision) can easily access the underlying tumor under direct vision. Another merit of VATS is the ability to perform talc pleurodesis. Instillation of 4–5 g of sterile medical grade talc is generally sufficient. Pleurodesis does not impact the ability to perform extrapleural pneumonectomy (EPP) or pleurectomy/decortication (PD) at a later stage (indeed it can often facilitate dissection), but can offer significant palliation in patients who are subsequently found not to be surgical candidates. It must be remembered, however, that talc will cause fluorodeoxyglucose (FDG) activity in the pleural distribution and in mediastinal lymph nodes on subsequent positron emission tomography (PET) imaging. For this reason it is ideal that PET imaging be performed prior to talc pleurodesis.

Despite the obvious benefits of VATS as a diagnostic and therapeutic procedure in mesothelioma, it requires general anesthetic and at least an overnight hospital stay. CT-guided core needle biopsy is a more convenient method of establishing a tissue diagnosis. It has a high accuracy for diagnosis of mesothelioma but is probably less sensitive for determination of true histologic subtype as generally only a single tumor site is biopsied. The incidence of tumor seeding may be also less than with thoracoscopic biopsy [1]. At the University of Texas M.D. Anderson Cancer Center CT-guided biopsy is the initial method of diagnosis used for patients with suspected mesothelioma. VATS is reserved for patients in whom there is diagnostic uncertainty or for patients in whom treatment of an associated effusion is indicated.

Thoracotomy, “mini” or otherwise, is to be avoided as a diagnostic method. It not only causes the patient unnecessary trauma but often hampers the performance of subsequent cytoreductive surgery because of disruption of the

extrapleural plane and potential contamination of the incision with tumor. The worst situation occurs when a thoracotomy is performed and a partial parietal pleurectomy is undertaken in the mistaken belief that "more is better." In this setting it is virtually impossible to perform an adequate cytoreductive procedure at a later time.

7.4 Staging

The American Joint Commission on Cancer (AJCC)/International Mesothelioma Interest Group (IMIG) staging system is based primarily on pathologic data [56]. As such it has significant limitations when applied to clinical staging. Many of the factors that contribute to stage designation such as pericardial invasion, invasion of the endothoracic fascia, lymph node metastases, and diaphragmatic invasion, to name but a few, are simply not possible to determine accurately with current diagnostic imaging techniques. Though PET can identify occult distant metastatic disease in up to 25% of cases, it is insensitive for determining lymph node involvement or transdiaphragmatic invasion – factors that significantly worsen outcome and generally contraindicate extrapleural pneumonectomy [21, 22].

7.4.1 Laparoscopy

Transdiaphragmatic invasion is a manifestation of advanced disease (Stage IV) and precludes any form of cytoreductive surgery. Involvement may occur either through direct and contiguous invasion of tumor across the diaphragmatic muscle or by lymphatogenous spread via communicating lymphatics between the pleura and the abdomen. This latter form of metastatic spread may lead to peritoneal carcinomatosis

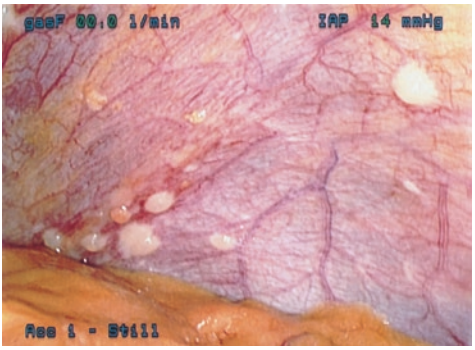

Fig. 7.1 Laparoscopic image showing small volume subdiaphragmatic tumor nodules in a patient with left-sided malignant pleural mesothelioma. Disease of this nature is impossible to detect with current imaging modalities

(Fig. 7.1) and is not necessarily dependent on the degree of tumor bulk within the hemithorax. Because of the inability of axial imaging (MRI, CT or PET) to accurately differentiate transdiaphragmatic from superficial invasion or tumor abutment, Conlon investigated the use of laparoscopy and identified transdiaphragmatic invasion in 6 of 12 patients with equivocal CT findings [15]. Importantly, of the remaining six patients, all underwent thoracotomy and none was found to have transdiaphragmatic invasion. Based on these findings in 1999 we began routinely performing laparoscopy in patients being considered for extrapleural pneumonectomy. Laparoscopy is performed as an outpatient procedure in combination with mediastinoscopy (or, more recently, endobronchial ultrasound (EBUS)), usually utilizing a 10 mm periumbilical port and a 5 mm subcostal port on the same side as the mesothelioma. After initial inspection of both diaphragms and the entire peritoneal cavity the abdomen is irrigated with 1,000 cc normal saline. A 0-degree 5 mm laparoscope is then placed through the subcostal port and advanced beneath the surface of the saline to closely inspect the underside of the ipsilateral diaphragm. The saline helps surrounding organs

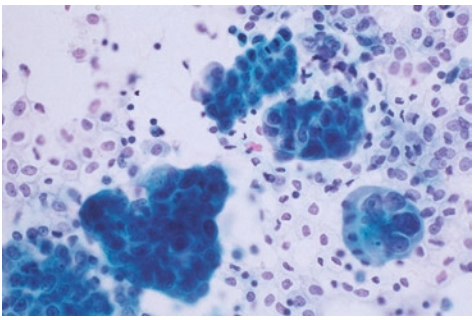

Fig. 7.2 Occult mesothelioma tumor cells obtained from peritoneal lavage during laparoscopic staging

(liver, spleen, and omentum) be atraumatically displaced away from the diaphragmatic surface while preserving visibility. Suspicious lesions are biopsied, which generally requires placement of an additional 5 mm port. The lavage fluid is routinely submitted for cytologic analysis (Fig. 7.2). In 109 patients with potentially resectable mesothelioma 9 (8.3%) patients were found to have transdiaphragmatic extension of tumor, and 1 (0.9%) patient had diffuse peritoneal carcinomatosis [51]. CT scans were suspicious for diaphragmatic invasion in only 3 (33%) of these patients. In addition, of 78 patients who underwent peritoneal lavage, 2 (2.6%) patients were found to have peritoneal micrometastases without obvious diaphragmatic invasion. Thus, 12 (11.0%) patients were identified with unsuspected abdominal involvement and thus were able to avoid futile cytoreductive surgery.

7.4.2 Mediastinoscopy

The high prevalence of lymph node metastases in MPM (up to 50% of patients undergoing trimodality therapy) and the poor prognosis that extrapleural nodal involvement confers, are justifications for preoperative assessment of mediastinal nodal metastases [47, 59]. Unfortunately, current radiographic modalities are inaccurate. The sensitivity of CT for detecting mediastinal N2 disease in mesothelioma is only 50–60% as there is difficulty in differentiating enlarged mediastinal nodes from adjacent areas of tumor nodularity. Similarly, PET has relatively low accuracy at correctly defining N stage [22]. The efficacy of surgical staging of the mediastinum with cervical mediastinoscopy (CM) is well established for non-small cell lung cancer; however, the utility of the procedure in mesothelioma is less clear. Schouwink and associates performed CM in 43 patients with MPM and compared the staging accuracy of CM with that of CT scanning [62]. Sensitivity, specificity, and accuracy were 80%, 100%, and 93%, respectively, for CM compared with 60%, 71%, and 67% for CT. Mediastinoscopy failed to identify 9 (21%) patients who were found to have positive intrathoracic nodes at thoracotomy, despite the fact that three of these patients had positive nodes in sites that were potentially accessible by CM. We routinely perform mediastinal nodal sampling (now with EBUS) at the time of staging laparoscopy. We reported use of mediastinoscopy in 62 patients with mesothelioma and identified N2 metastases in 10 (16.1%) [51]. Of these, 46 underwent extrapleural pneumonectomy. Fourteen (30.4%) patients were found to have extrapleural (N2) nodes at thoracotomy, of which CM identified only five preoperatively. The sensitivity and accuracy of CM for detecting N2 disease was only 36% and 80%, respectively. One of the reasons for the low sensitivity is that extrapleural nodal metastases in mesothelioma frequently occur in regions that are inaccessible to mediastinoscopy such as the internal mammary artery chain, the aortopulmonary window, the anterior mediastnal fat and thymic tissue, the intercostal spaces and the retrocrural and anterior diaphragmatic regions. Combined laparoscopy and mediastinoscopy identified 15 of 118 patients (12.7%) in whom either contralateral nodal disease (N3) or abdominal involvement precluded further surgical therapy.

7.4.3 Thoracoscopy

More recently, laparoscopy and mediastinoscopy have been combined with bilateral thoracoscopy for surgical staging of patients with mesothelioma. Alvarez et al identified contralateral chest involvement in 3 of 30 (10%) patients and five (20%) were upstaged to stage IV [4]. Additionally, two patients were reclassified from epithelioid to non-epithelioid histology. Surgical staging identified 26% of patients who would have received no benefit from trimodality therapy. Though experience with bilateral VATS is yet limited, it may have a role in patients who present with a contralateral effusion or noncalcified pleural plaques.

7.4.4 Endoscopic Staging

While generally safe, CM requires a cervical incision and is associated with a small risk of recurrent nerve injury, pneumothorax, tracheal injury, hemorrhage, and even death [34]. Endobronchial ultrasound (EBUS) and esophageal ultrasound (EUS)-guided fine needle aspiration (FNA) of mediastinal lymph nodes have been highly effective for staging non-small cell lung cancer (NSCLC) [18, 20, 28, 85]. Since 2006 we have replaced mediastinoscopy with EBUS for assessment of mediastinal nodes in patients being considered for radical resection of MPM (Fig. 7.3). We compared 50 consecutive patients with mesothelioma who underwent CM with 38 patients who underwent EBUS [53]. Sensitivity and negative predictive value for mediastinoscopy were 28% and 49%, and 59% and 57% for EBUS. Furthermore, 11 patients had EUS preoperatively, which revealed infradiaphragmatic nodal metastases in 5 patients (Fig. 7.4). Tournoy et al performed EUS and FNA in 32 patients with presumed early stage mesothelioma and identified N2 metastases in 4 (12.5%) [70]. Of the patients who subsequently underwent extrapleural pneumonectomy and mediastinal node dissection ($n = 17$) there was only one false negative (4.7%). Mediastinoscopy did not identify

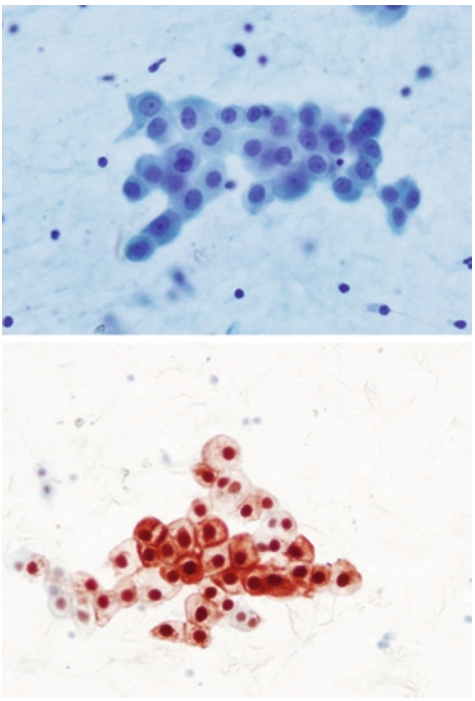

Fig. 7.3 Mesothelioma cells in a lymph node aspirate obtained from a mediastinal node using EBUS

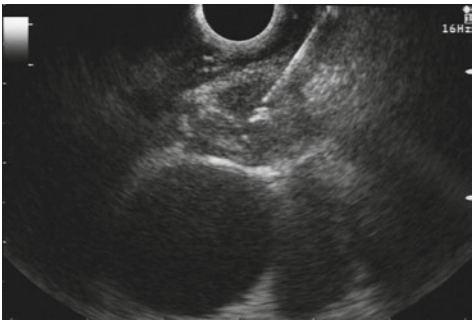

Fig. 7.4 Esophageal ultrasound-guided fine needle aspiration biopsy of a perigastric node in a patient with left-sided malignant pleural mesothelioma

additional nodal metastases. The data for EBUS and EUS staging in mesothelioma are preliminary, however, and further studies will be needed to ascertain their benefit. Though these minimally invasive techniques are safe and less traumatic than mediastinoscopy, there is a risk for false positivity because of the danger of mistaking tumor nodules adjacent to the trachea or esophagus as enlarged lymph nodes. Therefore, the procedure should be performed by an operator skilled in endoscopic ultrasound and familiar with mesothelioma and only well-defined, circumscribed nodes should be biopsied. It is also important that there is evidence of lymphoid tissue in any positive aspirate.

7.5 Palliative Surgery

Symptoms in patients with mesothelioma predominately consist of dyspnea, chest pain, cough and constitutional symptoms such as fatigue, fever, and anorexia. Respiratory symptoms are secondary to atelectasis and shunting caused by pleural effusion or lung encasement; or to altered respiratory mechanics secondary to chest wall contraction and impaired movement of the ribs and diaphragm. Surgical palliation is centered around two issues – treatment and prevention of pleural effusion, and tumor debulking to allow lung expansion and improved chest wall mechanics.

7.5.1 Pleural Drainage

Treatment of pleural effusion depends on the size of the effusion, the degree to which it is causing atelectasis and the degree of lung encasement by tumor. Simple thoracentesis is rarely effective in providing long-term relief of mesothelioma-related effusion; however, it is a reasonable initial procedure to establish a diagnosis and to evaluate the degree to which the lung will re-expand. In the absence of complete re-expansion, pleural symphasis is unlikely to occur with sclerotherapy. If the lung is trapped because of tumoral involvement of the visceral pleura (as is most often the case except in Stage I disease) placement of an indwelling pleural catheter such as the PleurX® catherer (CareFusion, San Diego, CA) is preferable. This procedure is most easily performed on an outpatient basis and avoids hospitalization. In addition, complete lung re-expansion is not required to obtain control of the effusion. Tumor progression along the tract of the catheter has been described but is uncommon [30, 63]. VATS is the preferred method for pleurodesis, particularly in cases where the effusion may be loculated, but will ultimately only be successful in cases where expansion of the majority of the lung can be achieved. In addition to drainage of effusion, VATS provides large quantities of tissue for diagnosis and histologic subtyping. Limited visceral decortication can occasionally free entrapped lung, but the case must be taken to limit air leaks as these can lead to the requirement for prolonged chest tube drainage.

7.5.2 Pleurectomy

Pleurectomy and decortication (PD) have long been used for the control of malignant effusions [8, 10]. The aim of palliative PD is to enable lung re-expansion, ameliorate the contracting effect of tumor on the ribs and intercostal muscles, and to create pleural symphasis. Palliative PD is best accomplished via a posterolateral thoracotomy. Although limited PD can be easily accomplished through a muscle sparing incision, if there is significant tumor burden division of the latissimus dorsi muscle and resection of the seventh rib can greatly facilitate exposure and resection. Dissection is begun by establishing a

plane between the involved pleura and the endothoracic fascia. This is most easily accomplished using sharp dissection initially followed by blunt finger dissection. Chest wall bleeding may be controlled using gauze pads for tamponade or use of electrocautery, argon beam coagulation, or radiofrequency such as the highly effective AquaMantys® radiofrequency system (Salient Surgical Technologies, Portsmouth, NH). Once the lung and parietal pleura have been completely mobilized, dissection of the visceral pleura away from the underlying lung parenchyma is performed. The tumor rind is incised on the lateral aspect of the mobilized lung and using sharp dissection a plane is created immediately beneath the visceral pleura. Once established, dissection is continued in all directions using a peanut retractor or using a finger and gauze pad. The pericardium and diaphragm are frequently involved, or at least inseparable from tumor. If palliation is the intent of the procedure rather than cytoreduction, these structures should remain intact, leaving tumor in place where necessary.

Quality of life improvements after palliative PD have not been extensively documented and no prospective comparisons between best supportive care and PD exist. Martini et al performed PD on 14 patients with MPM and obtained control of pleural effusion in all patients. Brancatisano et al. performed subtotal parietal pleurectomy in 45 patients and combined this with decortication in 28 patients [10]. There was only one (2%) case of symptomatic recurrence of effusion. In a prospective study evaluating the efficacy of subtotal pleurectomy and intrapleural (i.p.) for MPM, Sauter and colleagues performed pleurectomy only ($n = 7$) or pleurectomy and i.p. cisplatin and cytosine arabinoside ($n = 13$) on 20 patients with early stage MPM [60]. Pleurectomy prevented recurrence of effusion in 80% of patients, with or without chemotherapy, however dyspnea was improved in less than half the patients and pain relief was improved in only 21%. The largest study that has evaluated symptom outcomes following PD was that reported by Soysal et al who retrospectively reviewed 100 consecutive cases of PD performed for palliation of MPM [64]. Chest pain was the most common presenting feature (71%) followed by pleural effusion (54%) and dyspnea (37%). Pleural effusion was controlled in 52/54 (96%) of patients who presented with symptomatic effusion, chest pain was relieved or improved in 85% and cough and dyspnea improved in all patients. Importantly, symptom relief was achieved for up to 6 months.

Though palliative pleurectomy can achieve excellent control of pleural effusion, it requires a thoracotomy and the associated morbidity may negate some of the potential advantages of pleurectomy, particularly with respect to the control of pain. For this reason video-assisted thoracoscopic surgery (VATS) debulking has emerged as a possible option for palliative pleurectomy. Waller initially described this technique in 19 patients with malignant effusion [79]. At a median follow-up of 12 months, symptomatic recurrent effusion had developed in 3 (16%) patients. It is of concern that tumor seeding at thoracostomy sites developed in 5 of 13 (38%) patients with MPM. The same group later reported their experience with palliative surgical debulking in 51 patients with MPM [36]. Parietal pleurectomy was performed in 17 (34%) patients while pleurectomy and decortication was required in the remainder (3 by VATS and 31 by thoracotomy). Morbidity included prolonged air leaks in 19% and empyema in 2%. Thirty-day mortality was 8% and was 14% by 6 weeks. Significant improvement in dyspnea and pain score was achieved at 6 weeks and 3 months. Patients with epithelial cell type and no weight loss were significantly more likely to retain symptomatic control than those without these features. Symptom relief was found to persist until tumor recurrence, and median survival for patients with non-epithelioid tumors in this study was only 4.4 months, suggesting that surgical palliation may not be appropriate for patients

with biphasic or sarcomatoid tumors. There is currently a prospective randomized phase III trial (MESOVATS) ongoing in the UK, which compares VATS pleurectomy with talc pleurodesis in patients with MPM [http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=1352].

7.6 Cytoreductive Surgery

The aim of cytoreductive surgery is to provide a removal of all macroscopic tumor from the hemithorax [65]. It is postulated, though unproven, that R0/R1 cytoreduction may prolong survival in patients particularly those with epithelioid tumors who do not have lymph node metastases. Cytoreductive surgery is usually accomplished in the setting of bi- or tri-modality therapy. Local tumor control appears to be improved with R0/R1 cytoreduction and adjuvant radiation therapy. Because of the high rate of distant recurrences (as high as 50%), systemic therapy is usually also advisable, though the effect of chemotherapy on reducing distal recurrence is unproven. There are two approaches to cytoreduction: extrapleural pneumonectomy and extended pleurectomy/decortication (or radical pleurectomy/decortication). Each has its merits as well as limitations and will be discussed separately below.

7.6.1 Extrapleural Pneumonectomy (EPP)

7.6.1.1 Technique

Extrapleural pneumonectomy involves the *en-bloc* resection of the parietal and visceral pleura, lung, ipsilateral pericardium and diaphragm (Fig. 7.5). Preoperative placement of defibrillator EKG leads is performed in the event of an intraoperative rapid supraventricular arrhythmia that requires synchronized cardioversion. Because of the potential risk of injury to the superior vena cava during dissection of right-sided tumors, large bore femoral venous access is obtained. A nasogastric tube is placed, which

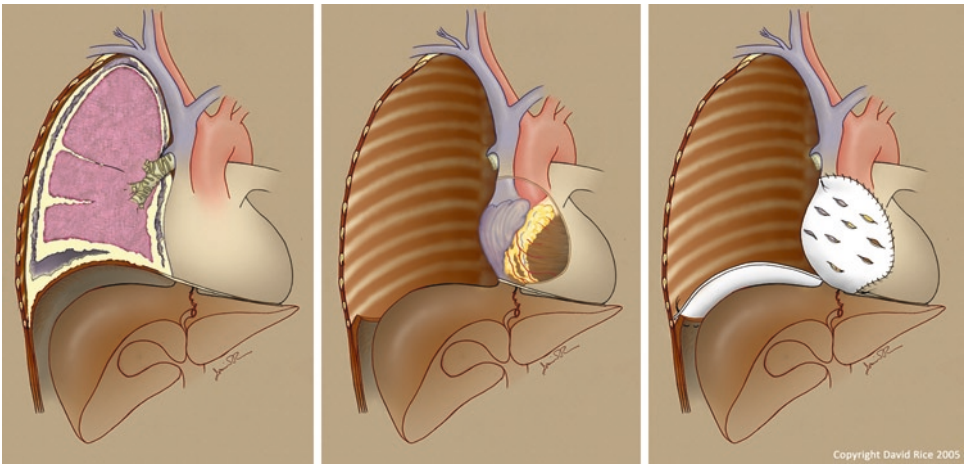

Fig. 7.5 Extrapleural pneumonectomy involves the en bloc resection of the parietal and visceral pleura, lung, ipsilateral pericardium, and diaphragm with reconstruction of the latter two structures, in this case with polytetrafluoroethylene (PTFE) membrane

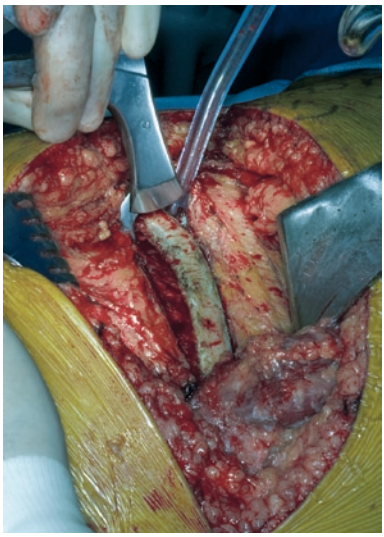

Fig. 7.6 For extrapleural pneumonectomy an extended posterolateral thoracotomy incision is made, resecting the sixth or seventh rib

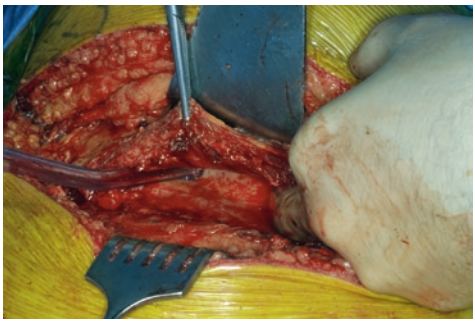

Fig. 7.7 The extrapleural plane is identified using sharp dissection and then developed using blunt dissection

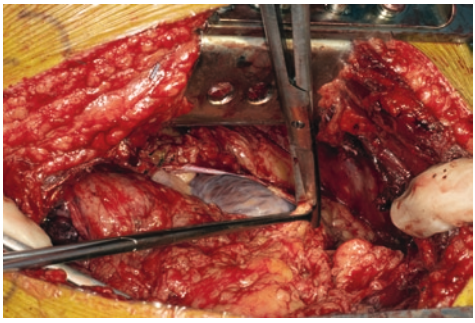

Fig. 7.8 The pericardium is incised sharply anterior to the fused pleura and resected en bloc with the lung

aids in identification of the esophagus during posterior dissection. A generous posterolateral thoracotomy incision is performed, extending the incision anteriorly in line with the underlying ribs. The latissimus dorsi muscle is divided but the serratus anterior muscle should be spared. In the event of a postoperative bronchopleural fistula, an intact serratus muscle is useful for repair. The anterior most attachments of the muscle should be elevated off the underlying chest wall and retracted superiorly. Removal of the seventh rib provides optimal access to the extrapleural plane, which should initially be developed sharply (Fig. 7.6). Once the correct plane is identified it may be extended in all directions using blunt dissection (Fig. 7.7). It is useful to place gauze packs in areas that have been dissected to tamponade oozing from the chest wall. We have found the preoperative intravenous administration of tranexamic acid to be useful to control chest wall oozing. The Aquamantys® radiofrequency system (Salient Surgical Technologies, Portsmouth, NH) or an argon beam coagulator is useful for direct control of chest wall bleeding. Once the extrapleural plane has been dissected to the level of the hilum anteriorly and posteriorly, an incision is made in the pericardium anterior to the phrenic nerve, and the pericardium attached to the overlying pleura and tumor is resected en-bloc with the specimen (Fig. 7.8). Finally, the diaphragm is resected along with the associated overlying lung and tumor. Generally, the diaphragmatic fibers can be bluntly avulsed from their peripheral attachments followed by sharp or cautery dissection of intervening fibers (Fig. 7.9). Once the peripheral attachments are taken down, blunt dissection with sponge forceps allows the

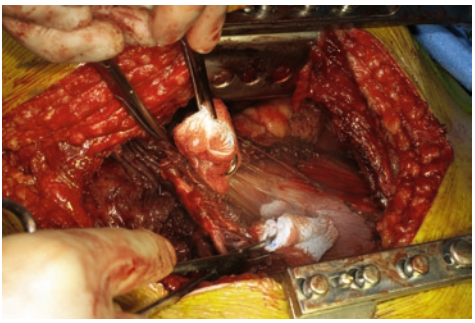

Fig. 7.9 The diaphragm fibers are bluntly avulsed from their lateral attachments and the diaphragm then resected en bloc with the lung. Use of sponge forceps is helpful in preserving the peritoneum. Small defects can later be closed with a running absorbable suture

muscle to be separated from the underlying peritoneum. It can be difficult to keep the peritoneum entirely intact, especially in the region of the central tendon; however, lacerations in the peritoneum can be easily repaired with a fine absorbable suture. The unproven rationale for maintaining the integrity of the peritoneum is that it preserves the integrity of the abdominal cavity from potential contamination with tumor from the chest. In the region of the esophageal hiatus, it is ideal to preserve some of the crural fibers to mitigate against herniation of the stomach into the post-pneumonectomy space. Once the entire specimen has been mobilized the hilar structures can be divided. The pulmonary artery and veins should be divided first. The main bronchus is freed of surrounding tissue to the level of the carina. A firing of the stapling device (generally a TA-30 3.0 mm) is placed on the distal bronchus first. This allows the anesthesiologist to retract the end of the left-sided double lumen endotracheal tube back into the trachea while preventing ventilation of the left lung for left-sided tumors. Additionally, it prevents migration of bronchial secretions into the chest cavity after division of the main bronchus. The stapling device is then placed across the main stem bronchus at the level of the carina and two separate rows of staples fired before division of the bronchus. Application of the stapler under direct bronchoscopic examination can be useful to ensure that the bronchial stump is flush with the carina and that there is no redundant bronchus left that will retain secretions. Once the specimen is removed from the chest cavity, hemostasis is secured and the cavity irrigated with at least 3 L of weak betadine solution [68]. The anterior and inferior margins of resection are marked with numerous titanium clips to aid in planning of adjuvant radiotherapy (Fig. 7.10).

Reconstruction of the diaphragm is then performed, most often using a large membrane of polytetrafluoroethylene (PTFE, Gore, Flagstaff, AZ). The PTFE patch is secured to the remaining diaphragmatic fibers medially using interrupted 0.0 or 1.0 polypropylene (Fig. 7.11). Laterally, the patch is secured to the chest wall

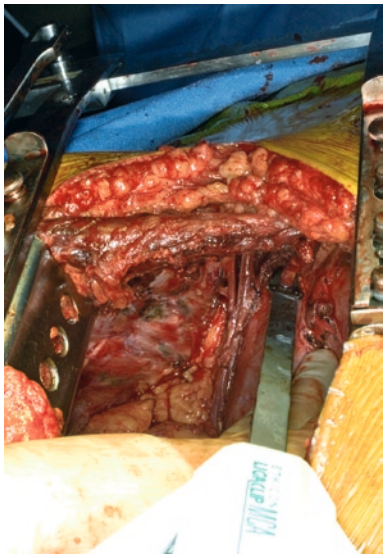

Fig. 7.10 If postoperative radiation is to be administered the anterior and inferior margins of resection should be marked with titanium clips as this will allow more accurate targeting of the entire at-risk area during dosimetry planning

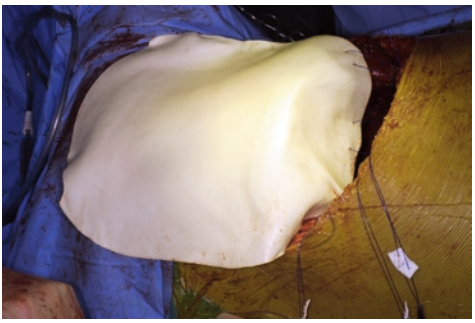

Fig. 7.11 The diaphragm is then reconstructed using nonabsorbable material, in this case 2 mm thick polytetrafluoroethylene mesh (DualMesh, Gore, Flagstaff, AZ)

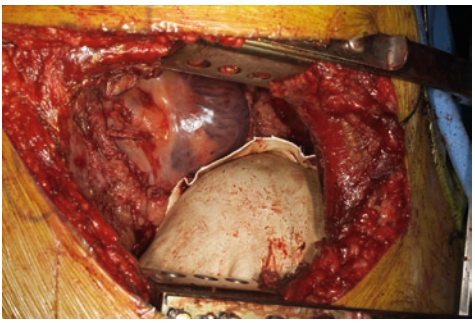

Fig. 7.13 The diaphragm should be reconstructed as low down on the chest wall as possible which facilitates postoperative adjuvant radiation planning and limits surrounding organ toxicity

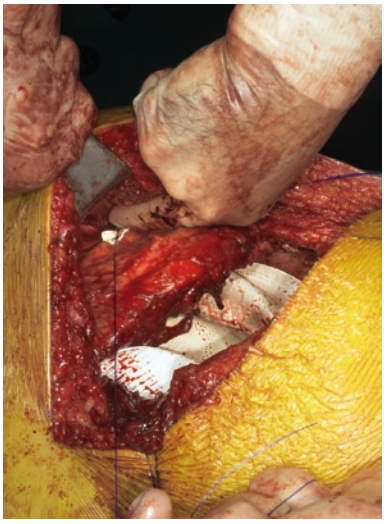

Fig. 7.12 The diaphragm is secured laterally to the intercostal spaces using nonabsorbable pledgeted horizontal mattress sutures

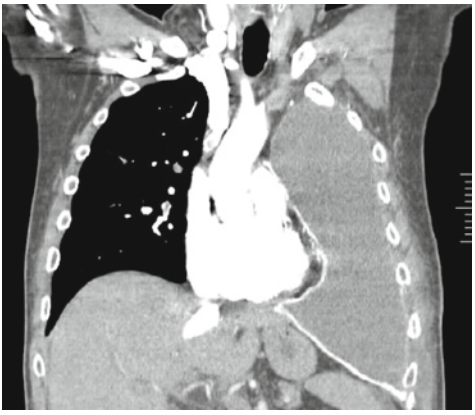

Fig. 7.14 The completed reconstruction of the diaphragm

using pledgeted horizontal mattressed sutures through the intercostal spaces (Fig. 7.12) [68]. Although sutures can be placed around the ribs themselves, there is the risk of nerve entrapment and greater postoperative discomfort with this technique. The patch should be placed as low down as possible in the chest cavity to enable optimal targeting of the entire thoracic cavity, however care must be taken not to place the mesh under undue tension as this can adversely affect ipsilateral movement of the mediastinal structures in the postoperative period, and also lead to suture disruption (Fig. 7.13). Medially, the patch is sewn to the remaining pericardium and care should be taken to ensure that the cut ends of the polypropylene sutures are not at risk for injury to the heart. Use of a softer nonabsorbable suture such as Ethibond may be a better choice in this location (Fig. 7.14). Once the diaphragm has been reconstructed, the pericardium is then replaced using either Dexon mesh or

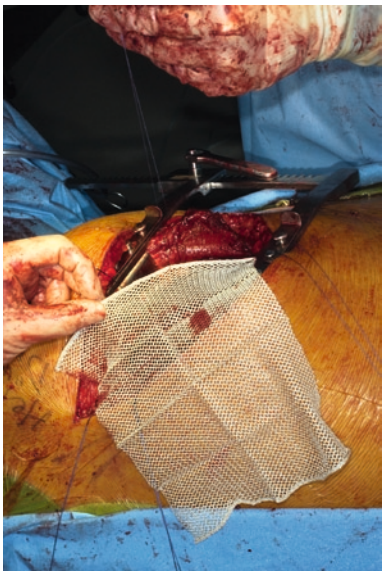

Fig. 7.15 The pericardium is reconstructed using fenestrated mesh, in this case polyglycolic acid (Dexon) mesh

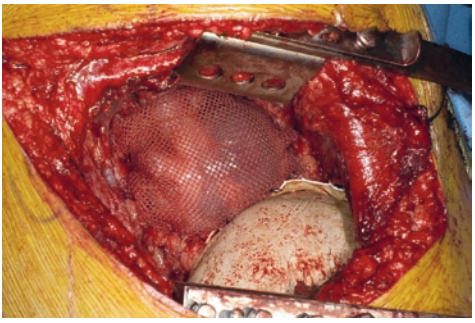

Fig. 7.16 The completed pericardial reconstruction. Care should be taken to ensure that the mesh is placed loosely to avoid compression of the right atrium once the patient is returned to a supine position

fenestrated PTFE membrane (Fig. 7.15). This can be sewn to the edges of the remaining pericardium with interrupted 2.0 or 3.0 polyethyleneglycol sutures. The pericardial patch should be reconstructed loosely to allow for the heart and mediastinum to shift slightly toward the pneumonectomy space (Fig. 7.16). Too tight a patch can result in hypotension and limit desired ipsilateral mediastinal shift [68]. After reconstruction of the diaphragm and pericardium the chest cavity is irrigated with normal saline and a single large bore thoracostomy tube placed which is connected to a balanced pneumonectomy drain.

7.6.1.2 Postoperative Care

Though postoperative care is similar to that of any pneumonectomy, certain points are worthy of mention. Early mobilization should be encouraged to lessen the risk of contralateral atelectasis and pneumonia. Transient gastroparesis can occur following EPP, especially where one or both vagus nerves have been injured or sacrificed during dissection, therefore nasogastric drainage should be continued during the first 24 h and great care taken when advancing diet. Because of the greater degree of chest wall oozing and drainage after EPP compared to standard pneumonectomy, it is advisable to leave the chest drain in place for at least 48 h. Earlier withdrawal may allow excessive amounts of fluid to accumulate early in the pneumonectomy space which may cause contralateral mediastinal shift and cardiopulmonary dysfunction. Additionally, excellent control of postoperative pain is required not only for patient comfort but also for optimal respiratory function. Epidural analgesia generally provides better control of pain than intravenous narcotics, and because of the extended thoracotomy incision epidural analgesia should be continued for at least 4–5 days after surgery.

7.6.1.3 Adjuvant Therapy

Extrapleural pneumonectomy generally provides a more complete cytoreduction compared to radical P/D since the entire lung is removed, limiting the area at risk for local recurrence to the chest wall and mediastinum contiguous with

the resected tumor. As the lung is resected, adjuvant radiation may be administered to the post-pneumonectomy space. Hemithoracic radiation following P/D is problematic because it is technically difficult to deliver adequate tumoricidal doses of radiation to the entire at-risk area without causing severe toxicity to the underlying lung. Furthermore, conventional photon/electron beam radiotherapy has not been shown to decrease local recurrence after P/D [26, 33]. EPP is associated with significantly higher postoperative morbidity than P/D, and in most series mortality is also higher (3–8% in experienced centers, Table 7.1) [24, 37, 59, 68, 69, 74].

Extrapleural pneumonectomy is usually performed as part of a multimodality therapeutic regimen (Table 7.2). In the absence of adjuvant therapy local recurrence rates range between 30% and 50%. Two recent studies have demonstrated the efficacy of hemithoracic radiation in reducing local recurrence after EPP. In a phase II multicenter study from Memorial Sloan Kettering Cancer Center (MSKCC), Rusch et al delivered 54 Gy of irradiation to 54 patients who had undergone EPP [59]. Radiotherapy was performed using anteroposterior photon beams, placing specially designed blocks over radiation sensitive structures after threshold doses for those organs had been achieved. The corresponding underdosed areas of the chest wall were then treated with matched electron beams. Local recurrences occurred in only 13% and were mainly in the posteroinferior paravertebral sulcus, areas difficult to adequately treat with this radiotherapy technique. Patients with stages I and II had a median survival of 33.8 months whereas the median survival of patients with stage III or IV was only 10 months. A retrospective study, from the M.D. Anderson Cancer Center (MDACC), evaluated 63 patients treated with intensity modulated radiation therapy (IMRT) (median dose 45 Gy) after EPP [52]. IMRT has advantages over conventional radiation because the entire hemithorax can be more accurately targeted while limiting radiation toxicity to surrounding structures. In-field recurrences occurred in only 5% and overall locoregional recurrence was 13%. It should be kept in mind that the patients treated in both these studies were of advanced stage − 69% stage III/IV in the MSKCC study; 87% stage III/IV in the MDACC study. Despite excellent local control, however, distant metastases occurred in 63% and 54% of patients in each study, respectively, suggesting the need for systemic treatment in addition to local therapy.

Accordingly, trimodality therapy incorporating adjuvant or neoadjuvant chemotherapy is now recommended by most specialist centers. The Brigham and Women's Hospital has utilized trimodality therapy since the early 1980s. The regimen originally included EPP followed by platinum-based chemotherapy and hemithoracic radiation to 30 Gy. In 1999, Sugarbaker reported the results in 183 consecutive patients with MPM treated with this regimen [67]. Although seven patients who died within 30 days were excluded from the final survival analysis, median survival was 19 months and 2-year and 5-year survival was 38% and 15%, respectively. Of 31 (18%) patients with epithelioid, node-negative tumors and negative margins (and who survived surgery), median survival was 51 months, and 2-year and 5-year survival was 68% and 46%, respectively. Local recurrence rates were high, however, most likely due to the lower doses of radiation used and the fact that only regions of the hemithorax thought to be "at risk" for recurrence were targeted rather than the entire hemithorax. Details of the radiation treatment of a subset of these patients who received their radiation treatment at the Brigham and Women's Hospital were reported by Baldini and colleagues [7]. Local recurrence developed in 46% patients. Reasons for failure were likely twofold. First, radiation doses less than 45 Gy are generally not tumoricidal for MPM. Second, diaphragm reconstruction was performed well

Table 7.1 Studies including extrapleural pneumonectomy: tumor characteristics, operative mortality and survival

Author	Year	*n*	Age (years)	Epithelial (%)	Stage III/IV (%)	N2 (%)	Perioperative Mortality (%)	Survival			
								Median (mo)	1-year (%)	2-year (%)	5-year (%)
Butchart [11]	1976	29	52	38	NR	NR	31	5		10	3.5
Ruffie [55]	1989	23	61	NR	NR	NR	13	9		17	
Rusch [57]	1991	20	60	NR	NR	NR	15	11		33	
Sugarbaker [66]	1991	31	53	53	NR	29	6	21	70	48	
Allen [3]	1994	40	55	64	49	NR	8	13	53	23	10
Sugarbaker [67]	1999	183	57	59	NR	23	4	19		38	15
Aziz [6]	2002	64	57	54	NR	22	9	13–35	84		
Weder [80]	2004	16	57	74	NR	38	0	23	79	37	
dePerot [16]	2007	50	58	72	76	42	8	11			
Rice [52]	2007	100	60	67	87	40	8	10		26	
Weder [81]	2007	45	59	69	25	11	2	23			
Rea [48]	2007	17	59	95	76	24	0	28	82	59	24
Flores [23]	2007	208	NR	69	78	NR	5	14			
Edwards [19]	2007	105	NR	74	85	42	7	15	59	31	
Flores [24]	2008	385	60	69	75	NR	7	12			
Yan [84]	2009	70	55	83	NR	24	6	20	62	41	15
Trousse [74]	2009	83	60	82	53	20	5	15	62	32	14
Tilleman [69]	2009	96	60	55	81	NR	4	13			
Hasani [27]	2009	18	57	67	22	39	11	19	76		
Krug [31]	2009	54	63	82	NR	27	4	22	65	37	
dePerot [17]	2009	45	60	73	58	36	7	14			10

NR Not reported

Table 7.2 Studies incorporating multimodality therapy with extrapleural pneumonectomy in which both survival and recurrence rates were documented

Study	Year	*n*	Epithelial (%)	Stage III/IV (%)	Chemotherapy	Radiotherapy	Local failure (%)	Distant failure (%)	Median survival (mo)
Baldini [7]	1997	49	71	NR	Adjuvant systemic	Hemithoracic, 31 Gy	46	29	22
Rusch [59]	2001	54	68	69	None	Hemithoracic, 54 Gy	13	56	17
Schouwink [61]	2001	28	61	68	Intra-op PDT	None	31	40	10
Aziz [6]	2002	51	54	All cI-II	Adjuvant systemic	None	17	49	35
Yajnik [83]	2003	35	74	57	None	Hemithoracic, 54 Gy	37	NR	NR
Weder [80]	2004	13	56	80	Adjuvant systemic	Local, 45–60 Gy or hemithoracic, 30 Gy	62	NR	23
Rice [52]	2007	63	71	87	None	Hemithoracic IMRT, 45–50 Gy	13	54	14
Allen [3]	2007	39	64	69	Adjuvant systemic	Hemithoracic, 30 Gy	41	49	19
De Perot [16]	2007	50	72	76	Neoadjuvant systemic	Yes†48%	35	36	11
Miles [41]	2008	13	77	76	Adjuvant systemic	Hemithoracic IMRT, 45 Gy	46	31	NR
Flores [24]	2008	385	69	75	Adjuvant systemic	Type not specified	33	66	12
vanSandick [77]	2008	15	93	NR	None	Hemithoracic, 54 Gy	33	67	29
Tilleman [69]	2009	92	58	84	Intraop hyperthermic chemotherapy	None	17	62	13
Krug [31]	2009	54	82	46	Neoadjuvant systemic	Hemithoracic, 46 Gy	20	28	22

NR Not reported

above the original site of insertion of the diaphragmatic fibers. Radiation fields extended to the reconstructed diaphragm, but not below, thereby leaving a large area of the inferior and posterior chest untreated. Not surprisingly it was in this area where most recurrences occurred.

7.6.2 Pleurectomy/Decortication (P/D)

The term "pleurectomy/decortication" can mean different things to different surgeons. It can refer to a partial debulking of tumor from the parietal and visceral pleural surfaces leaving large amounts gross tumor behind, it can be a subtotal resection of the parietal and visceral pleura leaving behind only minimal amounts of macroscopic tumor, or it can include complete removal of all macroscopic tumor, which usually entails resection and reconstruction of the diaphragm and pericardium in addition to total pleurectomy (Fig. 7.17). In terms of cytoreductive surgery, the latter procedure is optimal and is frequently termed "extended" or "radical" pleurectomy/decortication to distinguish it from lesser debulking procedures.

7.6.2.1 Technique

Radical P/D begins with a complete extrapleural mobilization of the lung to the level of the hilar structures similar to that performed during the initial dissection for EPP. If the pleura/tumor is inseparable from the pericardium or diaphragm (as it most often is) these structures are resected and reconstructed in a manner similar to that of EPP. Once the lung and overlying pleura have been completely mobilized, an incision is made in the parietal pleura and taken through the tumor and visceral pleura down to the level of the lung parenchyma. Using sharp dissection a plane is created immediately underneath the visceral pleura. This plane is then further elaborated using blunt dissection with a peanut sponge or a gauzed finger (Fig. 7.3). Paradoxically, this is often more easily accomplished in patients who have a significant tumor rind as it can be difficult to completely remove minimally involved pleura. Although the lung parenchyma often bleeds it will usually abate quickly. In this way the entire visceral pleura and overlying tumor and parietal pleura can be resected down to the hilar

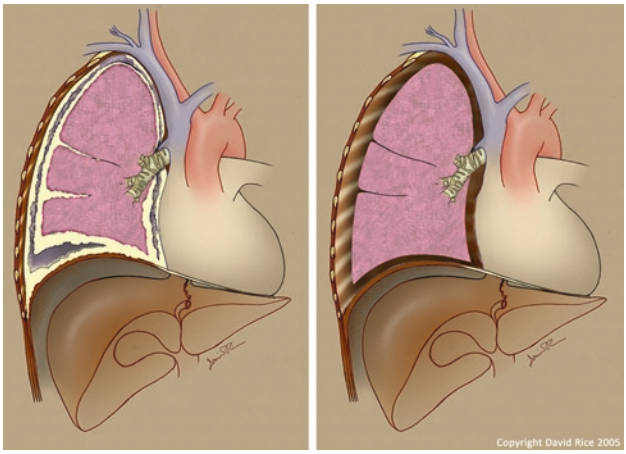

Fig. 7.17 Pleurectomy/decortication involves resection of the tumor involved parietal and visceral pleura, and leaves the lung in situ. If tumor involves the pericardium and diaphragm these structures can be resected and reconstructed in a manner similar to extrapleural pneumonectomy

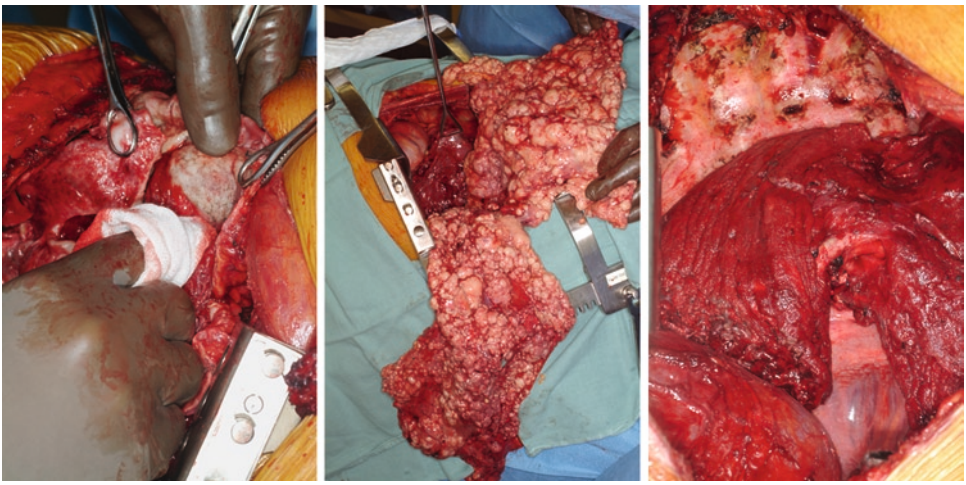

Fig. 7.18 Once the tumor rind is incised down to the level of the underlying parenchyma the lung tissue can be bluntly swept away from the overlying visceral pleura. If the fissures are involved with disease they should be dissected down to the level of the pulmonary vessels to remove all macroscopic tumor

structures. The pleura is traced all the way into the fissures, and the pulmonary artery and veins will usually be encountered and should be completely freed of any overlying pleura or tumor (Fig. 7.18). Occasionally, lung parenchyma that has been atelectatic for lengthy periods from overlying tumor will seldom expand, and these areas are often best resected with a linear stapler. Similarly, portions of lung that have been devitalized during dissection or those with significant lacerations are often best removed. Though usually all tumor can be resected from the underlying lung, occasionally and in particular in early stage disease, there can be a multitude of tiny subpleural tumor deposits that remain adherent to the lung after visceral pleurectomy. These may be directly removed using sharp dissection or may be ablated using thermal energy (argon beam [82], electrocautery, radiofrequency ablation, or cryoablation (personal observation)) (Fig. 7.19). Typically, there are three large-bore chest drains : one over the diaphragm coursing posteriorly to drain the costovertebral recess, one in the posterior sulcus, and one anteriorly.

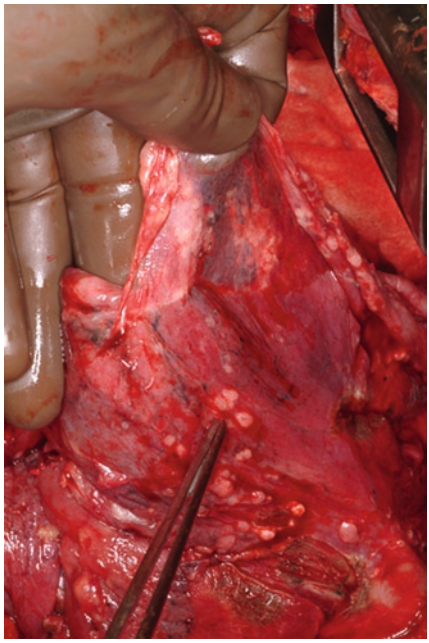

Fig. 7.19 Occasionally multiple small subpleural deposits will be encountered which remain after visceral decortication. These deposits can be individually resected or locally ablated using thermal energy

7.6.2.2 Postoperative Care

Because the chest wall can continue to slowly ooze blood and maximum expansion of the lung is ideal postoperatively, it can be helpful to keep patients intubated overnight following pleurectomy/decortications. This ensures maximal expansion of atelectatic lung and the inflated lung aids in tamponading diffuse chest wall oozing. Air leaks are prominent, particularly on positive pressure ventilation, but will usually subside within a week. Chest drains are placed at the lowest amount of suction that is sufficient to maintain complete expansion of the lung, usually negative 10–20 cm H_20.

7.6.2.3 Adjuvant Therapy

Because the lung is left in situ, P/D offers less complete cytoreduction than EPP but impacts pulmonary function significantly less. This is reflected in the lower perioperative mortality reported in most series compared to EPP (Table 7.3), and also in the higher incidence of local recurrence, which generally ranges from 50% to 100% (Table 7.4). Unlike EPP, the intact lung that remains limits the ability to administer effective radiation postoperatively. Gupta et al reported 123 patients who received hemithoracic radiation therapy (median 43 Gy) similar to the regimen used at MSKCC for EPP [26]. Despite a preponderance of patients with stage I and II (59%) median survival was only 14 months, and local recurrence occurred in 56% of patients. Similarly, Lee and colleagues performed P/D on 26 patients using intraoperative radiation followed by postoperative 3-dimensional conformal radiation or IMRT [33]. 69% of patients had stage I disease and so it is not surprising that the median survival was reasonably good (18 months). Fifty percent of patients had recurred or died by 1 year however, and although the exact frequency of local recurrences was not reported, the authors stated that most patients died from progressive disease, and that the "site of failure was mostly locoregional."

7.6.3 Intrapleural Therapies

The relatively high local recurrence rate following cytoreductive surgery alone has prompted use intrapleural therapies after PD or EPP (Table 7.5). These have primarily involved intrapleural administration of platinum-based chemotherapy or intracavitary photodynamic therapy (PDT) with preoperatively administered photosensitizers. The concept behind intrapleural therapy is straightforward – extrapleural dissection of mesothelioma cannot reliably achieve an R0 resection and microscopic tumor deposits are frequently left behind. This is evident in local recurrence rates of up to 30–50% following EPP alone. Because of the even greater propensity for microscopic, and even macroscopic tumor remnants following pleurectomy/decortication, local recurrence rates can be as high as 70–100% with this procedure. Intrapleural chemotherapy is theoretically able to treat the entire at-risk area of the hemithorax and has been shown to permeate up to 5 mm into tissue. Most trials of ip chemotherapy however have been small phase I and II studies with limited numbers of patients. Rates of local recurrence have varied between 17% and 100% (Table 7.6). Earlier studies tended to rely on the instillation of chemotherapeutic agent into the chest cavity via chest drains in the postoperative period. More recently, capitalizing on the tumoricidal effect of hyperthermia, investigators have evaluated intraoperative intrapleural perfusion of cytotoxics heated to 42°C. The largest study of this nature was recently reported by Tilleman and colleagues from the Brigham and Women's Hospital [69]. Ninety-two patients were enrolled on a phase II study which included EPP and intraoperative heated chemoperfusion with cisplatin. Renal function was maintained by

Table 7.3 Studies including pleurectomy/decortication: tumor characteristics, operative mortality and survival

Author	Year	*n*	Age (years)	Epithelial (%)	Stage III/IV (%)	Perioperative mortality (%)	Survival			
							Median (mo)	1-year (%)	2-year (%)	5-year (%)
McCormack [39]	1982	33	NR	100	NR	0	21	NR	NR	NR
Hilaris [29]	1984	41	58	68	NR	0	21	65	40	NR
Allen [2]	1994	56	64	50	NR	5	9	30	9	5
Rusch [58]	1994	27	62	70	52	4	18	69	40	NR
Martin- Uncar [36]	2001	51	63	67	NR	8	7	31	NR	NR
Ceresoli [12]	2001	54	60	73	41	NR	12.5–14	50–63	NR	NR
Aziz [6]	2002	47	NR	NR	NR	0	14	NR	NR	NR
Colaut [13]	2004	40	60	NR	23	3	11	NR	28	3
Flores [23]	2007	176	NR	NR	NR	3	16	NR	NR	NR
Flores [24]	2008	278	63	64	65	4	16	NR	NR	NR
Bolukbas [9]	2009	35	65	77	54	3	30	69	50	NR

NR Not reported

Table 7.4 Studies incorporating multimodality therapy with pleurectomy/decortication in which both survival and recurrence rates were documented

Study	Year	*n*	Epithelial (%)	Stage III/IV (%)	Chemotherapy	Radiotherapy	Local failure (%)	Distant failure (%)	Median survival (mo)
Hilaris [29]	1984	41 PD	68	NR	Adjuvant systemic	Brachytherapy, intrapleural 32P, hemithoracic 45 Gy	71	54	21
Rusch [58]	1994	27 PD	70	52	Adjuvant intrapleural, systemic	None	85	20	18
Lee [32]	1995	15 PD	46	NR	Adjuvant intrapleural, systemic	Type not specified	100	0	12
Monneuse [42]	2003	17 PD	NR	NR	Adjuvant intrapleural	None	59	18	18
Colaut [13]	2004	40 PD	NR	23	Adjuvant systemic	Local, 10 Gy	86	0	11
Matzi [38]	2004	25 PD	56	100	Intraop PDT + hyperbaric O2 (14 pts)	None	48	NR	14
Richards [54]	2006	44 PD	55	39	Intraop hyperthermic chemotherapy	None	57	43	13
Lucchi [35]	2007	49 PD	80	82	Adjuvant intrapleural, systemic	Local 30 Gy	90	14	26
Flores [24]	2008	278 PD	64	65	Adjuvant systemic	Type not specified	65	35	16
Bolukbas [9]	2009	35 PD	77	54	Adjuvant systemic	Local, 21 Gy–50 Gy	36	24	30

NR Not reported

Table 7.5 Studies including intrapleural therapy: tumor characteristics, operative mortality, and survival.

Author	Year	Surgery	Intrapleural therapy	Epithelioid (%)	Stage III/IV (%)	Perioperative Mortality (%)	Survival		
							Median (mo)	2-year (%)	3-year (%)
Rusch [58]	1994	27 PD	Postop ip Cis/MMC	70	52	4	18	40	
Rice [50]	1994	9 PD/10 EPP	Post-op ip Cis/MMC (PD) or Cis (EPP)	NR	NR	5	13		17
Lee [32]	1995	15 PD	Postop ip Cis/cytosine arabinoside	46	NR	0	12		7
Colleoni [14]	1996	20 PD	Postop ip Cis/cytosine arabinoside	50	NR	0	12		
Pass [46]	1997	11 PD/14 EPP	Intraop Porfimer Na PDT	68	84	4	14		
Moskal [43]	1998	33 PD/7 EPP	Intraop Porfimer Na PDT	63	NR	8	15	23	
Schouwink [61]	2001	28 EPP	Intraop Tetrahydroxyphenylchlorin PDT	61	68	11	10		
Aziz [6]	2002	51 EPP	Postop ip Carboplatin	54	All c I-II	9	35		48
Monneuse [42]	2003	17 PD	Intraop ip hyperthermic MMC (7) MMC/Cis (10)	NR	NR	6	18	50	42
Friedberg [25]	2003	19 PD/7 EPP	Intraop Foscan PDT	64	NR	10	12	40	
van Ruth [76]	2004	12 PD/8 EPP	Intraop hyperthermic Cis/Doxorubicin	80	NR	0	11	<20%	NR
Matzi [38]	2004	14 PD	Intraop Porphyrin PDT + hyperbaric O2	56	100	0	14		
Richards [54]	2006	44 PD	Intraop ip hyperthermic Cis	55	39	11	13	30	20
Lucchi [35]	2007	49 PD	IL-2 + Epidoxorubicin	80	82	0	26		
vanSandick [77]	2008	12 PD/8 EPP	Intraop ip hyperthermic Cis	80	NR	0	11	15	10
Tillenam [69]	2009	92 EPP	Intraop ip hyperthermic Cis	58	84	4	13		25

NR Not reported

Table 7.6 Combined series of extrapleural pneumonectomy and pleurectomy/decortication with multimodality intrapleural therapy

Study	Year	*n*	Epithelial (%)	Stage III/IV (%)	Chemotherapy	Radiotherapy	Local failure (%)	Distant failure (%)	Median survival (mo)
Pass [45]	1997	11 PD/ 14 EPP	68	84	Intraop PDT, Adjuvant systemic	None	76	16	14
Pass [45]	1997	12 PD/ 11 EPP	70	83	Adjuvant systemic, αIFN	None	74	8	14
Friedberg [25]	2003	19 PD/ 7 EPP	64	NR	Intraop PDT	None	15	15	12
van Ruth [76]	2004	12 PD/ 8 EPP	80	NR	Intraop hyperthermic chemotherapy	Local 24 Gy, 3 fx	55	40	11
vanSandick [77]	2008	12 PD/ 8 EPP	80	NR	Intraop hyperthermic chemotherapy	Local, 24 Gy	80	55	11

NR Not reported

the concomitant administration of sodium thiosulfate and amifostine. Though recurrence within the ipsilateral chest was low (17%) and operative mortality 4%, median survival was only 13 months. Admittedly, nearly half of the patients had stage III disease and 42% had non-epithelioid histology. Thirty-two percent recurred in the contralateral chest and 26% in the abdomen, highlighting the need for more effective systemic therapies. The same group previously published their experience using a similar regimen in 44 patients who were ineligible for EPP and who underwent PD instead [54]. Local recurrence was 57% and treatment related mortality was 11%, probably at least somewhat related to the fact that this was an older, higher risk group.

Photodynamic therapy has been evaluated in at least four phase I/II studies [25, 38, 43] and a single phase III trial [45]. Local recurrence rates have varied between 15% and 76% and median survival ranged from 10 to 15 months. Treatment-related toxicity has been an issue and one study reported two deaths, one related to a bronchopleural fistula, and another due to esophageal fistulization [61]. A single randomized study has been conducted which compared patients who underwent cytoreduction surgery with or without PDT [45]. Adjuvant immunochemotherapy was administered to both groups. No differences in overall or progression free survival was noted between groups.

7.6.4 Extrapleural Pneumonectomy Versus Pleurectomy/Decortication

There is considerable controversy over the selection of which operation is the most appropriate. Some surgeons perform only EPP, others only P/D, and many tailor selection of operation to the patient and the degree of tumor load. As previously mentioned, in addition to the oncologic pros and cons of either operation, selection must also take into account the application of adjuvant therapies as well as patient and tumor-related factors. Clearly, an elderly patient or one with poor cardiopulmonary function is unlikely to tolerate EPP and would be better served with P/D. Patients with non-epithelioid histology

(especially sarcomatoid) have poor outcome after EPP and these patients should also probably undergo P/D if surgery is even contemplated at all. The controversy exists mainly around good performance status patients with epithelioid tumors in whom either operation would be technically feasible. There have been no randomized prospective comparisons of these procedures in carefully staged and stratified patients. The largest retrospective comparison of EPP and P/D that exists was performed by Flores and colleagues who reported a combined series from three separate institutions that included 663 patients [24]. Overall median survival was 14 months and was slightly longer for the 278 patients who underwent P/D than for the 385 patients who had EPP (16 vs 12 months, p<0.001). However, it should be recognized that significantly more patients in the P/D/ group had early stage tumors (35% vs 25% ($p < 0.001$)). In addition, the institutions involved in this study performed P/D not only for patients who would not medically tolerate EPP, but also for fit patients when there was "minimal visceral involvement" [23] and for patients with low tumor volume [46]. This bias toward performing P/D on patients with biologically more favorable tumors makes it difficult to draw firm conclusions from the data. Furthermore, a previous analysis from one of the institutions revealed no difference in survival among 222 patients with EPP and 126 patients with P/D [23].

Another controversial area relates to whether to offer EPP to patients with known nodal metastases, which are known to occur in up to 50% of patients undergoing EPP. Survival of patients with nodal metastases is significantly reduced compared to that of node negative patients. Nevertheless, there are occasional long-term survivors among patients with N2 disease who have undergone trimodality therapy. A recent retrospective study from the UK compared outcomes of node positive patients who underwent EPP and P/D, and found no survival benefit for EPP [37]. As survival is limited for this subset of patients (median survival ≈ 10 months) performing a less morbid procedure such as P/D may indeed be justified. There remains the problem, however, of accurately identifying N2 positive patients prior to EPP. As described above, mediastinoscopy has poor sensitivity (≈ 30–40%) and although EBUS and EUS may offer improved accuracy, a large number of positive nodes occur in locations where preoperative histologic sampling is not possible. For this reason we now perform extensive lymph node sampling following the initial extrapleural dissection in patients planned to undergo EPP. If nodal metastases are identified on frozen section, a decision is usually made to perform radical P/D rather than EPP [49].

7.6.5 Does Cytoreductive Surgery Improve Survival?

Both EPP and P/D are extensive surgeries that carry significant risk of morbidity and mortality. The excellent five-year survival of 46% reported by Sugarbaker and colleagues applied to a relatively small fraction of patients (17%), mainly those with epithelioid node negative tumors who could be completely resected [67]. There have been no surgical series that have included internal controls. Survival times in surgical series are of significance only within the context of the surgically treated group and cannot be reliably compared to survival times of patients treated nonoperatively, for the many reasons previously described. Even within non-surgically treated patients, there is wide variation in survival depending on disease stage, tumor burden, and performance status. Though EPP probably results in a more complete cytoreduction compared to P/D, this has not been shown to translate into improved overall survival. The larger issue, however, is whether any form of aggressive cytoreduction actually

confers a survival benefit over systemic therapy and symptom control [71]. There are no randomized data available yet, however a prospective randomized trial was commenced in 2005 in the UK and was designed to answer this question. The Mesothelioma and Radical Surgery (MARS) trial enrolled patients with MPM who were deemed eligible for EPP and were without evidence of extrapleural (N2) nodal metastases [72]. All patients received three cycles of platinum-based chemotherapy and were subsequently randomized to either receive EPP and adjuvant radiotherapy, or best supportive care. The trial recently completed a pilot feasibility phase in which 50 patients were successfully randomized [73]. The proposed sample size of the MARS trial was 670 patients; however, the trial has subsequently been closed.[http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=1189]. The survival and recurrence outcomes have not yet been disclosed, however with only 24 and 26 patients in the surgical and nonsurgical arms, any conclusions from the data will likely be of limited clinical significance. At the present time there are no plans to continue the trial in its original form, however, a new trial, MARS II, may be launched in the near future. If a cytoreductive surgical arm is included it will likely not be EPP but rather P/D (personal communication: Dr. Jeremy Steele). Without MARS or trials like it that compare cytoreductive surgery in a randomized fashion to a nonsurgical arm, we will have to continue to base treatment decisions on limited and fundamentally biased data.

7.7 Summary

Controversy remains regarding the optimal therapy for MPM. In fit patients with epithelioid tumors and negative nodes, cytoreductive surgery combined with appropriate adjuvant or neoadjuvant therapy may improve survival compared to best supportive care or chemotherapy alone, though this is unproven. Complete removal of all macroscopic disease should be the goal of any potentially curative surgical procedure, whether EPP or P/D. EPP has been associated with lower rates of local recurrence, particularly when combined with hemithoracic radiation; however, it is also associated with higher perioperative morbidity and mortality in comparison to P/D. Currently, there is no convincing evidence of any survival difference between the two procedures. Distant failure remains a significant issue that limits long-term survival in patients who have undergone EPP. However, it is possible that if micrometastatic disease can be successfully treated in the future with improved chemotherapeutic or immunotherapeutic strategies, then the local control of achievable with cytoreduction might translate into improved survival.

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