Pleuropneumonectomy in the Treatment of Malignant Pleural Mesothelioma*

Sean C. Grondin, MD; and David J. Sugarbaker, MD, FCCP

Study objectives: Malignant pleural mesothelioma (MPM) is predominantly a local/regional disease that results in a survival time that ranges from 4 to 12 months without treatment. Single-modality therapy using surgery, chemotherapy, or radiotherapy alone is largely ineffective. The objective of the study was presentation of the use of pleuropneumonectomy in a multimodality treatment setting and the results.

Design: Didactic presentation.

Setting: Academic tertiary-care hospital.

Patients: One hundred eighty-three patients who underwent multimodality therapy.

Interventions: Of all the single-modality treatment approaches, pleuropneumonectomy has been associated most consistently with long-term disease-free survival and has provided the greatest amount of tumor cytoreduction. The technique of pleuropneumonectomy traditionally has been linked with high perioperative mortality and morbidity when compared with that of other cytoreductive techniques such as pleurectomy/decortication. Recently, improvements in operative mortality (<5%) have been reported, largely due to improvements in patient selection and perioperative management. Multimodality therapy, including chemotherapy, radiotherapy, and extrapleural pneumonectomy, was used to treat patients.

Results: Outcomes were presented for 183 patients with MPM who underwent multimodality therapy.

Conclusions: With the development of multimodality therapy, pleuropneumonectomy followed by sequential chemotherapy and radiotherapy has demonstrated a significant survival benefit, especially for patients who have epithelial tumor histology, tumor-free resection margins, and tumor-free extrapleural node status. (CHEST 1999; 116:450S–454S)

Abbreviations: MPM = malignant pleural mesothelioma; SV40 = simian virus 40

Malignant pleural mesothelioma (MPM) is a rare disease that affects 2,000 to 3,000 Americans each year.1,2 It arises primarily as a result of exposure to asbestos, although other etiologies have been described.3 Recently, the presence of a simian virus 40 (SV40) gene-like sequence in mesothelial tumor cells has been reported, suggesting that a viral etiology also may be implicated in the development of this disease.4 This causal relationship is supported by data demonstrating that SV40 injected into hamsters resulted in mesothelioma in 100% of subjects.5 If this relationship is confirmed, significant public health implications exist, because a portion of the world population received SV40-contaminated polio vaccine between 1955 and 1963.6,7

The presentation of MPM is usually nonspecific with symptoms of dyspnea, cough, and chest pain predominating. Physical examination frequently demonstrates a pleural effusion. Bilateral involvement of the hemithoraces is rarely evident. Commonly, there is a delay of 3 to 6 months from the onset of symptoms to diagnosis, resulting in a large subgroup of patients having advanced disease at the time of diagnosis.5

The tests available to confirm the diagnosis of MPM include radiologic procedures (chest radiograph, chest CT scans, and MRI) as well as invasive techniques such as thoracentesis and pleural biopsy (closed or open).9,10 Biopsy using video-assisted thoracoscopic surgery is frequently employed at the Brigham and Women’s Hospital in an effort to obtain optimal satisfactory tissue samples to confirm the diagnosis.

Three histologic varieties of MPM are described in the literature.11,12 These variants are epithelial, sarcomatous, and mixed histology tumors. Distinguishing these from other pathologies such as adenocarcinoma can be problematic and frequently requires the assistance of an experienced pathologist. Histochemical, immunohistochemical, and electron microscopy techniques may be needed to make this distinction.12

Once a diagnosis of MPM is established, a thorough workup is required to determine the extent of disease. CT and MRI are frequently used to rule out mediastinal invasion, whereas thoracoscopy or laparoscopy may be used to assess transdiaphragmatic involvement.13–15 Notably, head CT and bone scans are not indicated unless the patient has specific complaints such as headache or limb pain.

Staging patients with MPM can be difficult because no single classification system is widely accepted. The Butchart, the TNM, and the revised Brigham staging systems are frequently used, although the former two do not stratify disease stage with survival.16–18

The treatment options available to patients diagnosed with MPM include supportive care, traditional single-modality therapy (surgery, radiotherapy, and chemotherapy), and combined modality therapy.19 To date, only multimodality therapy using aggressive surgical cytoreduction (extrapleural pneumonectomy) followed by adjuvant chemotherapy and radiotherapy has demonstrated an improvement in patient survival for early disease.18,20,21 Novel therapies such as intracavitary heated chemotherapy, photodynamic therapy, gene therapy, immunotherapy, and vaccination therapy show promise but have yet to demonstrate improvement in long-term patient survival.22

At the Brigham and Women’s Hospital, patients with Brigham stage I disease are considered suitable candidates for resection of MPM as part of a combined modality protocol. To determine operability, a preoperative evaluation with biochemical laboratory tests, arterial blood gas analyses, pulmonary function testing, and ventilation/per-
fusion scanning (if FEV\textsubscript{1} is < 2 L/min) is carried out. Operative exclusion (physiologic) criteria include the following: FEV\textsubscript{1}, < 1 L/min; ejection fraction, < 45%; room air Pco\textsubscript{2}, > 45 mm Hg; room air arterial Po\textsubscript{2}, < 65 mm Hg; and creatinine clearance within normal limits. Notably, echocardiography in this setting is useful in ruling out mediastinal invasion in addition to assessing ventricular function.\textsuperscript{23}

**Surgical Techniques**

**Right Pleuropneumonectomy**

Anesthetic preparation for pleuropneumonectomy includes the placement of a continuous oximetry probe, arterial and central venous lines, and a thoracic epidural catheter, which may be used both intraoperatively and postoperatively for pain management. A nasogastric tube also is positioned to aid in the identification of the esophagus intraoperatively and to prevent gastric distension postoperatively. The patient is placed in the left lateral decubitus position following anesthetic induction and verification of the placement of the double-lumen endotracheal tube by bronchoscopy.

To begin the surgery, a limited subcostal incision is made along the sixth intercostal space to rule out possible transdiaphragmatic involvement. The procedure is aborted if peritoneal involvement is identified and documented with biopsy. Laparoscopy may be used by surgeons experienced in this technique. If the tumor is deemed resectable, exposure is obtained by elongating the incision posteriorly near the costovertebral junction and anteriorly to the costochondral junction along the bed of the sixth rib. Typically, the sixth rib is excised, allowing a wide-based extrapleural dissection to be started posteriorly. This dissection progresses superiorly toward the apex of the chest using a combination of blunt and sharp dissection. Once the posterior dissection has been adequately performed superiorly and inferiorly, the mediastinal structures can be viewed safely and accessed. At this point, the placement of two chest retractors will improve exposure, and then the dissection may be continued toward the apex of the chest. The subclavian artery and vein are carefully exposed in the brachial triangle to prevent avulsion injury. Similarly, dissection of the internal mammary artery and vein must be carefully performed to avoid bleeding from the superior vena cava or subclavian artery (Fig 1).\textsuperscript{24}

The dissection proceeds in the posterosuperior direction until the azygos vein is identified. Once the right mainstem bronchus and right upper lobe bronchus have been identified, the dissection plane becomes intrapleural. The extrapleural tissues are carefully mobilized away from the azygos vein and the superior vena cava. Opening the pericardium and palpating the pericardial sac is undertaken to rule out the presence of intrapericardial metastases or direct tumor extension. Specifically, palpation of the posterior pericardial space ensures that extension of the tumor into the aorta or esophagus is not present. If no signs of tumor unresectability exist, the diaphragmatic dissection is commenced.

---

To begin this dissection, the lateral margin of the diaphragm is incised circumferentially to the anterior border of the pericardium (Fig 2).\textsuperscript{24} The pleural envelope should be preserved by dissecting the envelope off the diaphragm before its division. Blunt dissection is used to separate the diaphragm from the peritoneum. After the anterior dissection of the diaphragm along the pericardium has been performed, it is incised along the cavo-esophageal hiatus. Palpation of the nasogastric tube prevents unintentional injury to the esophagus and assists mobilization of the tumor from the aorta. To complete the diaphragmatic dissection, the posterior attachments are divided. The pericardial dissection is now begun.

The pericardial incision is first completed anteromedially between the phrenic nerve and hilar structures. In this manner, the pulmonary artery can be isolated using the endo-leader technique.\textsuperscript{25} Once the pulmonary artery is divided intrapericardially, the superior pulmonary veins can be isolated and stapled in a similar manner (Fig 3).\textsuperscript{24} The pericardial dissection is completed by dividing the pericardium posteriorly, allowing the specimen to be

---

**Figure 1.** Internal mammary artery and vein originating from the subclavian artery and superior vena cava, respectively. Reprinted with permission from Garcia et al.\textsuperscript{24}

**Figure 2.** Dissection of the pleural envelope off the diaphragm. Reprinted with permission from Garcia et al.\textsuperscript{24}
displaced anteriorly. This maneuver allows the right mainstem bronchus to be isolated proximally to the carina and a subcarinal node dissection to be performed. The bronchus is stapled with a heavy-gauge wire bronchial stapler, and the specimen is removed for pathologic assessment of margins. Roughly 20 sections are examined from each specimen, including the chest wall, the bronchus, the pericardium, and the diaphragm, as well as mediastinal lymph nodes, to rule out the presence of residual or metastatic disease.

The bronchial stump is reinforced using a pericardial fat pad sewn circumferentially around the stump. On the right side, the pericardium is reconstructed using a prosthetic patch (Goretex; W.L. Gore and Associates; Flagstaff, AZ) to avoid cardiac herniation. Similarly, the diaphragm is reconstructed using a prosthetic patch (Goretex) sewn circumferentially to the diaphragmatic remnant posteriorly, the chest wall anteriorly, and the hiatal musculature medially (Fig 4). In addition, the pericardial patch is fenestrated to prevent the accumulation of intrapericardial fluid leading to tamponade (Fig 5). Conversely, an impermeable diaphragmatic patch is employed to prevent peritoneal fluid from filling the pneumonectomy space, which could lead to tamponade from mediastinal shift.

Prior to closure, areas of gross residual disease are outlined by radiopaque clips, which allow easier targeting of postoperative radiotherapy. A 12-mm red, rubber catheter is always placed in the chest to allow mediastinal positioning. Before extubation, air is aspirated from the chest (1,000 mL in men; 750 mL in women) via the catheter using a 50-mL syringe and a three-way stopcock. A postoperative chest radiograph in the recovery room is used to confirm the midline position of the mediastinum. The catheter is removed if no adjustment in the position of the mediastinum is required. If repositioning is required, it is achieved by adding or removing air via the catheter. Standard chest tube drainage is reserved for drainage of a hemothorax, allowing drainage to be monitored overnight.

**Left Pleuropneumonectomy**

In order to perform a left pleuropneumonectomy, an endobronchial blocker or a right double-lumen tube is required to isolate ventilation to the lung. The dissection is similar to the right side except for a few important differences.

Surgically, the dissection is less demanding on the left side. Care must be taken in the dissection posteromedially and of the aortodiaphragmatic hiatus to avoid avulsing intercostal vessels from the aorta. During this dissection, the esophagus should be identified and protected. The hilar dissection is performed in a similar fashion except for the isolation of the right pulmonary artery. Due to the shorter length of the left pulmonary artery, it is usually isolated and divided in the extrapleural, extrapericardial plane.

Reconstruction of the left pericardium is not routinely

---

**Figure 3.** The superior pulmonary vein is dissected within the pericardium. *Inset:* Illustration of a safe technique for dissection of the hilar vessels using a pliable, plastic, self-dilating guidance catheter. One jaw of the endoscopic stapler will fit into the end of this catheter, thus allowing safe placement of the staple. Reprinted with permission from Garcia et al. 24

**Figure 4.** The pericardium and diaphragm are reconstructed, and a fat pad is placed over the bronchial stump. Reprinted with permission from Garcia et al. 24

**Figure 5.** Fenestrations in the pericardial patch are made to prevent tamponade. Reprinted with permission from Garcia et al. 24
performed due to the low incidence of cardiac herniation. Removal of air on the left side is performed in a fashion similar to that on the right side (750 mL in men; 500 mL in women).

**Hemostasis**

Typically, the blood loss for the right-sided procedure is 750 mL, and for the left-sided procedure blood loss is 500 mL. A combination of electrocautery and packing is used during the extrapleural mobilization to minimize blood loss. Once the specimen is removed, the argon beam coagulator and electrocautery are used to stop bleeding from the chest wall surface prior to reconstruction and closure.

**Postoperative Management**

Postoperatively, patients are monitored in a thoracic stepdown unit with a 1:2 ratio for nursing care. Arterial lines, continuous oximetry, and respiratory rate monitors are used for patient monitoring. Patient placement on bed rest for 48 h helps to facilitate mediastinal stabilization. Routine components of postoperative care include ambulation and chest physiotherapy. Deep vein thrombosis prophylaxis is maximized with pneumatic boots and subcutaneous heparin.

A thoracic epidural catheter is used for the first 3 to 5 days to control pain and to help prevent atelectasis that may lead to respiratory compromise. A fluid restriction of 1 L/24 h is enforced for 3 to 5 days postoperatively. Desaturation of oxygen levels is treated aggressively with a combination of diuresis, chest physiotherapy, and bronchoscopy, if required. Daily chest radiographs are routinely performed. The nasogastric tube is removed on the first postoperative day to allow the patient to cough effectively. To prevent aspiration, oral intake is not begun until there is clear evidence of gastric function.

**Multimodality Therapy**

Currently, Brigham and Women’s Hospital and the Dana-Farber Cancer Institute use a multimodality approach for eligible patients with MPM in which surgery consists of pleuropneumonectomy followed by sequential chemotherapy (carboplatin/paclitaxel) and adjuvant radiotherapy into the postoperative hemithorax (30 Gy delivered in 1.5-Gy fractions to the hemithorax and 40 Gy to the mediastinum, with a cumulative dose up to 54 Gy if the results of specimen testing from the margins and nodes are positive). The rationale for this approach is that once the tumor burden has been reduced by surgery, the effectiveness of chemotherapy and radiotherapy is maximized. Toxicity such as radiation pneumonitis from high-dose radiotherapy also can be limited if the treatment is administered postoperatively. Two previous reviews of 52 patients and 120 patients have demonstrated a survival advantage using this approach.

A recent review of 183 consecutive patients was published evaluating our experience from 1980 to 1997. The cohort included 43 women and 140 men with a mean age of 57 years. The operative mortality rate was 3.8%, with a major morbidity rate of 24%. Overall survival rates were 36% at 2 years and 14% at 5 years. Two- and 5-year survival rates were 52% and 21%, respectively, for patients with epithelial cell type tumors, and 16% and 0%, respectively, for patients with sarcomatous or mixed histology tumors. Extrapleural nodal involvement was a significant negative prognostic factor. Two and 5-year survival rates of 42% and 17%, respectively, were demonstrated for patients with tumor-free nodes, compared with 23% and 0%, respectively, for patients with positive extrapleural nodes. Patients with tumor-free resection margins had 2- and 5-year survival rates of 44% and 25%, respectively. By contrast, positive resection margins resulted in a 2- and 5-year survival of 33% and 9%, respectively. Thirty-one patients with epithelial tumors and negative resection margins, and without extrapleural nodal involvement had a 51-month median survival time, a 2-year survival rate of 68%, and a 5-year survival rate of 46%. Stage-stratified survival using the revised Brigham staging system demonstrated median survival times of 25, 17, and 11 months for disease stages I, II, and III (p = 0.0011), respectively.

From these data, it may be concluded that long-term survival is possible in selected patients diagnosed with MPM and treated with multimodality therapy. Furthermore, the Brigham staging system for MPM can accurately predict survival in this group. Three predictors of improved survival also were identified: tumor-free resection margins, epithelial histology, and tumor-free extrapleural nodes.

Despite the improved survival rates noted with multimodality therapy, a recent review by Baldini et al reported that 54% of patients return with recurrent disease. Of these recurrences, 35% were local (ipsilateral hemithorax) and 26% were abdominal. Distant metastases were rare. As a result, new and innovative therapeutic strategies have been explored. These techniques include intraoperative heated chemotherapy, photodynamic therapy, immunotherapy, gene therapy, and vaccination therapy. Ongoing trials are underway to assess these modalities.

**REFERENCES**

7. Pass HI, Kennedy RC, Carbone M. Evidence for and impli-
16 George SL, Desu MM. Planning the size and duration of a clinical trial studying the time to some critical event. J Chronic Dis 1974; 27:15–24
17 Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma: from the International Mesothelioma Interest Group Chest 1995; 108: 1122–1128