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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Surgical Treatment of Mesothelioma: Pleurectomy*

John R. Roberts, MD, FCCP

Malignant diffuse mesothelioma is the most common type of mesothelioma, with a median survival ranging from 8.5 to 18 months after diagnosis. Good performance status, absence of chest pain, age < 50 years, and epithelial histology are all associated with improved survival. Several investigators have described staging systems for this tumor and have emphasized the importance of thoracoscopy in the diagnosis and staging of the disease. Pleurectomy is the most common surgery employed to manage patients with diffuse mesothelioma, and this procedure is associated with minimal postoperative morbidity and mortality. Because mesothelioma usually recurs locally after surgery, efforts at optimizing local control have included both intraoperative phototherapy and chemotherapy. However, neither of these techniques has demonstrated any significant benefit to date and thus should not be considered as standards of care. No studies have compared pleurectomy to extrapleural pneumonectomy (EPP) in randomized trials. However, nonrandomized series suggest a significant improvement in disease-free survival for those undergoing EPP versus pleurectomy. Other data suggest that EPP may improve local control but may predispose the patient to distant metastases. A randomized comparison of these techniques may be beneficial in identifying the most effective procedure for patients with malignant diffuse mesothelioma.

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Abbreviations: EPP = extrapleural pneumonectomy; SEER = surveillance, epidemiology, and end results

Mesothelioma occurs as three types, each with distinctly different outcomes and treatments. Benign localized mesothelioma usually develops as a well-defined mass, quite often projecting on a stalk, on either the visceral or parietal pleura. These tumors are of variable size and generally only cause symptoms if very large. They are associated with hypoglycemia, arthralgias, and clubbing. Benign localized mesotheliomas are usually resected because of concern about the appropriate diagnosis, and resection is generally curative.

Malignant localized mesotheliomas may develop on either pleura and are associated with chest pain, fever, dyspnea, and cough. In contrast to benign localized mesotheliomas, clubbing is unusual. Malignant localized mesotheliomas are exceedingly rare, but the recommended

therapy has been resection, with generally good results. Without complete resection, the median survival is only 7 months.

Malignant diffuse mesothelioma is the most common of the three types of mesothelioma and will be the focus of the remainder of this paper.

MALIGNANT DIFFUSE MESOTHELIOMA

The diffuse malignant variant of mesothelioma may develop on any visceral or parietal surface. It is characterized by sheets of spreading, nodular tissues that infiltrate between lobes, along fissures, and along diaphragmatic and pericardial surfaces. The tumor more commonly presents in the lower lobes and tends to be more extensive inferiorly. The tumor may grow into the peritoneal cavity, pericardial spaces, or through wounds.

The diagnosis can be suspected because of the characteristic radiographic findings, but the differential diagnosis also includes other causes of malignant pleural effusions. Initial misdiagnosis is common. Pathologic differentiation between the other causes of malignant pleural effusions can not usually be done by thoracentesis but requires pleural tissue, obtained either by pleural biopsy or thoracoscopy. Bronchoscopy is important to exclude endobronchial disease. The literature on the natural history of malignant mesothelioma is summarized in Table 1. Antman et al¹ reviewed the pathologic diagnoses at the Dana-Farber Cancer Institute between 1965 and 1985 and found a median survival of 18 months. These authors also found that good performance status, absence of chest pain, age < 50 years, and epithelial histology all portended a better survival. Boutin et al² analyzed a large French series and found a median survival of 8.5 months with 1-year and 2-year survivals of 50% and 25%, respectively. This analysis emphasized the importance of thoracoscopy in staging and diagnosis. Ruffie et al³ summarized data from two large centers in Ontario and Quebec from 1965 to 1984. Their findings were similar to other analyses; and they reported a median survival of 9 months, and they found that median survival was better in patients with earlier disease, no weight loss, and epithelial histology. Finally, Spirtas et al⁴ reviewed Surveillance, Epidemiology, and End Results (SEER) data on 1,475 patients and also found a median survival of 9 months. These investigators found that age at diagnosis, gender, stage of disease, type of treatment, and geographic area of residence were important predictors of patient survival.

STAGING OF MESOTHELIOMA

Butchart et al⁵ described the first staging system for diffuse malignant mesothelioma (Table 2). These investigators reported the first large series of pleuropneumectomy for mesothelioma and described a hospital mortality of 31%. Boutin et al emphasized thoracoscopy in the diagnosis and staging of mesothelioma.² Sugarbaker and colleagues⁶ subsequently proposed a staging system based on nodal status that combined the stages II and III defined by Butchart et al into a new stage III and separated stage I into stages I and II (Table 3).⁶ They identified a 5-year survival of 45% in epithelial histology patients treated with

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Table 1—Natural History of Malignant Diffuse Mesothelioma*

Report (ref)	Survival			
	Median, mo.	1-Year, %	2-Year, %	5-Year, %
Antman et al ¹	18	60%	20%	< 5%
Boutin et al ²	8.5	50%	25%	< 10%
Ruffie et al ³	9	NR	NR	NR
Spirtas et al ⁴	9	40%	15%	< 5%

*The median survival of untreated diffuse mesothelioma ranges from 9 to 18 months, and survival beyond 5 years is uncommon. NR = not reported.

extrapleural pneumonectomy and postoperative chemoradiotherapy. Finally, the International Mesothelioma Interest Group proposed a TNM staging system that also incorporated both tumor and nodal descriptors.

SURGICAL TECHNIQUE OF PLEURECTOMY

Pleurectomy in the treatment of malignant mesothelioma includes the complete decortication of the lung (resection of visceral pleura) and the parietal pleura. Patients are placed in a full lateral position after placement of a double-lumen endotracheal tube. A posterolateral thoracotomy incision is made, completely dividing the latissimus muscle, and the chest is entered through either the fourth or fifth interspace. Occasionally, the serratus muscle can be spared, but usually must also be divided to have adequate access. An additional eighth or ninth interspace thoracotomy within the same skin incision may be necessary for adequate exposure of the inferior thorax.

Pleurectomy involves the complete resection of both visceral and parietal pleura and can include both pericardial and diaphragmatic resection, as well as resection of additional lung nodules. The parietal pleura is first dissected off the chest wall and then the mediastinum. The pleura is then opened and the visceral pleura removed. Although the procedure can allow extensive debulking, it is not generally possible to attain complete macroscopic debulking of tumor with this procedure.

Postoperative management requires good pain management with epidural catheters, intravenous patient-controlled analgesia, intercostal rib blocks, or a combination

Table 2—Butchart's Staging System For Malignant Mesothelioma Described by Buchart et al*

Stage I	Tumor confined to ipsilateral pleura, lung, and pericardium
Stage II	Tumor invading chest wall or involving mediastinal structures, or with lymph node involvement within the chest
Stage III	Tumor penetrating diaphragm to involve peritoneum directly, or with lymph node involvement outside the chest
Stage IV	Distant blood-borne metastases

*Data from Butchart et al.⁵

Table 3—Staging System of Malignant Mesothelioma Described by Sugarbaker et al*

Stage I	Disease confined to the capsule of the parietal pleura
Stage II	All of stage I with positive intrathoracic (N1 or N2) lymph nodes
Stage III	Local extension of disease into chest wall or mediastinum, heart or through diaphragm, peritoneum; with or without extrathoracic or contralateral (N3) lymph node involvement
Stage IV	Distant metastatic disease

*Data from Sugarbaker et al.⁶

of these maneuvers. Aggressive chest physiotherapy with early ambulation, incentive spirometry, and other methods of sputum mobilization are used to prevent atelectasis and pneumonia. Chest tubes are placed to evacuate both fluid and air. Sclerosing maneuvers (ie, talc, doxycycline) are often necessary to seal persistent air leaks.

RESULTS OF PLEURECTOMY

Table 4 summarizes the large studies describing results after pleurectomy that have been reported in the literature. Martini et al⁷ reported a series from Memorial Sloan-Kettering Cancer Center and found an operative mortality of 10% and perioperative morbidity of 29%. Achatzy et al⁸ described 245 patients treated in Germany, 118 of whom underwent either partial or complete pleurectomy. In this series, the median survival was 9.2 months, with a 5-year survival of 4.1%. The 30-day mortality was 8.5%. These authors noted that the long-term survival of patients treated nonoperatively (11.4%) was better than the surgically treated group (2.2%).

Brancatisano et al⁹ summarized results of 50 patients surgically treated at the Concord and Royal Prince Alfred Hospital, 45 of whom underwent pleurectomy. One patient died from the surgery, for a perioperative mortality of 2.2%; surgery-related morbidity was 16%. The authors described a median survival of 16 months and a 2-year survival of 21%. They also noted that pleurectomy was very effective in controlling pleural fluid accumulation.

Finally, Soysal et al¹⁰ reported a 19-year series of 100 patients undergoing pleurectomy at Inonu Universitesi Hospital in Malatya, Turkey. The results of this series suggested that the procedure was safe (postoperative mortality, 1%; morbidity, 22%) and resulted in good

Table 4—Surgical Results From Pleurectomy Trials*

Author/Location (ref)	Year	Patients, No.	Morbidity, %	Mortality, %
Martini et al ⁷ /MSKCC	1975	14	22	10
Achatzy et al ⁸ /Germany	1989	118	6	8.5
Brancatisano et al ⁹ /Australia	1991	45	16	2.2
Soysal et al ¹⁰ /Turkey	1997	100	22	1

*MSKCC = Memorial Sloan-Kettering Cancer Center.

palliation of symptoms. Postoperative recurrence of the tumor in the incision was prevented by prophylactic radiotherapy.

PLEURECTOMY AND INTRAPLEURAL THERAPY

Because mesothelioma usually causes death by local recurrence, even after resection, efforts at optimizing local control have included both intraoperative phototherapy and chemotherapy (Table 5). Pass and colleagues¹¹ have studied intraoperative phototherapy in 78 patients after resection (39 after pleurectomy, 39 after extrapleural pneumonectomy). In this series, the overall postoperative mortality and morbidity was 2% and 36%, respectively. Of 39 patients who underwent extrapleural pneumonectomy, 7 developed bronchopleural fistulae. Pass et al¹¹ described a slight improvement in long-term survival in patients who underwent pleurectomy (14.5 months) compared with those who underwent extrapleural pneumonectomy (9.4 months). The recurrence rate was equivalent in the two procedures, but one third of recurrences were distant in those patients who underwent extrapleural pneumonectomy, while only 10% of recurrences were distant in patients undergoing pleurectomy.

Rusch et al¹² described a trial involving pleurectomy for the treatment of malignant mesothelioma with intrapleural chemotherapy using cisplatin and mitomycin. The postoperative mortality was 3.6%, and significant perioperative morbidity was also reported, especially grade 4 renal toxicity. The median survival was 17 months, but locoregional relapse occurred in 16 of 20 patients, despite the aggressive regimen designed to optimize local control.

Takita et al^{13,14} described results in 31 patients undergoing combined resection and intraoperative phototherapy. Twenty-three patients underwent pleurectomy followed by intraoperative phototherapy, while 6 underwent extrapleural pneumonectomy. Fifty percent of patients suffered some significant postoperative morbidity (including a 10% bronchopleural fistulae rate), and one of 22 patients died (mortality rate, 4.5%). The median survival for all patients after treatment was 12 months; patients with earlier stage (I and II) disease had a median survival of 21 months.

Sauter and colleagues¹⁵ reported a small series of 13 patients who underwent pleurectomy, followed by treatment with intrapleural cisplatin and cytarabine as well as subsequent systemic cisplatin and mitomycin. They reported minimal morbidity (6%) and no treatment-related mortality. Median survival and time to progression were significantly longer in patients who did not receive intrapleural chemotherapy (21 vs 9 months, $p = 0.04$; 12 vs 6 months, $p = 0.01$) compared with those who did.

The addition of intrapleural therapies, whether chemotherapy or phototherapy, have not demonstrated any significant benefit to date. Indeed, the overall perioperative morbidity and mortality appear to have worsened with these therapies. In addition, the study by Sauter et al¹⁵ suggests that intrapleural chemotherapy may actually decrease long-term survival. Thus, neither of these therapies should be considered standard.

SELECTION OF SURGICAL PROCEDURE IN MALIGNANT PLEURAL MESOTHELIOMA

No studies have randomized similarly staged patients to pleurectomy or extrapleural pneumonectomy (EPP); thus the most effective surgery for patients with malignant pleural mesothelioma has not been defined. EPP is a very demanding procedure, and even the busiest thoracic surgeons perform the procedure rarely unless they work at a center known for the care of mesothelioma.

Several studies have compared nonrandomized series of patients with mesothelioma who underwent either pleurectomy or extrapleural pneumonectomy, depending on the surgeon's choice. Rusch et al reported a Lung Cancer Study Group trial in which 20 patients underwent EPP and 63 underwent pleurectomy.¹⁶ The postoperative mortality rate for those undergoing EPP was 15%, while the mortality rate for those having pleurectomy was not reported. Although there was no difference in overall survival between the two procedures, there was significant improvement in disease-free survival for those undergoing EPP compared with pleurectomy ($p = 0.03$).

Some data suggest that performing EPP may improve local control but perhaps predispose to distant spread. The analysis by Pass et al¹¹ identified a striking difference in the proportion of distant relapse compared with local relapse for the two procedures. Ninety percent of recurrences in those undergoing pleurectomy occurred in the chest, while > 30% of recurrences in those undergoing EPP occurred distantly.

CONCLUSIONS

Pleurectomy can be safely performed, and it effectively controls the symptoms of pleural effusion that develop with malignant pleural mesothelioma. The addition of postoperative phototherapy or intrapleural chemotherapy does not improve long-term survival or result in symptom palliation. Limited data suggest that EPP may give a greater chance of long-term survival in patients with favorable histology and earlier stage disease.

Table 5—Results After Pleurectomy and Intrapleural Therapy*

Author/Location (Ref)	Year	No. Patients	Morbidity, %	Mortality, %
Rusch et al ¹² /MSKCC	1994	28	26	3.6 (pleural chemotherapy)
Pass et al ¹¹ /NCI	1997	39	15	2 (phototherapy)
Takita et al ¹⁴ /Roswell Park	1995	22	50	4.5 (phototherapy)
Sauter et al ¹⁵ /Fox Chase	1995	13	6	0

*MSKCC = Memorial Sloan-Kettering Cancer Center; NCI = National Cancer Institute.

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