Multimodality Therapy for Malignant Pleural Mesothelioma*

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Mesothelioma is a rare disease for which neither single modality nor bimodality therapy improves survival. For this reason, from 1980 to 1995, we used trimodality therapy in an attempt to improve survival in selected patients at Brigham and Women’s Hospital and Dana-Farber Cancer Institute. One hundred twenty patients underwent trimodality treatment involving extrapleural pneumonectomy followed by combination chemoradiotherapy. Twenty-seven women and 93 men (mean age, 56 years) were evaluated for response and treatment-related morbidity. The operative mortality rate was 5%, and 22% of patients experienced major morbidity. Cell type and nodal status were significant prognostic variables. The respective 2- and 5-year survival rates were 45% and 22% overall, 70% and 37% for patients with epithelial cell type, 20% and 0% for patients with sarcomatous or mixed-histologic-type tumors, and 74% and 39% for patients who were node-negative with epithelial histologic type. Positive resection margins impacted survival only in the case of full-thickness, transdiaphragmatic invasion. A revised staging system stratified survival with median intervals of 22, 17, and 11 months for stages I, II, and III disease, respectively (p=0.04). Thus, extrapleural pneumonectomy with adjuvant therapy is appropriate and effective treatment for patients with stage I disease according to the revised staging system.

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Malignant pleural mesothelioma, a rare disease whose etiology is tied to asbestos exposure,1 has been steadily increasing in incidence despite industrial regulation of asbestos during the 1960s.2 As many as 3,000 new cases are expected to be diagnosed in the United States in 1997.3-4 The rising incidence can be attributed to the disease’s long exposure-to-diagnosis interval. Left untreated, patients survive a median of 4 to 12 months.5-8 The failure of single-modality and bimodality therapy to improve the survival of patients with malignant pleural mesothelioma led us to evaluate a trimodality approach of extrapleural pneumonectomy followed by combination chemoradiotherapy. Our rationale behind using extrapleural pneumonectomy as opposed to pleurectomy9 was that a complete or near-complete resection would be expected to improve survival in patients with this primarily locally recur-

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Malignant pleural mesothelioma is primarily a disease of 50- to 70-year-old men. Approximately 80% of patients present with dyspnea or pleural effusion. Common symptoms include cough (60%), chest pain (40%), fever, and weight loss. Five percent of patients present with bilateral involvement. In advanced disease, wasting, ascites, or chest wall deformity is seen.

Malignant pleural mesothelioma is not easy to diagnose. For example, only 75 to 80% of patients will have known asbestos exposure. Pleural effusions, with or without pleural calcifications, are commonly noted on chest radiograph. CT (or, more recently, MRI)13 is a more useful tool for assessing disease spread, particularly beyond the thoracic cavity, whereas echocardiography is helpful in assessing pericardial involvement and ventricular function. The preoperative physiologic status of these patients is evaluated using pulmonary function testing as a screening tool followed by ventilation-perfusion scan in patients who will benefit from extrapleural pneumonectomy. Thoracentesis is sometimes useful in diagnosing mesothelioma, as the pleural fluid obtained is usually yellow in comparison to the sanguineous fluid characteristic of adenocarcinoma. Cytologic examination of the fluid specimen may be helpful, but more commonly, a pleural biopsy specimen is needed for sufficient tissue diagnosis.

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Materials and Methods

Thus, in our study, candidate patients were evaluated on the basis of spirometry, oximetry, arterial blood gases, chest radiograph and CT, chest MRI (after 1988), ventilation-perfusion scan (if FEV1 was <1 L), and echocardiography. Patients without medical contraindications whose tumor was clinical stage I according to Butchart et al14 and considered completely resectable were candidates for trimodality therapy if they had an Eastern Cooperative Oncology Group performance status of 0 or 1 and normal renal and hepatic function. Patients were excluded if they exhibited compromised cardiac function (ejection fraction <50%), preoperative partial pressure of CO2 >45 mm Hg, room air partial pressure of O2 <65 mm Hg or predicted postoperative FEV1 of <1 L, or mediastinal or transdiaphragmatic invasion on MRI.

The technical aspects of extrapleural pneumonectomy have been described in detail.15 Briefly, the operation involved en bloc resection of the lung, parietal pleura, and ipsilateral pericardium and diaphragm, with diaphragmatic and pericardial reconstruction. Any previous biopsy sites or thorascopy ports were also resected.

Chemotherapy was administered 4 to 6 weeks following extrapleural pneumonectomy. Before 1985, patients (n=9) received doxorubicin, 50 to 60 mg/m2, and cyclophosphamide, 600 mg/m2, for four to six cycles; after 1985, cisplatin (70 mg/m2) was added to the regimen.

External-beam radiotherapy (4 to 10 MV) was administered following chemotherapy, initially including the entire ipsilateral...
hemithorax and mediastinum to a dose of about 30 Gy, followed, if possible, by a boost dose (typically 50 to 55 Gy) to regions of previous bulk disease.

A recent analysis of this trimodality protocol in 120 consecutive patients undergoing extrapleural pneumonectomy at the Brigham and Women’s Hospital from 1980 to 1995 has been reported. To summarize, complete follow-up was available through February 1996, with a median follow-up of 15 months (range, 2 to 91 months). Median patient age was 56 years (range, 31 to 74 years), and the onset of symptoms occurred a median of 2 months (range, 0.5 to 27 months) prior to diagnosis. Eighty patients (67%) were current or former smokers, and 94 patients (75%) reported asbestos exposure. Presenting symptoms included chest pain in 61 patients (51%) and dyspnea in 88 (73%).

RESULTS

Median length of hospital stay following extrapleural pneumonectomy was 9 days (range, 5 to 101 days). Perioperative (30-day) mortality was 5%, resulting from myocardial infarction (two patients), pulmonary embolus (two), respiratory failure (one), and cardiac herniation through the pericardial defect (one). Morbidity was 22%. Fifteen patients (12.5%) experienced one or more of the following major complications: hemorrhage (four patients), respiratory failure (four), pneumonia (five), disrupted diaphragmatic patch (one), perforated duodenal ulcer (two), empyema (one), upper GI tract bleed (one), and deep venous thrombosis (three).

Median overall survival was 21 months (range, 1 to 96 months). The 2- and 5-year survival rates were 45% and 22%, respectively (Fig 1). A multivariate Cox proportional hazards model revealed that epithelial cell type and lack of lymph node involvement ( hilar, mediastinal, and intrapulmonary) were significant positive prognostic factors. The subset of cases with pure epithelial cell type tumors (n=67; 59%) were associated with significantly longer survival (2- and 5-year survival rates of 65% and 27%, respectively) than the subset (n=47) with either sarcomatous or mixed- histologic-type tumors (20% and 0%, respectively; p=0.0001). The subset of patients with negative lymph nodes in the pathologic specimen (n=66) survived significantly longer (2- and 5-year survival rates of 50% and 25%, respectively) than did the subset with nodal involvement (n=48; 35% and 0%, respectively; p=0.02). Within the epithelia cell type patient subgroup, node status further stratified survival (Fig 2). Of the 67 patients with epithelial tumors, the 39 with node-negative specimens had significantly better survival rates (74% 2-year survival, 39% 5-year) than the 28 patients with node-positive specimens (52% 2-year survival, 10% 5-year survival, p=0.002).

Survival was not affected by gross residual tumor in the specimen, age, gender, cigarette smoking, asbestos exposure, length of operation, side of tumor, microscopically compromised margins (Fig 3), or neoplasia involving (but not fully penetrating the full thickness of) either the pericardium or diaphragm. Microscopic invasion of tumor through the diaphragm was significantly associated with poorer survival (median, 11 months; n=14), regardless of cell type or node status.

A revised mesothelioma staging system based on an earlier analysis of a subset of these patients (n=52) has been published. Stage I indicates disease that is resectable by pleurectomy or extrapleural pneumonectomy. Stage II includes patients with involved lymph nodes detected on MRI, at mediastinoscopy, or at thoracotomy. Stage III (combines Butchart stages II and III) tumors extend into the mediastinum or across the diaphragm and are therefore considered unresectable. Stage IV includes patients presenting with evidence of extrathoracic metastasis.

Survival in the entire cohort (n=120) was significantly stratified by stage using this revised system (Fig 4). Median survival rates for patients classified as having stage I (n=57), II (n=43), or stage III (n=14) disease by this system were 22, 17, and 11 months, respectively (p=0.04).

DISCUSSION

In appropriately selected patients, extrapleural pneumonectomy with adjuvant chemotherapy and radiotherapy is safe and effective treatment for malignant pleural mesothelioma. Overall median survival (21 months, Fig 1) of patients receiving this trimodality therapy is superior to that obtained with single-modality therapy. Nodal involvement, cell type, and transdiaphragmatic invasion are prognostic factors that stratify survival of patients treated in

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21753/)

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21753/)
in this manner. The results described herein validate a revised staging system that is based on resectability and nodal involvement.

Previous staging systems for mesothelioma are of limited practical value because they are based on treatment strategies that do not include stratification of survival. The most commonly used staging system was proposed by Butchart et al in 1976, based on the treatment of 29 patients who underwent pleural pneumonectomy. According to this system, stage I disease is confined to the capsule of the pleural envelope, lung, pericardium, and diaphragm; stage II disease includes tumors extending into the chest wall, esophagus, heart, or contralateral pleura, with or without thoracic lymph node involvement; stage III disease includes tumors extending through the diaphragm into the peritoneum with positive extrathoracic lymph nodes; and stage IV disease classifies rare patients presenting with blood-borne metastases. This system does not reliably predict survival probability by stage.

A second system based on the international TNM staging variables has been proposed, but this has not correlated with patient survival. In malignant pleural mesothelioma, tumors tend to extend beyond their appar-

ent clinical stage, complicating estimation of preresectional T stage. Tumor extent can be accurately assessed following complete gross resection (extrapleural pneumonectomy). The use of nodal designations such as N1, N2, or N3 is not clinically meaningful in mesothelioma. In contrast to non-small cell lung cancer, lymphatic flow away from the tumor is inconsistent and therefore does not necessarily represent disease progression. The rarity of metastatic disease in patients dying of mesothelioma renders M status irrelevant in most cases.

The revised staging system proposed by us stratified the survival of 120 patients according to stage (Fig. 4). Resectability, histologic type, and node status provide a basis for preoperative assessment and selection of appropriate patients for trimodality therapy. MRI has been found to be useful in estimating transdiaphragmatic and mediastinal invasion. New techniques for detecting lymph node involvement, including positron emission tomography scanning, could be used in conjunction with mediastinoscopy, laparoscopy, and thoracoscopy for more reliable preresectional staging.

Trimodality therapy has been successful in increasing survival of patients with negative-node and epithelial-type tumors, with the best survival seen in patients with both negative nodes and epithelial tumors. Stage-specific adjuvant therapies may form the basis of clinical trials examining this treatment strategy.

References


