Multimodality Management of Malignant Pleural Mesothelioma*

David J. Sugarbaker, MD, FCCP; and Jose J. Norberto, MD

In this article, we explain the currenttrimodality approach used to treat malignant pleural mesothelioma. Our current approach employs extrapleural pneumonectomy as the cytoreductive procedure followed by combination chemoradiotherapy. Trimmodyality therapy was performed at the Dana-Farber Cancer Institute/Brigham and Women’s Hospital Thoracic Oncology Program. From 1980 to 1995, we prospectively followed up a series of 120 patients with confirmed malignant pleural mesothelioma who underwent trimodality therapy. Two- and 5-year survival rates for the entire cohort were 45% and 22%, respectively. Survival rates were 65% and 27%, respectively, at 2 and 5 years for patients with epithelial histology. Patients with sarcomatous or mixed histology had the poorest prognosis, with 2- and 5-year survival rates of 20% and 0%, respectively. For patients with epithelial tumors and negative nodes, survival at 2 and 5 years was 74% and 39%, respectively. Extrapleural pneumonectomy in the context of trimodality therapy is a potential surgical option for a selected group of patients with malignant pleural mesothelioma.

(CHEST 1998; 113:618-658)

Malignant pleural mesothelioma (MPM) is an uncommon tumor of the chest. Typically, there is pernicious local invasion of the pleural space and surrounding organs. Previous studies have shown the strong association between exposure to asbestos, in particular the amphibole type, and the development of this malignancy.1 The geometry of amphibole asbestos enables it to traverse the respiratory tree and lodge in the subpleural space, where carcinogenesis occurs.

The potential link between simian vaculating virus 40 (SV40) and certain types of cancers, including mesothelioma and brain tumors, has recently been reported. In 1994, Carbone et al2 reported fragments of SV40 in 60% of mesotheliomas. It is epidemiologically disconcerting that SV40 may have been given to millions of children who received polio vaccines in the 1950s and 1960s. The impact of SV40-infected patients on the incidence of pleural mesotheliomas has yet to be seen.

Two to three thousand new cases of mesothelioma are reported each year in the United States.3-5 The incidence of this tumor has been rising in our country since 1980, which may be reflective of the 20- to 40-year latency period between asbestos exposure and disease presentation. Previous environmental legislation curbing asbestos use will not influence the disease incidence until the next century. The aggressive behavior of the tumor is reflected in the median survival of 4 to 12 months in untreated patients.6-7

Three major histologic types of MPM have been described: epithelial, sarcomatous, and mixed. The epithelial type has been equated with better patient prognosis.7 The clinical presentation of MPM is varied and depends on the stage of disease. Men between 50 and 60 years of age are most often stricken. Most patients (80%) present with dysnea secondary to a pleural effusion; cough (60% of patients), chest pain (40%), and weight loss are also common symptoms. In late stages, the disease may cause chest wall deformity, abdominal mass with or without bowel obstruction (30%), ascites, and cachexia. In most cases, the patient ultimately dies from the mechanical effect of the invasive tumor on vital organs (heart and lungs).

The radiologic workup of the patient suspected of having MPM includes chest radiograph (posterior-anterior and lateral), CT scanning, and, more recently, MRI of the chest and upper abdomen. The usual finding is pleural effusion with or without pleural calcifications. The combination of chest CT scan and chest MRI has increased our ability to detect mediastinal and transdiaphragmatic tumor invasion, which are signs of unresectable disease.8

The histopathologic diagnosis can be difficult, especially in differentiating MPM from adenocarcinoma. During the initial evaluation, thoracentesis may reveal yellow pleural fluid that is different from the sanguineous effusion frequently seen with adenocarcinoma. Although the cytologic diagnosis of mesothelioma is possible, most often a pleural biopsy specimen is necessary to confirm the diagnosis. Although pleural biopsy specimens have been obtained using a closed technique, the thoracoscopic technique is preferred as it provides more reliable tumor specimens.

Histologic staining (periodic acid-Schiff and mucicar- mine) is a useful tool to differentiate MPM from adenocarcinoma, yielding negative results in patients with MPM. MPM is usually diagnosed with certain immunostaining techniques (vimentin and cytokeratin), which also help differentiate it from adenocarcinoma. The electron microscope can definitely differentiate the two diseases.9

Our ability to evaluate the results of therapy for MPM has been hindered by several factors: the lack of a standard staging system, the relative rarity of MPM, the unknown biological behavior of this tumor, and the lack of randomized trials of current treatment modalities.

An accurate staging system should be able to stratify survival, predict prognosis according to pathology, guide treatment, and evaluate the success of that treatment. The current staging systems for MPM have not shown a correlation between stage and survival. The staging system of Butchart et al.10 currently the most widely used, defines tumor location but does not specify tumor burden (Table 1).

The International Union Against Cancer proposed a

---

*From the Division of Thoracic Surgery (Drs. Sugarbaker and Norberto), Brigham and Women’s Hospital, Division of Surgical Services (Dr. Sugarbaker), Dana-Farber Cancer Institute, and Harvard Medical School (Dr. Sugarbaker), Boston.

Reprint requests: David J. Sugarbaker, MD, FCCP, Division of Thoracic Surgery, Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115
TNM (tumor, node, metastasis) staging system based on the more traditionally used TNM categories. However, the clinical T category frequently underestimates the pathologic extent of MPM tumors, and the N category is the same as that for the lung cancer staging system, despite the fact that the pattern of lymphatic nodal involvement of MPM is unknown. Furthermore, this system has not been validated in terms of survival based on stage.

Previously, we proposed a staging system for MPM in which subgroups of Butchart stages II and III are combined into stage III. This system is also based on resectability, histology of the tumor, and node status (Table 2). Our staging system, based initially on the survival of 52 patients, subsequently stratified the survival of 120 patients. We believe this may be the only system prospectively validated based on survival (Fig 1).

The therapeutic approach to MPM has gone from single-modality to bi-modality and, more recently, to multimodality management. Single-modality and bi-modality therapy have not been effective in improving survival. Early series investigating surgery as a single-modality therapy reported significant palliation but no impact on long-term survival.

Single-modality chemotherapy has had no impact on survival and provided poor palliation. More recently, combination chemotherapy using cyclophosphamide, doxorubicin, and cisplatin (CAP) produced a 20 to 30% response rate, yet had no effect on long-term survival. Radiotherapy by itself has also been ineffective in improving survival but has produced mild to moderate palliation in some series.

**MULTIMODALITY MANAGEMENT**

The current multimodality approach to the treatment of MPM employs cytoreductive surgery followed by chemotherapy and radiotherapy. The theoretical basis for this approach is that debulking the tumor mass maximizes the effectiveness of chemotherapy and radiotherapy. Pleurectomy/decortication and extrapleural pneumonectomy are the two cytoreductive operations used for MPM.

Patients with MPM undergoing pleurectomy/decortication in a multimodality setting have achieved median survivals ranging between 9 and 17 months with an operative mortality rate in the range of 1.5 to 5.4%. The disadvantage of this procedure relates to its limited cytoreduction, especially when the tumor invades the fissures; it is further limited by the amount of postoperative radiotherapy that can be delivered without the patients developing radiation pneumonitis. An increased recurrence rate has also been observed.

Initially employed as a surgical treatment for tuberculous empyema, extrapleural pneumonectomy (EPP) is currently used as a debulking procedure in multimodality therapy for MPM, making possible the delivery of higher doses of postoperative radiation. Our 1996 report demonstrated a rise in median survival (21 months) and a lowered operative mortality rate (5%) compared with previous series. The disadvantage of EPP is the requirement that the patient be able to tolerate a pneumonectomy.

The surgical steps in an EPP include posterolateral thoracotomy incision, exposure of parietal pleura, dissection of parietal pleura from the endothoracic fascia, control of pulmonary vessels and main bronchi, removal of the specimen, and reconstruction of the diaphragm and pericardium. The specimen consists of parietal and visceral pleura, lung parenchyma, pericardium, and diaphragm.
phragn. Postoperative patient care involves pain control, aggressive pulmonary toilet, early ambulation, and careful fluid management.

At the Dana-Farber Cancer Institute/Brigham and Women’s Hospital Oncology Program, patients offered a trimodality protocol undergo EPP as the cytoreductive procedure followed by chemotherapy (four to six cycles) and radiotherapy. Prior to initiating the protocol, patients are evaluated by a multidisciplinary thoracic oncology team to assess their resectability, premorbid conditions, and their physiologic status. Our preoperative/preprotocol evaluation includes complete history and physical examination, arterial blood gases, pulmonary function test, ventilation perfusion scan, echocardiogram to assess pericardial involvement and cardiac function, and CT scan and MRI of the chest and upper abdomen. Eligibility requirements for aggressive therapy include a positive tissue diagnosis for mesothelioma, no mediastinal or transdiaphragmatic involvement seen on CT scan/MRI, Karnofsky performance status >70, creatinine <1.5 mg/dL, ejection fraction >45%, and a predicted postoperative FEV₁ >1 L.

Patients begin adjuvant chemotherapy 4 to 6 weeks after surgery. Our initial series received four to six cycles of CAP chemotherapy (doxorubicin, 50 to 60 mg/m²; cyclophosphamide, 600 mg/m²; and cisplatin, 70 mg/m²).13 We have recently changed our adjuvant chemotherapy to reduce the myocardial depression associated with CAP chemotherapy. Current therapy begins with paclitaxel (200 mg/m² by continuous IV 3-h infusion) and carboplatin (at an area under [plasma concentration time] the curve of 6) for two cycles administered 3 weeks apart. Radiation therapy is then given with concurrent weekly paclitaxel, 60 mg/m². Following radiation therapy, two cycles of paclitaxel and carboplatin are repeated.

External-beam radiotherapy is administered after the chemotherapy. Utilizing linear accelerators (4 to 10 megavolts), a dose of approximately 30 Gy is delivered to the ipsilateral hemithorax and mediastinum, with subsequent boosts given to positive margins and areas of previous bulky disease. The total maximum dose is 50 to 55 Gy.

From 1980 to 1995, 120 consecutive patients (median age, 56 years; range, 31 to 74 years) were enrolled in the above treatment protocol.13 Median follow-up was 15 months (range, 2 to 91 months). Symptoms appeared at a median of 2 months (range, 0.5 to 27 months) before diagnosis. Chest pain and dyspnea were the initial complaints in 51% (n = 61) and 73% (n = 88) of patients, respectively. Asbestos exposure was reported in 78% of cases (94 patients); 67% of patients (n = 80) were current or former smokers.

Hospital stays averaged 9 days (median) with a range of 5 to 101 days. There were six perioperative deaths: two due to myocardial infarction, two to pulmonary embolism, and one each to cardiac herniation and respiratory failure. At least one major complication was experienced by 12.5% of patients (n = 15), including bleeding (4 patients), respiratory failure (4 patients), pneumonia (5 patients), disrupted diaphragmatic patch (1 patient), perforated ulcer (2 patients), empyema (1 patient), upper GI bleed (1 patient), and deep venous thrombosis (3 patients).

In this series, survival at 2 and 5 years was 45 and 22%, respectively (Fig 2) with a median survival of 21 months (range, 1 to 96 months). Analysis by a multivariate Cox proportional hazards model showed two positive prognostic factors: epithelial cell type and lack of nodal involvement. Patients with sarcomatous or mixed histology tumors (n = 47) had 2- and 5-year survival rates of 20% and 0%, respectively. Patients with pure epithelial cell type tumors (n = 67; 59%) had significantly longer 2- and 5-year survival rates (65% and 27%, respectively; Fig 3).13 Patients with negative lymph nodes in the EPP specimen (n = 66) had better survival at 2 and 5 years (50% and 25%, respectively) than did the group with positive lymph nodes (n = 48), who had survival rates of 35% and 0%, respectively (p = 0.02) (Fig 4).

Nodal status additionally stratified patient survival based on histologic group (Fig 5). Thirty-nine of the 67 patients (58%) with epithelial histologic findings had negative lymph nodes. This particular subgroup had 2- and 5-year survival rates of 74% and 39%, respectively. Of the remaining 28 patients with epithelial histologic findings and positive lymph nodes, 52% and 10%, respectively, survived 2 and 5 years (p = 0.002) (Fig 5). The variables that influenced survival were microscopically compromised margins, partial-thickness involvement of diaphragm and/or pericardium, size of tumor, length of

![Figure 2. Kaplan-Meier survival curve for all patients surviving surgery (n = 114). Median survival was 21 months. Reprinted from Sugarbaker et al.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21758/)

![Figure 3. Kaplan-Meier survival curve for all patients with epithelial tumors vs those with nonepithelial (sarcomatous or mixed) tumors. Patients with epithelial tumors had a longer survival (p = 0.0001). Reprinted from Sugarbaker et al.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21758/)
operation, asbestos exposure, cigarette smoking, gender, and age. Full-thickness microscopic diaphragmatic involvement was related to poorer survival (median, 11 months; n=14) irrespective of histologic type or nodal status.

In this series of 120 patients, the Brigham staging system predicted survival. Patients categorized as having stage I disease (n=57) survived a median of 22 months. Patients with stages II and III disease survived a median of 17 and 11 months, respectively (p=0.04) (Fig 1).

CONCLUSION

It has not been determined what percentage of patients present with each stage, ie, resectable vs unresectable. Because we are a surgical service, all patients referred to us for evaluation have been preselected by primary care physicians as surgical candidates. This inherent bias precludes our ability to estimate what percentage of the entire disease population is suitable for surgical therapy.

Aggressive trimodality therapy for MPM is indicated in a select group of patients who have Brigham stage I or II or Butchart stage I disease, ie, confined to a single pleural space without mediastinal organ invasion or full-thickness transdiaphragmatic invasion. EPP with adjuvant chemotherapy and radiotherapy has been demonstrated to be safe and effective in this setting.13

In patients with surgically resectable disease, this trimodality approach stratifies survival by cell type and prognostic factors contained in our revised staging system. These factors include nodal involvement, histologic type, and transdiaphragmatic invasion. In our series, the subgroup of patients with epithelial histology and negative lymph nodes had the best prognosis. Irrespective of cell type or nodal status, full-thickness involvement of the diaphragm was related to poor prognosis. Evaluation of this treatment strategy, as well as the revised staging system, in multi-institutional prospective trials would facilitate surgeons’ ability to treat patients with resectable disease.

ACKNOWLEDGMENT: The authors thank Mary S. Viscanio and Dr. Michael T. Jaklitsch for editorial assistance.

REFERENCES


