Mesothelioma and Radical Multimodality Therapy: Who Benefits?

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The incidence of malignant pleural mesothelioma is increasing. Untreated, patients with this disease experience a rapid and horrendous clinical decline. Surgery plays a role in the diagnosis, staging, and treatment of this malignancy. Surgery, chemotherapy, and radiotherapy alone have been unable to achieve major improvements in survival for most patients. More recent phase II trials suggest that surgery, at one time a purely palliative approach, may have a potentially curative role when used in combination with chemotherapy and radiotherapy. (CHEST 1995; 107:545S-550S)

Malignant pleural mesothelioma is an uncommon yet devastating malignancy. The National Cancer Institute Cancer Statistics Branch reports the incidence of invasive mesothelioma has steadily increased from 0.5 cases per 100,000 population in 1975 to 0.9 cases per 100,000 population in 1990. This translates to a modest increase from the 1,500 cases diagnosed in 1986. Additionally, there is a geographic maldistribution of cases in the United States, with an incidence in some areas of New England four times greater than the national average.

Asbestos exposure has been causally linked to diffuse malignant pleural mesothelioma. Owing to its unique combination of pliability and heat resistance, asbestos was commonly used as an insulating agent prior to 1970. An estimated 8 million workers in the United States have been exposed to asbestos in the workplace. Additionally, the families of workers have been frequently exposed to fibers embedded in work clothes or to insulation in schools and playing rooms. The peak incidence of mesothelioma occurs 35 to 45 years after exposure. Because the danger of asbestos was not recognized until the 1960s, a continued increase in the annual incidence of the disease is expected into the next century.

At our institution, the typical clinical presentation of malignant pleural mesothelioma occurs in male smokers in their 40s to 60s who have had a remote occupational exposure. In New England, many patients were exposed to asbestos in construction or the shipbuilding industry prior to government restrictions in the 1970s.

The disease is characterized by an insidious onset of symptoms, with a rapid and progressive decline in health after diagnosis. Malignant pleural mesothelioma is a relentless local disease. Patients rarely die of complications of systemic spread, but instead die because of failure of local control. Median survival of untreated patients is 4 to 12 months.

Three cell types of pleural mesothelioma have been identified. Epithelial cell type has been associated with a better prognosis both with and without treatment. Sarcomatous cell type has been associated with a worse outcome. The mixed-cell type, or biphasic pattern, contains elements of both the epithelial and sarcomatous cell types and may behave like the sarcomatous variety.

The first challenge in evaluating a patient suspected of having diffuse malignant pleural mesothelioma is to establish a clear histologic diagnosis. Reactive mesothelial cells seen with pleural needle biopsy specimens and pleural fluid cytologic studies can be difficult to distinguish from cancerous mesothelioma cells. In addition, the epithelial variant of mesothelioma can be difficult to distinguish from subpleural adenocarcinoma or small cell carcinoma, tumors with very different treatment options. Video-assisted thoracoscopic has been very useful in obtaining a sufficient pleural biopsy specimen to establish clearly the diagnosis.

**Single-Modality Treatments of Pleural Mesothelioma**

**Surgery**

Surgery has been used to establish a pathologic diagnosis, palliate symptoms, and to resect gross tumor in an effort to cure the patient with malignant pleural mesothelioma.

Extrapleural pneumonectomy has been applied as a single-modality treatment for diffuse malignant pleural mesothelioma; reports of this treatment are summarized in Table 1. In general, the operative mortality rate in these reports was high.

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Table 1—Summary of Trials Utilizing Extrapleural Pneumonectomy as Single-Modality Treatment*

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>No. of Cases</th>
<th>Adjuvant Therapy</th>
<th>2-Year Survival, %</th>
<th>Hospital Mortality, %</th>
</tr>
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<tbody>
<tr>
<td>Worn,16 1974</td>
<td>62</td>
<td>None</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Butchart et al,14 1976</td>
<td>29</td>
<td>None</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>DaValle et al,17 1986</td>
<td>33</td>
<td>Doxorubicin (52% of patients)</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Ruch et al,18 1991</td>
<td>20</td>
<td>None</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Totals and averages</td>
<td>144</td>
<td></td>
<td>28</td>
<td>18</td>
</tr>
</tbody>
</table>

*NS=not significant; CAP=cyclophosphamide (600 mg/m² day 1)/doxorubicin (60 mg/m² day 1)/cisplatin (70 mg/m² day 1) given q21d for four to six cycles; RT=radiation therapy.
[^2]Patients with other disease cell types.

ranging from 9 to 31%. A lesser surgical procedure, parietal pleurectomy without pneumonectomy, has been associated with an improved operative mortality rate of between 1.5 and 5.4%.19-21 Although both operations appear to offer a period of local control, neither provides a substantial improvement in overall survival when applied as a single-modality treatment to this disease.

Radiation Therapy

Because the entire ipsilateral pleural surface is at risk for involvement by diffuse malignant pleural mesothelioma, the entire ipsilateral hemithorax is treated with radiation therapy (RT). The dose-limiting thoracic structures are the spinal cord (45 Gy), heart (45 Gy), and lung (20 Gy).22 Thus, safe thoracic radiation doses are below the 60- to 70-Gy doses thought to be necessary to control 3-cm masses of solid tumor.6 The smaller doses, however, may be effective in controlling microscopic disease after surgical debulking. Small series12,23 using RT as palliative single-modality therapy have reported symptomatic relief without a significant improvement in survival in patients receiving more than 40 Gy.

If RT is used as adjuvant therapy after debulking, 40 to 45 Gy should be delivered to the entire hemithorax, with a 5- to 5.5-Gy boost to areas at high risk for recurrence. When the lung is not included in the resection (as after pleurectomy), tangential fields need to be used to prevent severe radiation pneumonitis.6 When a pneumonectomy has been performed, a shift of the abdominal viscera into the inferior hemithorax may limit the safe dose to 30 Gy.

Chemotherapy

Single-agent doxorubicin has produced response rates of 0 to 40% in patients with malignant mesothelioma; similarly, response rates for chemotherapy combinations have only been 40% or less.24 In a randomized multi-institutional trial of cisplatin and doxorubicin vs cisplatin and mitomycin, the Cancer and Leukemia Group B reported response rates of 13% in both treatment arms.25

Supportive Care

The failure of individual modality treatments in controlling diffuse malignant pleural mesothelioma has contributed to a nihilistic outlook on the part of many caregivers. The poor overall results and considerable toxic reactions associated with these treatments have led many authors to recommend supportive care alone for these patients. However, the natural progression of this disease is horrible to witness.

Patients treated with supportive care alone generally suffer from recurrent pleural effusions, dyspnea, and orthopnea. Fever combined with an enlarging tumor burden leads to profound cachexia, malaise, and weakness. Thoracentesis grants a reprieve of pulmonary symptoms for a few days, but further depletes the patient of protein. Pleurodesis is frequently unsuccessful or only partially successful. As the affected lung becomes encased in tumor, a significant ventilation/perfusion mismatch develops, leading to unrelenting orthopnea. Patients cannot sleep due to the sensation of smothering and soon have no ability to care for themselves. Some develop chest wall pain that responds poorly to high-dose narcotics. The side effects of the narcotics frequently contribute to the misery of the patient and the frustration of the family.

Multimodality Treatment

The failure of single-modality therapy to treat successfully malignant pleural mesothelioma has led to pilot studies of multimodality treatments. Since 1985, we have used an aggressive trimodality protocol combining extrapleural pneumonectomy with sequential postoperative chemotherapy (doxorubicin, cyclophosphamide, and cisplatin for four to six cycles) and up to 55 Gy adjuvant RT to the postoperative hemithorax.13 The treatment plan is suma-
rized in Figure 1. Although a toxic regimen, it offers the best chance of a long-term disease-free interval for a subgroup of patients.

Extrapleural pneumonectomy within this context is not meant as a curative procedure, but as a cytoreductive procedure. Its use in combination with two other modalities will, it is hoped, produce symptomatic relief, a long disease-free period, and possible cure for the individual patient. It entails the removal of the entire lung with its pleural envelope, along with the ipsilateral pericardium and diaphragm.

**Patient Selection**

Only patients with histologically proven mesothelioma and clinical evidence that the tumor is confined within the capsule of the parietal pleura are considered for extrapleural pneumonectomy. CT scan and chest MRI are used to determine the extent of intrathoracic and extrathoracic disease. The addition of MRI has aided in the preoperative evaluation of the extent of primary tumor. Chest MRI is particularly sensitive at detecting chest wall, mediastinal, and diaphragmatic invasion. Involvement of any of these structures or evidence of transdiaphragmatic extension has not been associated with any long-term survival. We consider patients with such involvement unlikely to benefit from extrapleural pneumonectomy and generally employ other forms of palliative therapy. The MRI graphically illustrates the thickened pleural peel, large pleural effusions, and impaction of the trapped lung with subsequent shunting of deoxygenated blood. Sagittal MRI cuts are superior to conventional CT scan at evaluating possible invasion of the paravertebral sulcus, great vessels within the mediastinum, trachea, esophagus, and diaphragm.

If peritoneal invasion cannot be adequately ruled out prior to planned resection, an initial minilaparotomy or laparoscopy is used to evaluate the undersurface of the diaphragm. Biopsy specimen proved-abdominal disease precludes thoracic resection.

Pulmonary function testing with dynamic spirometry, functional oximetry, and arterial blood gas measurement is obtained in patients being evaluated for surgery. A quantitative ventilation-perfusion scan is obtained if the initial FEV₁ is less than 2 L or the predicted postoperative FEV₁ is less than 1.2 L.

Echocardiography will frequently detect mediastinal invasion, and preoperative ventricular function is a useful predictor of perioperative morbidity and mortality. It also provides a baseline standard against which to judge any future doxorubicin-induced cardiac toxic reactions. We repeat the echocardiography halfway through the postoperative chemotherapeutic regimen to detect any deterioration in cardiac function.

At our institution, patients with a predicted postoperative FEV₁ of less than 1 L, an ejection fraction of less than 45% on echocardiogram, a room-air arterial carbon dioxide tension greater than 44 mm Hg, or oxygen tension less than 65 mm Hg receive palliative treatment without extrapleural pneumonectomy.

Mesothelioma is a locally aggressive disease that metastasizes very late in its clinical course. When metastases do occur, they are invariably accompanied by symptoms. Evaluation of occult distant metastases is unrewarding. Therefore, routine preoperative head CT scans and nuclear medicine bone scans are not indicated.

**Operative Procedure**

The technique of extrapleural pneumonectomy has been described in detail elsewhere.²⁶,²⁷ Briefly, it begins with a posterolateral thoracotomy incision over the sixth rib. The sixth rib is skeletonized of its surrounding periosteum and completely resected to provide wide exposure. Once the rib has been removed, the bed of the periosteum is incised and the pleura is stripped from the fifth and seventh ribs to begin the dissection. The pleural space is not deliberately entered. Particular attention is paid to achieving hemostasis because there is often diffuse bleeding from the chest wall after the pleura has been stripped away. Hemostasis is maintained by packing previously dissected areas of the operative field and through liberal use of the cautery in freshly dissected fields.

The margins of resection are limited by vital structures within the chest. The parietal pleura is bordered on three sides by the bony chest wall. The mediastinal border consists of the pericardium, great vessels, esophagus, trachea, and vertebral bodies.

The dissection is first completed anteriorly, from the apex to the diaphragm. As dissection approaches the apex, particular care is taken to preserve the subclavian vessels. In a similar fashion, the internal...
mammary artery and vein are carefully identified and preserved. Posteriorly, the azygous vein and superior vena cava are freed of their investing pleura on the right side. On the left side, the pleura is freed of the aorta. Involvement of the aorta may preclude resection.

Preserving the continuity of the pleural envelope necessitates resection of the diaphragm with the pleura. The peripheral margins of the diaphragm are dissected sharply until the underlying peritoneum is identified. The peritoneum is then dissected bluntly from the undersurface of the diaphragm with the assistance of a sponge stick.

The pericardium is then incised in front of the phrenic nerve. A flap of pericardium and the phrenic nerve are included in the specimen. The main pulmonary artery is divided with vascular staples, and the superior and inferior pulmonary veins are transected in a similar fashion. The pericardial resection is completed posterior to the hilum. The main stem bronchus is transected at the carina, generally with a stapler. The specimen is removed en bloc. Blood loss for pleuropneumonectomy is typically 500 to 750 mL.

The pericardium is repaired using a prosthetic patch after right-sided extrapleural pneumonectomies to prevent cardiac herniation. The patch is fenestrated with scissors after placement to prevent postoperative cardiac tamponade.

The bronchial staple line is reinforced with a vascularized pedicle or pericardial fat. If pericardial fat is not suitable, other options include vascularized intercostal muscle flaps or an omental flap brought up through the diaphragmatic defect prior to repair of the diaphragm.

The diaphragmatic defect is repaired with an impermeable prosthetic patch that prevents the displacement of abdominal contents into the empty hemithorax. Displacement of liver and bowel in the thorax may limit the dose of adjuvant radiotherapy that can be delivered to the posterior sulcus.

Analysis of the pathologic specimen explains much of the natural history of malignant pleural mesothelioma. The tumor generally has its primary focus at the base of the pleural space, where the heavy asbestos fibers accumulate. A markedly thickened peel extends over the entire surface of the lung and up into every fissure, and frequently invades the lung parenchyma. A decortication alone will leave islets of tumor within the lung. The pleural space is generally obliterated by the tumor at the site of the primary focus. The lung parenchyma is imbricated and trapped by the adherent peel along its surface. The volume of the lung is markedly reduced, and the red hepatization of the lung suggests marked shunting of deoxygenated blood.

### Table 2—Summary of Phase I Trials Employing Doxorubicin-Containing Chemotherapy*

<table>
<thead>
<tr>
<th>Combination</th>
<th>No. of Evaluable Patients</th>
<th>No. of Responders</th>
<th>Response Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin, cisplatin</td>
<td>29</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Doxorubicin, cisplatin, vincristine</td>
<td>15</td>
<td>5</td>
<td>33</td>
</tr>
<tr>
<td>Doxorubicin, cyclophosphamide, dacarbazine,</td>
<td>30</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>vincristine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin, cyclophosphamide, methotrexate,</td>
<td>12</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>vincristine, etoposide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Antman et al.*

### Sequential Adjuvant Chemotherapy and Radiotherapy

The chemotherapeutic agents we use for adjuvant therapy after extrapleural pneumonectomy were known to have activity against mesothelioma at the time the protocol began in 1980. Table 2 summarizes the phase I trials evaluating the response of malignant pleural mesothelioma to doxorubicin-containing combinations. The response rates ranged between 17 and 33%. The highest response rates were seen in therapy combining cisplatin with doxorubicin (29%) or cyclophosphamide and vincristine with doxorubicin (17 to 21%).

From 1980 to 1992, 52 selected patients at the Brigham and Women's Hospital received a trimodality protocol employing extrapleural pneumonectomy, adjuvant chemotherapy (cyclophosphamide, 600 mg/m²; doxorubicin, 60 mg/m²; and cisplatin, 70 mg/m² for four to six cycles, to a cumulative doxorubicin dose of 450 mg/m²), and 55 Gy adjuvant RT. We used extrapleural pneumonectomy as cytoreductive surgery combined with aggressive systemic chemotherapy, followed by radical external radiation to the hemithorax. The lack of lung tissue in the diseased hemithorax allowed doses of 55 Gy to be given in this protocol.

Median age of selected patients was 53 years (range, 33 to 69 years). The conditions of all patients were clinically staged as Butchart stage I preoperatively (tumor confined to the ipsilateral pleural envelope). Thirty-two patients had the epithelial cell type, while 20 patients had the sarcomatoid or mixed-cell type. A history of asbestos exposure was elicited in 77% of patients.

Thirty-day mortality in this group was 5.8% (three deaths), with a 17% morbidity rate. The average hospital stay was 12 days.

As noted before, median survival for diffuse malignant mesothelioma without trimodality therapy ranges between 4 and 12 months. Median
survival of the overall Brigham series was 16 months. Patients with the epithelial histologic variant had an improved median survival of 24 months. Furthermore, the subgroup of 25 patients with the epithelial cell type and no mediastinal nodal metastases at resection did quite well, with a 5-year survival of 45%. Figure 2\(^{13}\) stratifies expected survival of patients with epithelial cell tumors by nodal status.

CONCLUSIONS

We believe trimodality therapy for diffuse malignant pleural mesothelioma has an acceptable morbidity and mortality rate in selected patients. Nodal status has been found to be a predictor of survival in all cell types of pleural mesothelioma. Cell type is also a predictor of survival, with epithelial histologic condition associated with improved survival. Finally, resectability may ultimately prove to be a predictor of survival in this disease.

Patient selection for extrapleural pneumonectomy is important, both for the group selected and the group excluded. Operative mortality for this procedure has been higher than that for intrapleural pneumonectomy in several reports.\(^{14,18,34}\) Furthermore, the adjuvant chemotherapy and RT pose additional morbidity and mortality risks. Counterbalancing these disadvantages are the dismal survival statistics for patients with diffuse malignant pleural mesothelioma, as well as the significant morbidity of the untreated disease.

Even for those patients whose disease recurs, the palliation provided by extrapleural pneumonectomy is quite dramatic and cannot be appreciated by examining just the survival statistics. The clinical course of these patients is frequently a rapid and dramatic decline in function with progressive dyspnea, orthopnea, cachexia, and chest wall pain that is poorly controlled with narcotics. By eliminating the shunt fraction of the diseased lung, pneumonectomy can produce lasting palliation and local control for patients with recurrent disease.

The combination of several modalities seems to offer the best treatment for these patients. Our treatment plan continues to evolve. New protocols are being developed utilizing new chemotherapeutic agents and alterations in the timing of adjuvant RT. Furthermore, as experience with the protocol increases, the indications for operation are slowly expanding.

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