Despite many years of clinical research, there is still no effective therapy for malignant pleural mesothelioma (MPM). Untreated, the prognosis is poor, with a median survival of < 1 year. Single-agent or combination chemotherapy as well as radiotherapy have not shown persistent improvements in response or survival. In general, MPM is a disease confined to the pleural cavity for a long time before metastasizing. Therefore, focus on local treatment seems rational. Surgical resection has been considered the mainstay of treatment by some. However, surgery alone results in high recurrence rates, and the survival benefit remains questionable. In recent years, the emphasis has been on surgery combined with adjuvant therapies. In this article, the present state of surgical management of MPM will be reviewed.

Key words: adjuvant therapy; mesothelioma; pleural cavity; review; surgery

Abbreviations: EPP = extrapleural pneumonectomy; IMIG = International Mesothelioma Interest Group; MPM = malignant pleural mesothelioma; PDT = photodynamic therapy

Malignant pleural mesothelioma (MPM) is an aggressive tumor of the pleura. Presenting symptoms are dyspnea and chest pain in the majority of patients. Coughing, fatigue, and weight loss are less frequently observed. In general, MPM is a disease confined to the pleural cavity for a long time before metastasizing. The most common features are pleural thickening, nodularity, and pleural effusion. The growth pattern is characterized by involving the entire pleura and interlobular space. Malignant seeding along tracts of cytology or biopsy needles, chest tubes, thoracoscopy trocars, and surgical incisions is a common complication of diagnostic and therapeutic procedures in patients with MPM. In Western Europe, 5,000 patients die of mesothelioma each year. In the last decades, the incidence has increased twofold in the Netherlands, and it is expected to reach its maximum in the year 2020. The association with asbestosis is well known. In approximately 80% of MPM, an exposure to asbestos is reported. The latency period is between 20 years and 30 years. Recently, a virus has become a suspected agent too. Simian virus 40, a DNA tumor virus, has the potential to induce mesothelioma in hamsters and is reported to be identified in a number of patients with MPM. However, there are still discussions ongoing about the potential of simian virus 40 to induce MPM in humans. The prognosis of patients with MPM is poor; untreated, the median survival is 9 months.
Surgical resection has been considered the mainstay of treatment by some. However, it is almost impossible to achieve a microscopically complete resection with surgery alone because of the anatomy of the pleura and the property of MPM to infiltrate the underlying and neighboring structures. Surgery alone is associated with a high recurrence rate. Recently, most efforts have been put in the combination of cytoreductive surgery with some form of adjuvant therapy.

In this article, we review the surgical management of MPM. The different techniques and treatment outcome of surgery alone are described. Thereafter, emphasis is given to the adjuvant therapies.

**MATERIALS AND METHODS**

A systematic literature study was performed to identify all relevant articles until October 2001. A MEDLINE search was performed with key words focused on MPM. Studies with < 10 patients were not included unless they showed very interesting results. When there were several reports of the same institute including the same cohort of patients with the same treatment, we listed only the most recent report. A statistical analysis of all reviewed articles was not possible due to the lack of randomized studies, the small patient groups, and the diversity of patient groups and methods.

**Staging**

Staging is important in the treatment of MPM. Different staging systems are used (Table 1). To stage accurately, several staging methods are used. Thoracoscopy, CT, MRI, and laparoscopy can identify the T status. CT compared to MRI has nearly equivalent diagnostic accuracy. MRI is superior in imaging diaphragmatic muscle involvement, endoatlasic involvement, and revealing solitary foci of chest wall invasion. To accurately determine the nodal status is more often a problem. CT has a low accuracy regarding lymph nodes. Mediastinoscopy is useful; however, 25% of the patients with MPM have nodal involvement confined to areas such as peritumoral and internal mammary regions not accessible to the mediastinoscopy. Positron emission tomography seems to be useful to determine the extent of tumor. Unfortunately, correct staging is only possible during operation in a substantial number of patients. The accuracy of preoperative CT scans to determine the stage correctly varies, but is reported as low as 30%. The intraoperative tumor load is associated with outcome of MPM, and large volumes are associated with nodal spread.

**Prognostic Factors**

In studies of Rusch and Venkatraman and Sugarbaker et al., the stage, histology, and adjuvant therapy, but not type of resection, were significant prognostic factors. Stage is a clear prognostic factor. Rusch and Venkatraman reported a median survival after surgery with adjuvant therapy of 29.9 months for stage I, 19 months for stage II, 10.4 months for stage III, and 8 months for stage IV (International Mesothealloma Interest Group [IMIG] staging). Another study showed that when the visceral pleura was intact, the median survival was 32.7 months. The node status alone has also prognostic significance with survival advantage for lymph node-negative patients. Sarcomatous MPM shows a worse survival than the epithelial type. Rusch and Venkatraman found that female patients show better survival than male patients; however, Sugarbaker et al. could not confirm this. The type of resection, i.e., extrapleural pneumonectomy (EPP) or a pleurectomy/decortication, did not have impact on survival in the study of Rusch and Venkatraman. However, both procedures were performed only if they led to complete resection of all gross tumor. In patients with bulky tumor or confluent pleural tumor, an EPP was necessary to achieve complete resection.

**RESULTS**

**Surgery Alone**

Pleurectomy/Decortication: The technique of pleurectomy has been well described. After a posterolateral thoracotomy, an extrapleural plane between the parietal pleura and the endoatlasic fascia is entered. The dissection proceeds in a superior direction toward the apex over the posterolateral aspect of the chest wall. The dissection is continued to inferior and posterior. When the pleura and the lung are completely mobilized in the upper part of the thoracic cavity, the superior and posterior hilar structures of the lung are well exposed. After stripping or partial resection of the posterior pericardium, the dissection proceeds toward the posterior diaphragmatic sulcus. If there is only superficial involvement, dissection is performed through the diaphragmatic muscle, avoiding entering the abdomen; otherwise, a part of the diaphragm is removed. The en bloc specimen is mobilized back to the pericardium medially. When the dissection is completed to the hilar structures, the parietal pleural is opened and decortications of the visceral pleura is performed. The pericardium and diaphragm are eventually reconstructed.

The mortality of this procedure is limited (1 to 2%), when performed in specialized centers. The most common complication is prolonged air leakage, occurring in 10% of cases. Other reported complications are pneumonia, empyema, and hemorrhage. Pleurectomy and decortication are reported to be effective in controlling pleural effusion. The median survival reached by this procedure is reported in different studies between 9 months and 20 months (Table 2).

The technical problem is the difficulty of separating the visceral pleura from the lung parenchyma. This results frequently in incomplete resection. After pleurectomy/decortication, Hilaris et al. reported that residual tumor was left behind in 78% of the patients, most frequently on the visceral pleura. The most common site of recurrence is the ipsilateral hemithorax. In recent years, pleurectomy/decortication studies all included adjuvant therapy.
### Table 1—Staging Systems

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butchart et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Tumor confined to ipsilateral pleura, lung, and pericardium</td>
</tr>
<tr>
<td>II</td>
<td>Tumor invading chest wall or involving mediastinal structures, e.g., esophagus, heart, opposite pleura; lymph node involvement within the chest</td>
</tr>
<tr>
<td>III</td>
<td>Tumor penetrating diaphragm to involve peritoneum directly; lymph node involvement outside the chest</td>
</tr>
<tr>
<td>IV</td>
<td>Distant blood-borne metastases</td>
</tr>
<tr>
<td>Sugarbaker et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Disease confined to within capsule of the parietal pleura: ipsilateral pleura, lung, pericardium, diaphragm, or chest-wall disease limited to previous biopsy sites</td>
</tr>
<tr>
<td>II</td>
<td>All stage I with positive intrathoracic (N1 or N2) lymph nodes</td>
</tr>
<tr>
<td>III</td>
<td>Local extension of disease into chest wall or mediastinum; heart, or through diaphragm, peritoneum; with or without extrathoracic or contralateral (N3) lymph node involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastatic disease</td>
</tr>
<tr>
<td>IMIG&lt;sup&gt;24&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>T</strong> primary tumor and extent</td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Tumor limited to ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; no involvement of the visceral pleura</td>
</tr>
<tr>
<td>b</td>
<td>Tumor involving the ipsilateral parietal pleural, including mediastinal and diaphragmatic pleura; scattered foci or tumor also involving the visceral pleura</td>
</tr>
<tr>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:</td>
</tr>
<tr>
<td></td>
<td>• Involvement of diaphragmatic muscle</td>
</tr>
<tr>
<td></td>
<td>• Confluent visceral pleura (including the fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma</td>
</tr>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Describes locally advanced but potentially resectable tumor; tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:</td>
</tr>
<tr>
<td></td>
<td>• Involvement of the endothoracic fascia</td>
</tr>
<tr>
<td></td>
<td>• Extension into the mediastinal fat</td>
</tr>
<tr>
<td></td>
<td>• Solitary, complete resectable focus or tumor extending into the soft tissues of the chest wall</td>
</tr>
<tr>
<td></td>
<td>• Nontransmural involvement of the pericardium</td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Describes locally advanced technically irresectable tumor; tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:</td>
</tr>
<tr>
<td></td>
<td>• Diffuse extension or multifocal mass of tumor in the chest wall, with or without associated rib destruction</td>
</tr>
<tr>
<td></td>
<td>• Direct transdiaphragmatic extension of the tumor to the peritoneum</td>
</tr>
<tr>
<td></td>
<td>• Direct extension of tumor to the contralateral pleura</td>
</tr>
<tr>
<td></td>
<td>• Direct extension of tumor to one or more mediastinal organs</td>
</tr>
<tr>
<td></td>
<td>• Direct extension of tumor into the spine</td>
</tr>
<tr>
<td></td>
<td>• Tumor extending through the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium</td>
</tr>
<tr>
<td>N lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N&lt;sub&gt;0&lt;/sub&gt;</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Metastases in ipsilateral bronchopulmonary or hilar lymph nodes</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes</td>
</tr>
<tr>
<td>N&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Metastases in contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular scalene lymph nodes</td>
</tr>
<tr>
<td>M metastases</td>
<td></td>
</tr>
<tr>
<td>Mx</td>
<td>Presence of distant metastases cannot be assessed</td>
</tr>
<tr>
<td>M&lt;sub&gt;0&lt;/sub&gt;</td>
<td>No (known) metastasis</td>
</tr>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Distant metastasis present</td>
</tr>
<tr>
<td>Stage grouping</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>T1aN0M0</td>
</tr>
<tr>
<td>b</td>
<td>T1bN0M0</td>
</tr>
<tr>
<td>II</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>III</td>
<td>Any T3M0, any N1M0, any N2M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T4, any N3, any M1</td>
</tr>
</tbody>
</table>
EPP: EPP is a procedure consisting of en bloc resection of the lung, visceral and pleural pleura, pericardium, and ipsilateral diaphragm with reconstruction of the pericardium and diaphragm. After a posterolateral thoracotomy through the sixth intercostal space, a dissection between the chest wall and parietal pleura is started. A blunt dissection with fingers appears to work best. After reaching the apex of the chest, the dissection will be proceeded to inferior (diaphragm). The diaphragm is opened while aiming to preserve the peritoneum. The whole diaphragm is removed. Next, the pericardium is resected. The specimen is then elevated, and the dissection continues to the hilar structures. After stapling the vessels and the bronchus, the specimen is removed. A pericardial fat pad can be placed over the bronchial stump. Reconstruction of the diaphragm and pericardium is the last stage of the procedure. In the patch to reconstruct the pericardium, fenestrations are made to prevent cardiac tamponade.

The mortality of this procedure has decreased in the last decades from 30 to 5% when performed in specialized centers and in selected patients. Causes of death are respiratory failure, myocardial failure, and pulmonary embolus. The reported morbidity is considerable, mostly between 25% and 50%. Twenty-four percent of the patients undergoing pneumonectomy showed cardiac supraventricular dysrhythmias with a peak incidence at 3 to 4 days after resection. Patients are at risk of postoperative pneumonia, and the development of a bronchopleural fistula is reported in 10 to 20%, especially right-sided EPP. Median survival after EPP is ranges from 9 to 19 months (Table 3).

EPP is performed for locally advanced disease, usually in patients with confluent visceral pleural tumor not separable from the lung and a partially or totally fused pleural space. Compared with pleurectomy/decortication, a lower recurrence rate has been reported (10% after EPP vs 52% after pleurectomy). However, relapses in distant sites are more frequently seen than in the pleurectomy group, especially in adjacent cavities. Because of operative deaths, residual tumor, local recurrence, and metastatic disease, EPP has not gained wide acceptance as treatment on its own. There does not seem to be a survival benefit for patients undergoing EPP in comparison to patients undergoing pleurectomy.

Surgery alone is associated with a high recurrence rate, and therefore adjuvant therapy seems useful. Studies performed with the combination of surgery and adjuvant treatment are listed in Table 4.

Table 2—Studies With Pleurectomy Alone (Only Studies With > 10 Patients Are Listed)*

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Median Survival, mo</th>
<th>2-yr Survival, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chahinian et al</td>
<td>Pleurectomy</td>
<td>1982</td>
<td>30</td>
<td>13</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Brenner et al</td>
<td>Pleurectomy</td>
<td>1982</td>
<td>69</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Law et al</td>
<td>Pleurectomy</td>
<td>1984</td>
<td>28</td>
<td>20</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Challeux et al</td>
<td>Pleurectomy</td>
<td>1988</td>
<td>29</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ruffie et al</td>
<td>Pleurectomy</td>
<td>1989</td>
<td>63</td>
<td>10</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Brancatisano et al</td>
<td>Pleurectomy</td>
<td>1991</td>
<td>45</td>
<td>16</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Rusch et al</td>
<td>Pleurectomy</td>
<td>1991</td>
<td>26</td>
<td>10</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Allen et al</td>
<td>Pleurectomy</td>
<td>1994</td>
<td>56</td>
<td>9</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Soysal et al</td>
<td>Pleurectomy</td>
<td>1997</td>
<td>100</td>
<td>17</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Ceresoli et al</td>
<td>Pleurectomy</td>
<td>2001</td>
<td>38</td>
<td>13</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*NA = not available.
†Some patients received adjuvant therapy.

Table 3—Studies With EPP Alone (Only Studies With > 10 Patients Are Listed)*

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Median Survival, mo</th>
<th>2-yr Survival, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worn</td>
<td>EPP</td>
<td>1974</td>
<td>62</td>
<td>19</td>
<td>37</td>
<td>NA</td>
</tr>
<tr>
<td>Butchart et al</td>
<td>EPP</td>
<td>1976</td>
<td>29</td>
<td>10</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Ruffie et al</td>
<td>EPP</td>
<td>1989</td>
<td>23</td>
<td>9</td>
<td>NA</td>
<td>13</td>
</tr>
<tr>
<td>Rusch et al</td>
<td>EPP</td>
<td>1991</td>
<td>20</td>
<td>10</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Allen et al</td>
<td>EPP</td>
<td>1994</td>
<td>40</td>
<td>13</td>
<td>23</td>
<td>8</td>
</tr>
</tbody>
</table>

*See Table 2 for expansion of abbreviation.
†Some patients received adjuvant therapy.
Surgery and Emphasis on External Radiotherapy

In Table 4, series are collected that report on combination therapy of surgery with complete hemithoracic irradiation. Sugarbaker et al\(^67\) advocated that adjuvant radiotherapy should be 40 to 45 Gy to the entire hemithorax, with a 5- to 5.5-Gy boost to areas at high risk for recurrence. Doses limiting thoracic structures are spinal cord (45 Gy), heart (45 Gy), and lung (20 Gy).\(^68\) Hemithoracic radiotherapy equals a total loss of lung function.\(^69\) A shift of the abdominal viscera into the inferior hemithorax after a pneumonectomy limits the safe dose to 30 Gy in the inferior area.\(^67\)

The technique of EPP combined with hemithoracic radiation and systemic chemotherapy was described by Grondin and Sugarbaker.\(^70\) The largest series was described by Sugarbaker et al\(^46\) with 183 patients. The mortality rate was 3.8%. The morbidity rate was 50%, including cardiac arrest, respiratory failure, ARDS, sepsis, contralateral pneumothorax, arrhythmias, pulmonary embolism, empyema, and GI hemorrhage.\(^46\) The median survival in this patient group was 19 months, with a 2-year survival of 38%. In selected patients with the epithelial cell type and without mediastinal nodal metastases at resection, Sugarbaker et al\(^67\) reported a 5-year survival of 45%.

Despite aggressive local treatment including pericardium and diaphragm resection, the site of failure was in most instances the ipsilateral hemithorax (35%) followed by the abdomen (26%), the contralateral hemithorax (17%), and other distant sites (8%).\(^50\)

The application of brachytherapy after pleurectomy was studied in 41 patients by Hilaris et al.\(^44\) Measurable gross residual tumor was treated with permanent iodine 125 implantation and residual diffuse disease by temporary iridium 92 implantation or postoperative instillation of phosphorus 32. After this treatment, external radiotherapy on the hemithorax was administered (45 Gy). There was no mortality. Complications occurred in six patients (15%), including one case of radiation pneumonitis and one case of pericarditis. The median survival was 21 months, with a 2-year survival of 40%. At time of the report, 71% of the patients had relapsed. Local recurrence occurred in one third of the relapsed patients, and distant metastasis with or without local recurrence occurred in the other two thirds.\(^44\) An update, including the same patient cohort with larger follow-up, by Mychalczak et al\(^71\) could not confirm this treatment outcome; in this abstract, a median survival of 13 months was reported.

Alberts et al\(^53\) studied the combination of decor-

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Median Survival, mo</th>
<th>2-yr Survival, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormack et al(^52)</td>
<td>S, XRT, C</td>
<td>1982</td>
<td>181</td>
<td>16</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Hilaris et al(^44)</td>
<td>S, XRT, B</td>
<td>1983</td>
<td>41</td>
<td>21</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Alberts et al(^53)</td>
<td>S, XRT, C</td>
<td>1988</td>
<td>26</td>
<td>11</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mattsson et al(^54)</td>
<td>S, XRT, C</td>
<td>1992</td>
<td>100</td>
<td>8</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Sugarbaker et al(^32)</td>
<td>S, XRT, C</td>
<td>1996</td>
<td>120</td>
<td>21</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Rusch et al(^55)</td>
<td>S, XRT</td>
<td>2001</td>
<td>61</td>
<td>17</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Daville et al(^46)</td>
<td>S, C, XRT</td>
<td>1986</td>
<td>17</td>
<td>18</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Huncharek et al(^37)</td>
<td>S, C</td>
<td>1996</td>
<td>21</td>
<td>24</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hastürk et al(^55)</td>
<td>S, C, I</td>
<td>1996</td>
<td>20</td>
<td>12</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>Ceresoli et al(^43)</td>
<td>S, C</td>
<td>2001</td>
<td>16</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rice et al(^59)</td>
<td>S, IPC, C</td>
<td>1994</td>
<td>19</td>
<td>13</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Busch et al(^60)</td>
<td>S, IPC, C</td>
<td>1994</td>
<td>27</td>
<td>18</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Sauter et al(^61)</td>
<td>S, IPC, C</td>
<td>1995</td>
<td>13</td>
<td>9</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Lee et al(^52)</td>
<td>S, IPC</td>
<td>1995</td>
<td>15</td>
<td>12</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Colleoni et al(^63)</td>
<td>S, IPC, C</td>
<td>1996</td>
<td>20</td>
<td>12</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>NCI(^\dagger)</td>
<td>S, IPC</td>
<td>2001</td>
<td>20</td>
<td>11</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Pass et al(^64)</td>
<td>S, PDT, C, I</td>
<td>1997</td>
<td>25</td>
<td>14</td>
<td>NA</td>
<td>4</td>
</tr>
<tr>
<td>Moskal et al(^55)</td>
<td>S, PDT</td>
<td>1998</td>
<td>40</td>
<td>15</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>Schouwink et al(^66)</td>
<td>S, PDT</td>
<td>2001</td>
<td>28</td>
<td>10</td>
<td>NA</td>
<td>11</td>
</tr>
</tbody>
</table>

*S = surgery; XRT = external beam radiation therapy; B = brachytherapy; C = systemic chemotherapy; I = immunotherapy; IPC = intrapleural chemotherapy. See Table 2 for expansion of other abbreviation.

\(^\dagger\)Epithelial mesothelioma only.

\(^\ddagger\)Data from the Netherlands Cancer Institute (NCI) [not published].
tication, followed by systemic hemithoracic radiotherapy and systemic chemotherapy. Twenty-six patients were treated. The median survival was 10.9 months. Different combination of treatment modalities did not influence survival.53

Another study performed by Mattson et al.54 with 100 patients included, showed a median survival of 8 months and a 2-year survival of 20%. Five different radiotherapy and chemotherapy regimens were used, but no statistical differences were seen between the groups.54

The combination of pleurectomy, external radiotherapy, and systemic chemotherapy was also studied in Memorial Sloan-Kettering Cancer Institute.52,72 This multimodality treatment resulted in a median survival of 21s month for epithelial mesothelioma and 11 months for fibrosarcomatous mesothelioma.72

In a more recent study, Rusch et al55 reported results of hemithoracic radiotherapy after complete resection in 61 patients. Adjuvant radiotherapy at a median of 54 Gy was well tolerated, except for one esophageal fistula. Only 13% patients had a local recurrence. Distant metastases were seen in 70% of the patients. The median survival was 17 months, and a 3-year survival of 27% is described. For stage I/II, the median survival was 34 months. Based on these results, the group of Rusch et al55 adapted this treatment regimen as standard treatment for patients with limited pleural mesothelioma.

**Surgery and Emphasis on Intrapleural Chemotherapy**

Huncharek et al57 studied the combination of surgery with postoperative systemic chemotherapy (Table 4). The combination of chemotherapy consisted of cisplatin and doxorubicin or cisplatin and mitomycin C. The median survival was 21 months with a 2-year survival of 23.9%.54

A less favorable outcome was found by Ceresoli et al.43 In this small series (16 patients), the chemotherapy was mostly cisplatin, doxorubicin, or a combination of these agents. The median survival was 14 months.43

Hastürk et al58 treated 20 patients with pleurectomy followed by systemic chemotherapy (cisplatin and mitomycin C) and immunotherapy (α-interferon). This resulted in a median survival of 12 months and a 2-year survival of 15%. The survival was calculated from the onset of chemotherapy.58

DaValle et al59 reported a median survival of 17.5 months. Adjuvant therapy consisted of doxorubicin alone or in combination with other agents or irradiation. The reported survival was no better than that of the 13 patients not receiving adjuvant therapy. This study was not a randomized controlled one.59

Surgery and Emphasis on Intrapleural Chemotherapy

Intracavitary chemotherapy has the advantage of high local concentrations of the cytostatic drug while having limited systemic side effects.73–78 Only direct cytotoxic agents appear rational. The pharmacokinetics of cisplatin and mitomycin are advantageous, but also show significant and sustained plasma levels.74–76 One of the limiting factors is that the penetration depth of chemotherapy is limited to a few millimeters.3 Therefore, intrapleural chemotherapy can only be profitable if it is preceded by optimal cytoreduction.

In a study performed by Lee et al52 with intrapleural cisplatin and cytosine arabinoside after incomplete surgery (pleurectomy/decortication), the median survival was 11.5 months. Rusch et al60 Colleoni et al63 Sauter et al,61 and Rice et al59 studied the use of intrapleural chemotherapy after complete cytoreduction. All patients in these studies received adjuvant systemic chemotherapy. Rusch et al60 studied the effect of instillation with cisplatin and mitomycin after pleurectomy or decortication. The median survival was 18 months, with a 2-year survival of 40%. The mortality was 3.7%, and significant morbidity was observed in 55%. Chemotherapy-related nephrotoxicity was seen in three patients (11%).60 Recurrences were seen in 17 of 27 treated patients (63%). All recurrences, except one, were ipsilaterally localized.51 Colleoni et al63 applied cisplatin and cytarabine as intrapleural instillation after pleurectomy in 20 patients. One patient had a grade IV nephrotoxicity requiring dialysis. The overall median survival was 11.5 months; patients with minimal residual disease after pleurectomy had a median survival of 24.5 months.63 In the study of Sauter et al.61 13 patients received subtotal pleurectomy followed by intrapleural cisplatin and cytosine arabinoside, resulting in a median survival of 9 months with a 2-year survival of 25%. Rice et al59 studied 19 patients with stage I MPM undergoing EPP or pleurectomy followed by postoperative intrapleural cisplatin and mitomycin. Grade I/II hematologic toxicity was seen in seven patients (58%). Mild ototoxicity was noticed in one patient. The mortality was 5%. Complications requiring reoperation developed in 16% of the patients. The median survival was 13 months. The site of recurrence was local (58%), distant (17%), or both local and distant (25%).59

Hyperthermia itself is cytotoxic; it enhances the cytotoxic effect of the cytostatic drugs, and it stimulates the penetration depth.77–81 Carry et al52 studied the addition of hyperthermia to surgery and intrapleural chemotherapy. Three patients with MPM stage I were included in this study. After pleurec-
tomy, an intrapleural perfusion with mitomycin C was performed during 60 min. Because the risk of pulmonary edema is present at temperatures $> 43^\circ C$, the maximal pleural temperature was $42.6^\circ C$. The technique was considered safe and feasible. No systemic toxic levels of mitomycin C were found. Two patients died after 4 months and 11 months, respectively, and one patient survived at least 22 months. Yellin et al. treated seven patients with mesothelioma. A combination of surgery and intraoperative hyperthermic pleural perfusion with cisplatin over 60 min was used. The technique was feasible, easy to perform, and relatively safe. A median survival of 15 months was reported, with two patients surviving $> 30$ months.

A multimodality therapy including surgery, pleural space perfusion with cisplatin, hyperthermia, and postoperative radiotherapy was studied by Ratto et al. The duration of perfusion was 60 min in this study. Radiotherapy ($55 \, Gy$) was administered to chest wall incisions. Ten procedures were without any death or toxicity. Ratto et al. found higher systemic drug concentrations after pleurectomy/decortication than after pleuropneumonectomy, indicating that the lung plays an important role in cisplatin absorption from the pleural space. Normothermic pleural space perfusion was performed in three patients. The local tissue/perfusate ratio of platinum concentrations tended to be higher after hyperthermic perfusion rather than normothermic perfusion.

In the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, we studied patients with MPM stage I treated with cytoreduction and intraoperative hyperthermic intrathoracic chemotherapy. Cisplatin and doxorubicin were perfused over 90 min under mild hyperthermic conditions ($40^\circ C$ to $41^\circ C$). Doxorubicin was chosen because its enhanced activity under hyperthermic conditions; however, the penetration depth is limited.

Radiotherapy ($8 \, Gy$ three times) on the thoracotomy scar and drainage tracts was administered to prevent scar recurrences. The treatment was feasible but was accompanied by considerable toxicity. In a report of 11 patients, a median survival of 8 months was found. Disease recurred in three patients after 4 months, 6 months, and 7 months, respectively. The longest survivor without disease was 8 months.

An update of our results in 20 patients showed a median survival of 11 months (unpublished data).

**Surgery and Emphasis on Intrapleural Photodynamic Therapy**

Photodynamic therapy (PDT) has been considered a new mode of adjuvant treatment to sterilize the surgical field. After systemic administration of a photosensitizer, (tumor) cell kill can be achieved by illuminating the resection field with laser light. This principle was first tested by Takita and Dougherty, who used a first-generation photosensitizer (Photofrin; Quadra Logic Technologies; Vancouver, BC). He treated 31 patients and reported a median survival of 12 months. The estimated median survival increased to 21 months when subdivided for stage I/II. Both pleurectomy and EPP were performed to achieve optimal cytoreduction. The mortality was 6.5%. Serious complications were observed in 48.3%, consisting of infection, bronchopleural fistula, cardiac arrhythmia, prolonged ventilatory support, chylothorax, hematothorax, and spontaneous rupture of the spleen. A long-term report of the same institute including 40 patients revealed a median survival of 15 months. In stage I/II, the median survival was 36 months.

An important randomized controlled study using PDT was performed by Pass et al. Photofrin, a first-generation photosensitizer with a long illumination time, was used. Forty-eight patients underwent debulking to, at most, 5-mm residue. He found no survival benefit or improved local control for patients undergoing EPP pleurectomy combined with PDT. The median survival was 14 months. The mortality and morbidity in this study were considerable: 2.1% and 20.8%, respectively. Complications such as death, bronchopleural fistula, esophageal perforation, and empyema are frequently seen when using PDT.

Baas et al. studied intraoperative PDT after EPP in five patients using a second-generation photosensitizer (meta-tetrahydroxyphenylchlorin). The feasibility study was promising, but in the extended phase I/II study of 25 patients, the median survival was only 10 months. In this study, three patients died in the perioperative period; one death was directly related to inappropriately delivered PDT, and two patients with advanced cases died as a result of cardiac complications. The considerable morbidity and mortality preclude this setup for widespread use.

Escalating the light dose, improvement of light delivery, and addition of chemotherapy and radiotherapy are currently being investigated. Distant tumor spread is not prevented by this combined treatment modality.

**Discussion**

**Prospects for the Future**

Reviewing the literature on treatment of MPM is not encouraging. Not only has little progress has...
been made in the treatment of this disease, it is also
true that very few systematic attempts have been
made to evaluate the effects of treatment strategies.
Almost without exception, reports are retrospective,
with poorly defined patient groups and large vari-
tions in treatment schedules. Most reported studies
can at best be classified as phase I type feasibility
studies. There are very few properly structured
phase II studies and no phase III studies at all, in
which a treatment schedule has been randomly
compared to no treatment. In this era of evidence-
based medicine, we can only conclude that no
evidence exists of proven effectiveness of any treat-
ment in MPM.

What lessons can be learned from the accumu-
lated experience? The staging of MPM remains
difficult by any standard. A preoperative CT scan
and mediastinoscopy seem at present to be the
minimum requirements for adequate staging. The
distinction between stage I and higher stages is often
possible. The distinction within stage I according to
the IMIG staging system, which is meant to deter-
mine operability, is far more difficult.24 Anyone
engaged in surgery for MPM is impressed by the
variation of growth characteristics in different pa-
tients. Sometimes, the tumor has a clear sharp
margin and can easily be separated from neighboring
structures; at other times, infiltrative growth with
accompanying fibrosis is so dense that any attempt
on removal is an illusion. In the present staging
system, these characteristics are not fully repres-
ted, but determine to a large extent the comple-
teness of any surgery, be it decortication or
pleuropneumonectomy. It seems evident that only
patients with stage I MPM are candidates who could
benefit from aggressive locoregional therapies. How-
ever, it is clear that this has not been the case in most
of the presently reviewed studies.

In this review, we could not find clear arguments
to choose between decortication and pleuropneumo-
nectomy as a first-choice surgical strategy. In many
cases, decortication is not feasible because involve-
ment of lung parenchyma. When technically possi-
ble, decortication seems to result in roughly the
same survival as does pleuropneumonectomy (or no
treatment?), but operative mortality is slightly de-
creased. In this review, we have focused on several
multimodality treatments. Surgery combined with
external radiotherapy included the whole hemithorax
as radiation field in contrast to those in which only
the surgical scars were radiated. In selected patients,
a clear survival benefit is found; however, when
critically analyzed, only 1 to 2% of all patients with
mesothelioma could benefit of this treatment.18,67
Although differences are limited, there remains an
impression that survival in the series with external
radiotherapy is somewhat longer than in the series
not including hemithorax radiotherapy (approx-
imately 20-month median survival in recent re-
ports52,55 vs approximately 15-month median survival
in other combination therapies43,56–60). Side effects
of radiotherapy on the liver and heart are mentioned
but not quantified, especially not in the long term.

Autopsy studies of patients with MPM revealed
that more than one half of the patients had dissem-
inated MPM.18 Therefore, systemic chemotherapy
seems to be a prerequisite, but the survival of series
with the combination of surgery with systemic che-
motherapy appears very similar to the surgery-alone
series.43,56–58 The same is valid for the studies on the
combination of surgery with intrapleural chemother-
apy.59–63 The intrapleural chemotherapy approach
has probably not yet shown its full potential, as only
few drugs (doxorubicin and cisplatin) have been
studied, and dosage can probably still be increased.
The combination of surgery with PDT has not shown
a clear improvement of median survival until now.
Furthermore, physical aspects like dosimetry of the
light makes general application of this treatment
difficult. PDT as part of a multimodality approach
cannot be recommended at this stage.64–66

The fact remains that the large majority of patients
with MPM die of locoregional failure despite aggres-
sive locoregional therapy. This is especially true if
recurrences in adjacent cavities (pericardium, con-
tralateral pleura, and abdomen) are considered as
regional failure, as we believe they should. The high
locoregional failure could be explained by the rela-
tive insensibility of MPM to radiotherapy and che-
motherapy. Intensifying the therapy is limited by the
intolerance of adjacent vital structures (especially the
lung).34

The conclusion of this review can only be that at
this moment no therapy has been adequately shown
to have any proven benefit in the treatment of MPM.
At this moment, the combination of complete sur-
gery, being decortication or pleuropneumonectomy,
in combination with hemithorax radiotherapy seems
promising only in selected patients. Intrapleural
hyperthermic chemotherapy clearly needs a better-
designed study. Future adjuvant therapies will also
focus on gene therapy, small molecules (like tyrosine
kinase inhibitors), and angiogenesis inhibitors.15 For
gene therapy, however, results have been disappoint-
ing given the remarkable results in animals.92 Future
studies would provide more useful information if
they used a randomized phase II design, comparing
the defined treatment with a no-treatment arm, espe-
cially if this would involve a quality-of-life as-
essment.
REFERENCES


8 Antman KH. Natural history and epidemiology of malignant mesothelioma. Chest 1993; 103:373S–376S


20 Rusch VW. Pleurectomy/decortication and adjuvant therapy for malignant mesothelioma. Chest 1993; 103:382S–384S


