Hyperthermic intracavitary chemotherapy in abdomen and chest
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CHAPTER TWO

Surgical treatment of malignant pleural mesothelioma: a review

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Chest 2003; 123: 551-561
Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor of the pleura. Presenting symptoms are dyspnoea and chest pain in the majority of people. 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 5000 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 and 30 years. Recently a virus has become a suspected agent too. Simian virus 40 (SV40), 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 SV40 to induce MPM in humans. The prognosis of patients with MPM is poor and untreated, the median survival is 9 months.

Systemic chemotherapy results in partial responses of between 15 and 20%; complete responses are rare. Radiotherapy as single treatment modality, given with curative intent, is considered not feasible because of the large target volume and the dose limiting toxicity of the adjacent organs and structures. Radiotherapy is considered useful for palliation and prevention of seeding after invasive diagnostic procedures.

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 paper we reviewed the surgical management of malignant pleural mesothelioma. The different techniques and treatment outcome of surgery alone are described. Thereafter emphasis is given to the adjuvant therapies.

Methods

A systemic literature study was performed to identify all relevant articles until October 2001. A PubMed search was performed with keywords focused on malignant pleural mesothelioma. Studies with less than ten patients were not reported 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 paper in the overview table. 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 malignant pleural mesothelioma. Different staging systems are used (Table 1).\textsuperscript{22-24}

To stage accurately several staging methods are used. Thoracoscopy, CT, MRI and laparoscopy can identify the T status.\textsuperscript{25,26} CT compared to MRI has nearly equivalent diagnostic accuracy. MRI is superior in imaging diaphragmatic muscle involvement, endo­thoracic involvement and revealing solitary foci of chest wall invasion.\textsuperscript{27} To accurately determine the nodal status is more often a problem. CT has a low accuracy regarding lymph nodes.\textsuperscript{27} Medi-

Table I. Staging systems.

Staging according to Butchart et al\textsuperscript{23}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

Staging according to Sugarbaker et al\textsuperscript{22}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

Stage according to the International Mesothelioma Interest group (IMIG)\textsuperscript{24}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Primary tumor and extent</td>
</tr>
<tr>
<td>T1</td>
<td>a Tumor limited to ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura No involvement of the visceral pleura</td>
</tr>
<tr>
<td></td>
<td>b Tumor involving the ipsilateral parietal pleural, including mediastinal and diaphragmatic pleura</td>
</tr>
</tbody>
</table>
Surgical treatment of malignant pleural mesothelioma

Scattered foci or tumor also involving the visceral pleura

T2 Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
- involvement of diaphragmatic muscle
- confluent visceral pleura (including the fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma

T3 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:
- involvement of the endothoracic fascia
- extension into the mediastinal fat
- solitary, complete resectable focus or tumor extending into the soft tissues of the chest wall
- nontransmural involvement of the pericardium

T4 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:
- diffuse extension or multifocal mass of tumor in the chest wall, with or without associated rib destruction
- direct transdiaphragmatic extension of the tumor to the peritoneum
- direct extension of tumor to the contralateral pleura
- direct extension of tumor to one or more mediastinal organs
- direct extension of tumor into the spine
- tumor extending through the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

N lymph nodes
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases in ipsilateral bronchopulmonary or hilar lymph nodes
N2 Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3 Metastases in contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular scalene lymph nodes

M metastases
Mx Presence of distant metastases cannot be assessed
M0 No (known) metastasis
M1 Distant metastasis present

Stage Grouping
I   a T1aN0M0
    b T1bN0M0
II  T2N0M0
III  Any T3M0
     Any N1M0
     AnyN2M0
IV  Any T4
    Any N3
    Any M1
astinoscopy is useful, however 25% of the MPM patients have nodal involvement confined to areas as peridiaphragmatic and internal mammary region not accessible to the mediastinoscopy. Positron Emission Tomography (PET) 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 et al 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. Rasch et al 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 (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 et al found that females show better survival than males, however Sugarbaker et al could not confirm this. The type of resection, i.e. extrapleural pneumonectomy or a pleurectomy/decortication, did not have impact on survival in the study of Rusch et al. 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 extrapleural pneumonectomy was necessary to achieve complete resection.

**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 endothoracic 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 towards 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 decortication of the visceral pleura is performed. Pericardium and diaphragm are eventually reconstructed.
The mortality of this procedure is limited (1-2%), when performed in specialized centers.\textsuperscript{34,35} The most common complication is prolonged air leakage, occurring in 10% of cases. Other reported complications are pneumonia, empyema and hemorrhage.\textsuperscript{3} Pleurectomy and decortication is reported effective in controlling pleural effusion. The median survival reached by this procedure is reported in different studies between 9 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.\textsuperscript{3} After pleurectomy/decortication Hiliaris et al\textsuperscript{16} reported that residual tumor was left behind in 78% of patients, most frequently on the visceral pleura. The most common site of recurrence is the ipsilateral hemithorax.\textsuperscript{34} In recent years pleurectomy/decortication studies all included adjuvant therapy.

\subsection*{Extrapleural pneumonectomy}

Extrapleural pneumonectomy (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.\textsuperscript{37} After a posterolateral thoracotomy through the sixth intercostal space, a dissection between chest wall and parietal pleura is started. Blunt dissection with fingers appear 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 the last decades from 30 to less than 5% when

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Year</th>
<th>N</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chahinian\textsuperscript{68}</td>
<td>Pleurectomy</td>
<td>1982</td>
<td>30</td>
<td>13</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Brenner\textsuperscript{7}</td>
<td>Pleurectomy</td>
<td>1982</td>
<td>69</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Law\textsuperscript{6}</td>
<td>Pleurectomy</td>
<td>1984</td>
<td>28</td>
<td>20</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Chailleux\textsuperscript{19}</td>
<td>Pleurectomy</td>
<td>1988</td>
<td>29</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ruffie\textsuperscript{11}</td>
<td>Pleurectomy</td>
<td>1989</td>
<td>63</td>
<td>10</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Brancatisano\textsuperscript{10}</td>
<td>Pleurectomy</td>
<td>1991</td>
<td>45</td>
<td>16</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Ruschi\textsuperscript{1}</td>
<td>Pleurectomy</td>
<td>1991</td>
<td>26</td>
<td>10</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Allen\textsuperscript{9}</td>
<td>Pleurectomy*</td>
<td>1994</td>
<td>56</td>
<td>9</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Soysal\textsuperscript{17}</td>
<td>Pleurectomy*</td>
<td>1997</td>
<td>100</td>
<td>17</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Ceresoli\textsuperscript{65}</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 extrapleural pneumonectomy alone (only studies with >10 patients are listed).

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Year</th>
<th>N</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worn²</td>
<td>EPP</td>
<td>1974</td>
<td>62</td>
<td>19</td>
<td>37</td>
<td>NA</td>
</tr>
<tr>
<td>Butchart²³</td>
<td>EPP</td>
<td>1976</td>
<td>29</td>
<td>10</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Ruffie¹¹</td>
<td>EPP</td>
<td>1989</td>
<td>23</td>
<td>9</td>
<td>NA</td>
<td>13</td>
</tr>
<tr>
<td>Rusch¹¹</td>
<td>EPP</td>
<td>1991</td>
<td>20</td>
<td>10</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Allen⁷</td>
<td>EPP*</td>
<td>1994</td>
<td>40</td>
<td>13</td>
<td>23</td>
<td>8</td>
</tr>
</tbody>
</table>

EPP: Extrapleural Pneumonectomy, NA: Not Available. *: Some patients received adjuvant therapy.

Surgery and adjuvant therapies

Surgery alone is associated with a high recurrence rate and therefore adjuvant therapy seems useful.²⁰ Studies performed with the combination of surgery and adjuvant treatment are listed in Table 4.

Surgery and emphasis on external radiotherapy (Table 4a)

In this Table series are collected that report on combination therapy of surgery with complete hemithoracic irradiation. Sugarbaker et al.¹⁴ advocated that adjuvant radiotherapy should be 40-45Gy to the entire hemithorax with a 5-5.5Gy boost to areas at high risk for recurrence. Doses limiting thoracic structures are spinal cord (45Gy), heart (45Gy) and lung (20Gy).¹⁵ Hemithoracic radiotherapy equals a total loss of lung function.¹⁶ A shift of the abdominal vis-
cera into the inferior hemithorax after a pneumonectomy limits the safe dose to 30Gy in the inferior area.44
The technique of extrapleural pneumonectomy combined with hemithoracic radiation and systemic chemotherapy was described by Grondin et al.47 The largest series was described by Sugarbaker et al38 with 183 patients. The mortality rate was 3.8%. The morbidity rate was

Table 4. Studies with surgery and adjuvant therapy (only studies with >10 patients are listed).

4a. Surgery and emphasis on external radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Year</th>
<th>N</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormack51</td>
<td>S, XRT, C</td>
<td>1982</td>
<td>18*</td>
<td>16</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Hilaris46</td>
<td>S, XRT, B</td>
<td>1983</td>
<td>41</td>
<td>21</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Alberts49</td>
<td>S, XRT, C</td>
<td>1988</td>
<td>26</td>
<td>11</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mattsson50</td>
<td>S, XRT, C</td>
<td>1992</td>
<td>100</td>
<td>8</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Sugarbaker52</td>
<td>S, XRT, C</td>
<td>1996</td>
<td>120</td>
<td>21</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Rusch53</td>
<td>S, XRT</td>
<td>2001</td>
<td>61</td>
<td>17</td>
<td>NA</td>
<td>8</td>
</tr>
</tbody>
</table>

4b. Surgery and emphasis on systemic chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Year</th>
<th>N</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davalle57</td>
<td>S, C, XRT</td>
<td>1986</td>
<td>17</td>
<td>18</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Huncharek51</td>
<td>S, C</td>
<td>1996</td>
<td>21</td>
<td>24</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hastürk56</td>
<td>S, C, I</td>
<td>1996</td>
<td>20</td>
<td>12</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>Ceresoli55</td>
<td>S, C</td>
<td>2001</td>
<td>16</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

4c. Surgery and emphasis on intrapleural chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Year</th>
<th>N</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice66</td>
<td>S, IPC, C</td>
<td>1994</td>
<td>19</td>
<td>13</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Rusch63</td>
<td>S, IPC, C</td>
<td>1994</td>
<td>27</td>
<td>18</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Sauter65</td>
<td>S, IPC, C</td>
<td>1995</td>
<td>13</td>
<td>9</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Lee64</td>
<td>S, IPC</td>
<td>1995</td>
<td>15</td>
<td>12</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Colleoni64</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**</td>
<td>S, IPC</td>
<td>2001</td>
<td>20</td>
<td>11</td>
<td>NA</td>
<td>0</td>
</tr>
</tbody>
</table>

4d. Surgery and emphasis on photodynamic therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Year</th>
<th>N</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass</td>
<td>S, PDT, C</td>
<td>1997</td>
<td>25</td>
<td>14</td>
<td>NA</td>
<td>4</td>
</tr>
<tr>
<td>Moskal</td>
<td>S, PDT</td>
<td>1998</td>
<td>40</td>
<td>15</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>Schouwink</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, PDT: Photodynamic therapy, NA: Not Available*: epithelial mesothelioma only, **: data from The Netherlands Cancer Institute, not published.
50%, including cardiac arrest, respiratory failure, acute respiratory distress syndrome, sepsis, contralateral pneumothorax, arrhythmia's, pulmonary embolism, empyema and gastrointestinal hemorrhage.\textsuperscript{38} 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\textsuperscript{44} reported a 5-year survival of 45%. Despite aggressive local treatment including pericardium en 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%).\textsuperscript{42}

The application of brachytherapy after pleurectomy was studied in 41 patients by Hilaris et al.\textsuperscript{1} Measurable gross residual tumor was treated with permanent \textsuperscript{125}Iodine implantation and residual diffuse disease by temporary \textsuperscript{103}Iridium implantation or postoperative instillation of \textsuperscript{32}PPhosphorus. After this treatment external radiotherapy on the hemithorax was given (45Gy). There was no mortality. Complications occurred in 6 patients (15%), including one radiation pneumonitis and one 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, distant metastasis with or without local recurrence in the other two-third.\textsuperscript{36} An update, including the same patient cohort with larger follow-up, by Mychalczak et al\textsuperscript{48} could not confirm this treatment outcome; in this abstract a median survival of 13 months was reported.

Alberts et al\textsuperscript{49} studied the combination of decortication, 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.\textsuperscript{49} Another study performed by Mattson et al\textsuperscript{60} 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.\textsuperscript{60}

The combination of pleurectomy, external radiotherapy and systemic chemotherapy was also studied in Memorial Sloan-Kettering Cancer Institute.\textsuperscript{51,52} This multimodality treatment resulted in a median survival of 21 months for epithelial mesothelioma and 11 months for fibrosarcomatous mesothelioma.\textsuperscript{52}

In a more recent study Rusch et al\textsuperscript{53} reported results of hemithoracic radiotherapy after complete resection in 61 patients. Adjuvant radiotherapy at a median of 54Gy was well tolerated, except for one esophageal fistula. Only 13% patients developed 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 al\textsuperscript{53} adapted this treatment regimen as standard treatment for patients with limited pleural mesothelioma.

\textit{Surgery and emphasis on systemic chemotherapy (Table 4b)}

Huncharek et al\textsuperscript{54} studied the combination of surgery with postoperative systemic chemotherapy. 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%.\textsuperscript{54}
A less favorable outcome was found by Ceresoli et al.\textsuperscript{55} In this small series (16 patients) the chemotherapy was mostly cisplatin, doxorubicin or a combination of these agents. The median survival was 14 months.\textsuperscript{55}

Hastürk et al\textsuperscript{56} treated 20 patients with pleurectomy followed by systemic chemotherapy (cisplatin and mitomycin C) and immunotherapy (alpha 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.\textsuperscript{56}

DaValle et al\textsuperscript{57} 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 adjunctive therapy. This study was not randomized controlled.\textsuperscript{57}

\subsection*{Surgery and emphasis on intrapleural chemotherapy (Table 4c)}

Intracavitary chemotherapy has the advantage of high local concentrations of the cytostatic drug while having limited systemic side effects.\textsuperscript{58,59} Only direct cytotoxic agents appear rational. The pharmacokinetics of cisplatin and mitomycin are advantageous, but also show significant and sustained plasma levels.\textsuperscript{59,60} One of the limiting factors is that the penetration depth of chemotherapy is limited to a few millimeters.\textsuperscript{3} Therefore intrapleural chemotherapy can only be profitable if it is preceded by optimal cytoreduction.

In a study performed by Lee et al\textsuperscript{61} with intrapleural cisplatin and cytosine arabinoside after incomplete surgery (pleurectomy/ decortication), the median survival was 11.5 months. Rusch et al\textsuperscript{63}, Colleoni et al\textsuperscript{64}, Sauter et al\textsuperscript{65} and Rice et al\textsuperscript{66} studied the use of intrapleural chemotherapy after complete cytoreduction. All patients in these studies received adjuvant systemic chemotherapy. Rusch et al\textsuperscript{63} 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 3 patients (11%).\textsuperscript{63} Recurrences were seen in 17 of 27 treated patients (63%). All recurrences, except one, were ipsilateral localized.\textsuperscript{63}

Colleoni et al\textsuperscript{64} applied cisplatin and cytarabine as intrapleural instillation after pleurectomy in 20 patients. One patient developed 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.\textsuperscript{64} In a study of Sauter et al\textsuperscript{65} 13 patients received subtotal pleurectomy followed by intrapleural cisplatin and ara-C resulting in a median survival of 9 months with a 2-year survival of 25%. Rice et al\textsuperscript{66} studied 19 patients with stage I MPM undergoing EPP or pleurectomy followed by postoperative intrapleural cisplatin and mitomycin. Grade I-II hematological toxicity was seen in seven patients (36%). Mild ototoxicity was noticed in one patient. The mortality was 5%. Complications requiring re-operation developed in 16\% of the patients. The median survival was 13 months. The site of recurrence was local (58\%), distant (17\%), both local and distant (25\%).\textsuperscript{66}

Hyperthermia itself is cytotoxic, it enhances the cytotoxic effect of the cytostatic drugs and
stimulates the penetration depth. Carry et al studied the addition of hyperthermia to surgery and intrapleural chemotherapy. Three patients with MPM stage I were included in this study. After pleurectomy an intrapleural perfusion with MMC was performed during 60 minutes. Because the risk of pulmonary edema is present at temperatures above 43°C, the maximal pleural temperature was 42.6°C. The technique was considered safe and feasible. No systemic toxic levels of MMC were found. Two patients died after respectively 4 and 11 months and one patient survived at least 22 months. 

Yellin et al treated 7 patients with mesothelioma. A combination of surgery and intraoperative hyperthermic pleural perfusion with cisplatin during 60 minutes was used. The technique was feasible, easy to perform and relatively safe. A median survival of 15 months was reported with two patients surviving more than 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 minutes in this study. Radiotherapy (55Gy) was given 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 during 90 minutes under mild hyperthermic conditions (40-41°C). Doxorubicin was chosen because its enhanced activity under hyperthermic conditions, however the penetration depth is limited. Radiotherapy (3x8Gy) on thoracotomy scar and drainage tracts was given to prevent scar recurrences. The treatment was feasible but was accompanied with considerable toxicity. In a report of 11 patients a median survival of 8 months was found. Three patients already recurred after respectively 4, 6 and 7 months. The longest survivor without disease was 8 months. An update of our results in 20 patients show a median survival of 11 months [unpublished data].

Surgery and emphasis on intrapleural photodynamic therapy (Table 4d)

Photodynamic therapy (PDT) has been considered a new way 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 laserlight. This principle was first tested by Takita et al who used a first generation photosensitizer named Photofrin. 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 extrapleural pneumonectomy 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, haematothorax and spontaneous
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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., using Photofrin®, a first-generation photosensitizer with a long illumination time, was used. Forty-eight patients underwent debulking to at most 5mm residue. He found no survival benefit or improved local control for patients undergoing extrapleural pneumonectomy or pleurectomy combined with photodynamic therapy. The median survival was 14 months. The mortality and morbidity in this study were considerable; respectively 2.1% and 20.8%. Complications such as death, bronchopleural fistula, esophageal perforation and empyema are frequently seen when using photodynamic therapy.

Baas et al. studied intraoperative photodynamic therapy after EPP in five patients using a second-generation photosensitizer (mTHPC). The feasibility study was promising but in the extended phase I/II study of 28 patients the median survival was only 10 months. In this study three patients died in the perioperative period; one death was directly related to inappropriate delivered PDT and two other advanced cases died as a result of cardiac complications. The considerable morbidity and mortality precludes 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 and prospects for the future

Reviewing the literature on treatment of malignant pleural mesothelioma is not encouraging. Not only little progress has been made in the treatment of this disease, it is also clear that very few systematic attempts have been made to evaluate the effects of treatment strategies. Almost without exception, reports are retrospective with poorly defined patients groups and large variations 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 treatment in MPM.

What lessons can be learned from the accumulated 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 stages I and higher stages is often possible. The distinction within stage I according to the IMIG staging system, which is meant to determine operability, is far more difficult. Anyone engaged in surgery for MPM is impressed by the variation of growth characteristics in different patients. 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 represented, but determine to a large extent the completeness of any surgery being decortication or
pleuropneumonectomy. It seems evident that only patients with stage I MPM are candidates who could benefit from aggressive loco-regional therapies. However, 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 pleuropneumonectomy as first choice surgical strategy. In many cases, decortication is not feasible because involvement of lung parenchyma. When technically possible, decortication seems to result in roughly the same survival as does pleuropneumonectomy (or no treatment?), but operative mortality is slightly less. 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 1-2% of all mesothelioma patients could benefit of this treatment.\textsuperscript{18,41} 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 (approximately 20 months median survival in recent reports\textsuperscript{32,53} versus approximately 15 months median survival in other combination therapies\textsuperscript{54-57,62-66,80,83,85}). Side effects of radiotherapy on the liver and heart are mentioned, but not quantified, especially not on the long term.

Autopsy studies of patients with malignant pleural mesothelioma revealed that more than half of the patients had disseminated MPM.\textsuperscript{18} Therefore systemic chemotherapy seems to be a prerequisite, but the survival of series with the combination of surgery with systemic chemotherapy appears very similar to the surgery alone series.\textsuperscript{54,57,62} The same is valid for the studies on the combination of surgery with intrapleural chemotherapy.\textsuperscript{62,66} 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 photodynamic therapy has not shown a clear improvement of median survival up till now. Furthermore physical aspects like dosimetry of the light makes general application of this treatment difficult. Photodynamic therapy as part of a multimodality approach cannot be recommended at this stage.\textsuperscript{80,83,85}

The fact remains that the large majority of patients with MPM die of loco-regional failure, despite aggressive loco-regional therapy. This is especially true if recurrences in adjacent cavities (pericardium, contralateral pleura and abdomen) are considered as regional failure as we believe they should. The high loco-regional failure could be explained by the relative insensitivity of MPM to radiotherapy and chemotherapy. Intensifying the therapy is limited by the intolerance of adjacent vital structures (especially the lung).\textsuperscript{54}

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 malignant pleural mesothelioma. At this moment the combination of complete surgery, 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.\textsuperscript{85} For gene therapy however, results have been disappointing given the remarkable results in animals.\textsuperscript{85}
Future studies would give a lot more useful information if they would use the randomized phase II design, comparing the defined treatment with a no treatment arm, especially if this would involve a quality of life assessment.

References

Chapter 2


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