A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma

T. D. Yan1, L. Welch2, D. Black3 & P. H. Sugarbaker1*

1Program in Peritoneal Surface Oncology, Washington Cancer Institute, Washington Hospital Center, Washington, DC; 2Center to Protect Worker’s Rights, Silver Spring, MD, USA; 3School of Public Health and Community Medicine, The University of New South Wales, Sydney, Australia

Received 21 July 2006; revised 13 October 2006; accepted 17 October 2006

Background: In the past, diffuse malignant peritoneal mesothelioma (DMPM) was regarded as a preterminal condition. The length of survival was dependent upon the aggressive versus indolent biologic behavior of the neoplasm. The overall median survival was ~1 year after systemic chemotherapy. Cytoreductive surgery (CRS) combined with perioperative intraperitoneal chemotherapy (PIC) has been used as a treatment alternative, but the efficacy of this combined treatment remains to be established.

Patients and methods: Searches for relevant studies published in peer-reviewed medical journals on CRS and PIC for DMPM before May 2006 were carried out on six databases. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. Expert academic surgeons in Washington, DC, USA were asked whether they knew about any important unpublished data. Two investigators independently evaluated each study according to predefined criteria. The quality of each study was assessed. Clinical effectiveness was synthesized through a narrative review with full tabulation of results of all included studies.

Results: Seven prospective observational studies from six tertiary institutions were available, allowing 240 DMPM patients for assessment. The median survival ranged from 34–92 months. The 1-, 3- and 5-year survival varied from 60% to 88%, 43% to 65% and 29% to 59%, respectively. The perioperative morbidity varied from 25% to 40% and mortality ranged from 0% to 8%.

Conclusions: This systematic review evaluated the current evidence for CRS and PIC for DMPM. Seven observational studies were available for assessment, which demonstrated an improved overall survival, as compared to historical controls, using systemic chemotherapy and palliative surgery.

Key words: asbestos, cisplatin, cytoreductive surgery, doxorubicin, intraperitoneal chemotherapy, peritoneal mesothelioma, peritonectomy

Introduction

Malignant mesothelioma arises from the serosal lining of the pleural, peritoneal and pericardial cavities [1–6]. It is a rare neoplasm and has been implicated to be associated with asbestos exposure [1–5]. The rising worldwide incidence of malignant mesothelioma is not expected to peak for another 10–20 years [5]. Diffuse malignant peritoneal mesothelioma (DMPM) represents one-fourth of all mesotheliomas with an annual incidence of DMPM of 300–400 cases in the United States [2, 3]. It is characterized macroscopically by thousands of whitish tumor nodules of variable size and consistency that may coalesce to form plaques, masses or layer out to uniformly cover the entire peritoneal surface. Although association of asbestos exposure with DMPM has been observed, the pathogenesis of this disease is largely unknown [7, 8]. In addition, DMPM has been reported following radiation therapy, mica exposure, recurrent peritonitis and administration of thorium dioxide [9–13].

A great majority of patients present with abdominal pain and distension caused by the accumulation of tumors and ascitic fluid [14]. Without aggressive treatments the disease is rapidly fatal [15]. In the past, DMPM was treated at most cancer centers with a combination of systemic chemotherapy, palliative surgery and in a few patients total abdominal radiation. The patients, however, did not seem to respond to these treatments, in that the median survival was uniformly ~1 year (Table 1) [16–22]. No randomized trials have been ever attempted, but it is likely that the survival associated with these palliative treatments showed little improvement over the natural course of the disease.
In most patients, DMPM remains localized within the abdominopelvic cavity throughout its course. An aggressive treatment plan to surgically eradicate gross disease combined with perioperative intraperitoneal chemotherapy (PIC) to control residual disease has a strong locoregional treatment rationale [23–25]. This combined modality has been used with success in patients with pseudomyxoma peritonei and peritoneal carcinomatosis from other gastrointestinal (GI) and gynecologic malignancies [26–31]. Treatment of peritoneal carcinomatosis through the use of intraperitoneal chemotherapy was declared the standard of practice by the National Cancer Institute, Bethesda, USA after a recent phase III study in ovarian cancer [32]. Especially in the last 5 years, as the cytoreductive surgical approach combined with PIC has expanded, the results of treatment of DMPM have dramatically improved, as compared to historical controls. The median survival has approached 5 years [14, 33–48] (T. D. Yan, M. Links, D. L. Morris, unpublished data).

Cytoreductive surgery (CRS) with PIC, however, has only become a treatment option for DMPM over the last decade. Due to the rarity of the disease, most centers simply do not have sufficient number of patients. The optimal adaptation of CRS plus PIC to this disease continues to be a challenge to the surgeon accepting the responsibility for managing these patients. The purpose of the present study was to conduct a systematic review of the current evidence to assess the efficacy of CRS with PIC for the treatment of DMPM.

**patients and methods**

**literature search strategy**

Electronic literature searches were carried out to identify all published peer-reviewed medical articles on CRS with PIC for DMPM. The following electronic databases were searched from their inception until May 2006: Medline, Pubmed, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Database of Abstracts of Review of Effectiveness. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. Finally, expert academic surgeons in Washington, DC, USA were asked whether they knew about any important unpublished data. All relevant articles identified were assessed with application of inclusion and exclusion criteria.

**inclusion criteria**

All the participants had a histological diagnosis of DMPM. Studies using the combined treatment modality of CRS or surgical debulking and PIC were included. CRS consisted of peritoneotomy procedures as described by Sugarbaker [23] (anterior parietal peritonectomy, omentectomy ± splenectomy, right and left subphrenic peritonectomy, pelvic peritonectomy and lesser omentectomy with stripping of the omental bursa ± cholecystectomy) and visceral resections (rectosigmoidectomy, right colectomy, total abdominal colectomy, hysterectomy and small bowel resection).

PIC regimens included intraperitoneal hyperthermic chemotherapy (IPHC) and/or early postoperative intraperitoneal chemotherapy (EPIC). Intrapерitoneal chemotherapy used in the operating room with hyperthermia has been referred to by many different nomenclatures: continuous hyperthermic peritoneal perfusion; heated intraoperative intraperitoneal chemotherapy; hyperthermic intraperitoneal chemotherapy or IPHC. In this review, IPHC was the designated terminology.

Experimental and observational studies were searched for inclusion. Studies were classified into four levels of evidence, level 1 evidence: randomized controlled trials (RCTs); level 2 evidence: controlled clinical trials; level 3 evidence: controlled observational studies and level 4 evidence: observational studies without control groups. The outcomes were selected for inclusion if reported in more than one trial and they included survival, disease status, morbidity, mortality, blood loss, operation duration, hospital stay, prognostic factors and quality of life. There was no restriction on a minimal number of patients treated. All studies selected were human trials, published in English language.

**exclusion criteria**

Studies reporting the effectiveness of surgical debulking alone for DMPM were excluded. Studies reporting the effectiveness of CRS with PIC for peritoneal surface malignancy, without specific documentation of DMPM or studies that included other peritoneal carcinomatosis when reporting aggregate outcomes were excluded. Abstracts, editorials, letters and expert opinions were excluded.

**data extraction and critical appraisal**

Data were extracted independently by two investigators (TDY and LW) by means of predefined criteria. Serial publications reporting accumulating numbers of patients or increased length of follow-up were identified. Only most recent or complete update(s) from each institution were included for appraisal and data extraction. The two investigators then independently appraised each included article, using a critical review checklist consisting of representativeness of sample, explicitness of inclusion criteria, similarity of disease progression at the time of treatment, adequacy of follow-up, objectivity of outcome measures and subseries analysis, as recommended by the National Health Service Center for Reviews and Dissemination case series quality assessment criteria (University of York) [49].

All data were extracted from the relevant articles’ texts, tables and figures. A meta-analysis was not appropriate because all studies lack a comparator. Clinical effectiveness was synthesized through a narrative review with full tabulation of results of all included studies. Discrepancies between the two reviewers were resolved by discussion and consensus. The final results were reviewed by the senior investigators (DB and PHS).

**results**

**quantity of evidence**

Electronic searches identified 171 publications. Initial evaluation of these abstracts identified 27 potentially relevant publications. Manual search of the reference lists identified further two potentially relevant publications. Experts in peritoneal surface oncology identified six additional recent

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. of patients</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chailleux et al.</td>
<td>1998</td>
<td>11/167</td>
<td>10</td>
</tr>
<tr>
<td>Antman et al.</td>
<td>1998</td>
<td>37/180</td>
<td>15</td>
</tr>
<tr>
<td>Sridhar et al.</td>
<td>1992</td>
<td>13/50</td>
<td>9.5</td>
</tr>
<tr>
<td>Markman and Kelsen</td>
<td>1992</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Yates et al.</td>
<td>1997</td>
<td>14/272</td>
<td>14</td>
</tr>
<tr>
<td>Neumann et al.</td>
<td>1999</td>
<td>74</td>
<td>12</td>
</tr>
<tr>
<td>Elshabakh et al.</td>
<td>1999</td>
<td>15</td>
<td>12.5</td>
</tr>
</tbody>
</table>

*Combined pleural and peritoneal mesothelioma.

Table 1. Median survival of diffuse malignant peritoneal mesothelioma using traditional treatment modalities.
studies, which were either submitted for publication or in press. When the inclusion and exclusion criteria were applied to all 35 publications, 18 articles remained for assessment (Table 2) [14, 33–48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). Several centers have published studies with accumulating numbers of patients or increased length of follow-up. Seven most complete updates from six institutions were included for appraisal and data extraction (Table 3) [38, 39, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). This resulted in a total of 240 patients for evaluation. One study had morbidity and mortality as the primary outcome measures [38]; one study had survival as the primary outcome measures [39] and the remaining five studies had survival, morbidity and mortality as primary outcome measures [42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data).

quality of evidence

All seven included articles were prospective observational studies without control groups and were classified as level 4 evidence [38, 39, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). There were no RCTs or comparative studies found. No prior systematic review or meta-analysis on this topic was identified.

All seven reports originated from six established tertiary referral centers, specializing in the treatment of peritoneal surface malignancy [38, 39, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). Three centers reported on relatively larger numbers of patients in four studies (n = 100, 70, 49 and 49) [38, 39, 42, 45]. The remaining three centers reported relatively smaller series (n = 15, 12 and 15) [47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). Four studies were

Table 2. Summary of outcomes presented in relevant publications of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma

<table>
<thead>
<tr>
<th>Chief investigator</th>
<th>Reference</th>
<th>Year</th>
<th>n</th>
<th>Survival</th>
<th>Disease status</th>
<th>Morbidity</th>
<th>Mortality</th>
<th>Blood loss</th>
<th>Operation duration</th>
<th>Hospital stay</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugarbaker</td>
<td>33</td>
<td>2000</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>2002</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>2003</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>2003</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>2006</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>2006</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>2006</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>2006</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alexander</td>
<td>40</td>
<td>1997</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>1999</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>2003</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deraco</td>
<td>43</td>
<td>1999</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>2005</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>2006</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glehen</td>
<td>46</td>
<td>2003</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>2006</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loggie</td>
<td>48</td>
<td>2001</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morris (unpublished data)</td>
<td>2006</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Literature review of most recent updates on cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma

<table>
<thead>
<tr>
<th>Chief investigator</th>
<th>Center</th>
<th>Evidence</th>
<th>Follow-up (months)</th>
<th>n</th>
<th>PIC</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugarbaker [38]</td>
<td>Washington, DC</td>
<td>Level 4</td>
<td>48</td>
<td>70</td>
<td>IPHC (Cisplatin + Doxorubicin) + EPIC (Taxol)</td>
<td>M&amp;M</td>
</tr>
<tr>
<td>Sugarbaker [39]</td>
<td>Washington, DC</td>
<td>Level 4</td>
<td>48</td>
<td>100</td>
<td>IPHC (Cisplatin + Doxorubicin) + EPIC (Taxol)</td>
<td>Survival</td>
</tr>
<tr>
<td>Alexander [42]</td>
<td>NCI, Bethesda</td>
<td>Level 4</td>
<td>28</td>
<td>49</td>
<td>IPHC (Cisplatin) + EPIC (5-FU/ Taxol)</td>
<td>Survival + M&amp;M</td>
</tr>
<tr>
<td>Deraco [45]</td>
<td>Milan</td>
<td>Level 4</td>
<td>20</td>
<td>49</td>
<td>IPHC (Cisplatin + Doxorubicin/MMC)</td>
<td>Survival + M&amp;M</td>
</tr>
<tr>
<td>Glehen [47]</td>
<td>Lyon</td>
<td>Level 4</td>
<td>47</td>
<td>15</td>
<td>IPHC (Cisplatin + MMC)</td>
<td>Survival + M&amp;M</td>
</tr>
<tr>
<td>Loggie [48]</td>
<td>Winston-Salem, NC</td>
<td>Level 4</td>
<td>45</td>
<td>12</td>
<td>IPHC (MMC)</td>
<td>Survival + M&amp;M</td>
</tr>
<tr>
<td>Morris (unpublished data)</td>
<td>Sydney</td>
<td>Level 4</td>
<td>14</td>
<td>15</td>
<td>IPHC (Cisplatin + Doxorubicin) + EPIC (Taxol)</td>
<td>Survival + M&amp;M</td>
</tr>
</tbody>
</table>

*Mean.
EPIC: early postoperative intraperitoneal chemotherapy; IPHC: intraperitoneal hyperthermic chemotherapy; M&M: Morbidity and mortality; MMC: Mitomycin C.
representative of the target population [38, 39, 42, 45]. Although one of the studies involved 100 DMPM patients, it was influenced by a temporal factor, with an evolution of the intraperitoneal chemotherapy treatment plans over the study period, where the initial 33 cases were treated with increasingly aggressive intraperitoneal chemotherapy regimens [39]. Three studies, due to limited number of patients, might not be reporting on a true representation of the target population [47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). The treatment protocols varied among the institutions, especially in terms of timing and regimens of PIC. Some institutions used IPHC alone [45, 47, 48] and others used IPHC combined with EPIC [38, 39, 42] (T. D. Yan, M. Links, D. L. Morris, unpublished data). All studies, however, shared two of the most important concepts in treatment rationale, maximal CRS to remove macroscopic disease and intraperitoneal chemotherapy delivered immediately after CRS to eradicate residual tumor cells.

All studies used explicit a priori inclusion and exclusion criteria [38, 39, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). To date there has been no formal staging system for DMPM, therefore it was not clear if patients were at different stages of disease progression at the time of the treatment. Six studies stated that only patients with intra-abdominal disease were included; however, lymph nodal status was not documented [38, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). The remaining study included seven patients with positive lymph nodes and four patients with extra-abdominal metastatic disease, which might represent a more advanced stage of disease progression [39].

Four studies had a median follow-up of >3 years, and were judged adequacy of follow-up [38, 39, 47, 48]. The remaining three studies had a median follow-up of <3 years and were judged inadequate follow-up [42, 45] (T. D. Yan, M. Links, D. L. Morris, unpublished data). Survival, morbidity and mortality were objective outcome measures. All studies attempted to analyze the data according to significant prognostic variables [38, 39, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data).

**assessment of survival**

Effectiveness of CRS and PIC on survival of patients with DMPM is demonstrated in Table 4 [39, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). The median survival ranged from 34–92 months [39, 42, 47, 48]. The median survival was not reached in two of the studies [45] (T. D. Yan, M. Links, D. L. Morris, unpublished data). The 1-, 2-, 3-, 5- and 7-year survival rates varied from 60% to 88%, 60% to 77%, 43% to 65%, 29% to 59% and 33% to 39%, respectively [39, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). One study reported disease status on 49 patients, which included that 29 patients had no evidence of disease, 10 patients were alive with disease and 10 patients had died from disease [45].

**assessment of perioperative outcomes**

Effectiveness of CRS and PIC on perioperative outcomes is demonstrated in Table 5 [38, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). The overall morbidity rate varied from 25% to 40% [38, 39, 42, 45, 47] (T. D. Yan, M. Links, D. L. Morris, unpublished data). The overall mortality rate varied from 2% to 20% [38, 39, 42, 45, 47] (T. D. Yan, M. Links, D. L. Morris, unpublished data). The overall mortality rate varied from 2% to 20% [38, 39, 42, 45, 47] (T. D. Yan, M. Links, D. L. Morris, unpublished data).

### Table 4. Effectiveness of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma

<table>
<thead>
<tr>
<th>Chief investigator</th>
<th>n</th>
<th>Median survival (months)</th>
<th>Survival rates (%)</th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>5-year</th>
<th>7-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugarbaker [39]</td>
<td>100</td>
<td>52</td>
<td>78</td>
<td>64</td>
<td>55</td>
<td>46</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Alexander [42]</td>
<td>49</td>
<td>92</td>
<td>86</td>
<td>77</td>
<td>59</td>
<td>59</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Deraco [45]</td>
<td>49</td>
<td>NA</td>
<td>88</td>
<td>74</td>
<td>65</td>
<td>57</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Glehen [47]</td>
<td>15</td>
<td>36</td>
<td>69</td>
<td>58</td>
<td>43</td>
<td>29</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Loggie [48]</td>
<td>12</td>
<td>34</td>
<td>60</td>
<td>60</td>
<td>50</td>
<td>33</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Morris (unpublished data)</td>
<td>15</td>
<td>NA</td>
<td>76</td>
<td>63</td>
<td>63</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

NA, median survival was not reached.
–, not reported.

### Table 5. Morbidity and mortality of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei

<table>
<thead>
<tr>
<th>Chief investigator</th>
<th>n</th>
<th>Morbidity (%)</th>
<th>Hematological toxicity (%)</th>
<th>Blood loss (ml)</th>
<th>Operation duration (h)</th>
<th>Reoperation (%)</th>
<th>Mortality (%)</th>
<th>Hospital stay (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugarbaker [38]</td>
<td>70</td>
<td>36</td>
<td>8</td>
<td>590</td>
<td>8.0*</td>
<td>11</td>
<td>3</td>
<td>23*</td>
</tr>
<tr>
<td>Alexander [42]</td>
<td>49</td>
<td>25</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Deraco [45]</td>
<td>49</td>
<td>27</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Glehen [47]</td>
<td>15</td>
<td>40</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Loggie [48]</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Morris (unpublished data)</td>
<td>15</td>
<td>36</td>
<td>–</td>
<td>–</td>
<td>9.6*</td>
<td>7</td>
<td>7</td>
<td>23*</td>
</tr>
</tbody>
</table>

*Mean
–, not reported.
M. Links, D. L. Morris, unpublished data). Hematological toxicity rate varied from 8% to 26% [38, 42]. Blood loss was reported to be 590 ml [38]. Mean operative duration ranged from 6.5–6.6 h [38, 42] (T. D. Yan, M. Links, D. L. Morris, unpublished data). Reoperation rates for postoperative adverse events were 4%–11% [38, 42] (T. D. Yan, M. Links, D. L. Morris, unpublished data). The overall mortality rates ranged from 0% to 8% [38, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). The median and mean hospital stay were 16 days [47] and 22–23 days [38] (T. D. Yan, M. Links, D. L. Morris, unpublished data), respectively.

**discussion**

DMPM represents one-fourth of all mesotheliomas and in the past it attracted little attention [2, 3]. Traditionally, there was a historic agreement among practitioners that peritoneal malignancy was virtually untreatable and therefore considered a preterminal condition. The patients were managed with systemic chemotherapy and palliative surgery. Eventually, however, nearly all patients died from the disease as a result of intestinal obstruction and/or terminal starvation [16–22]. The median survival in these patients before the year 2000 was <1 year (Table 1) [16–22]. Recently, there has been a reexamination of the peritoneal malignancy and its treatments involving CRS and PIC with a curative intent. There have already been several large studies and even a RCT examining the efficacy of this combined procedure for the management of peritoneal carcinomatosis from GI malignancies [26–31].

CRS is an important first step in the combined treatment, which attempts a removal of all peritoneal tumors together with complete lysis of adhesions between the bowel loops [23]. This provides an optimal situation for adjuvant intraperitoneal chemotherapy, which is given before the formation of any adhesions, allowing direct chemotherapy and tumor-cell contact, minimizing systemic toxicity [24, 25]. Hyperthermia has been known to have direct cytotoxic effects in both temperature and time-dependent manner [50, 51]. It also has been shown that a greater depth of penetration of the chemotherapy agents into the tumors is achieved; [52] in addition, heat synergizes the cytotoxic drugs selected for intraperitoneal use at the time of surgery [53].

Certainly, many decisions need to be made regarding the optimal treatment option. Intraoperatively, those drugs are selected, which show high area under the curve (AUC) ratios of intraperitoneal chemotherapy concentration to plasma chemotherapy concentration. Also, chemotherapy agents that have an acute onset of their activity, especially when they are augmented in their cytotoxicity by heat, are selected [24, 25]. Doxorubicin has recently shown to be actively transported into the mesothelioma cancer cell (P. H. Sugarbaker, T. D. Yan, O. A. Stuart, unpublished data). This finding along with the minimal systemic toxicity of this drug makes it an important choice for intraoperative hyperthermic chemotherapy treatments. The extremely high AUC ratio of intraperitoneal chemotherapy concentration to plasma concentration seen with paclitaxel recommends it for EPIC [54]. This cell cycle-specific drug can be safely used during the early postoperative period before intra-abdominal adhesions develop. This allows for a prolonged exposure of the cancer cells to paclitaxel.

At the Washington Cancer Institute, the results of the treatment of 100 DMPM patients demonstrated that the overall median survival was 52 months (range 1–148 months), with 1-, 2-, 3-, 5- and 7-year survival of 78%, 64%, 55%, 46% and 39%, respectively [39]. Fifty-two patients (52%) were alive at the last time of contact [39]. Treatment plans were an evolution of increasingly aggressive protocols on the basis of a series of pharmacologic studies in the first 33 patients. The median survival of the subsequent 67 consecutive patients who were treated uniformly with CRS and IPHC (cisplatin 50 mg/m² and doxorubicin 15 mg/m²) and followed with EPIC (paclitaxel 20 mg/m²) was 79 months (range 1–148 months) [39].

At the National Cancer Institute, Bethesda, the most recent study of CRS plus IPHC included patients treated with cisplatin at 250 mg/m² combined with systemic thiosulfate protection against renal toxicity [42]. At postoperative day 2 to day 10, patients received 5-flourouracil and paclitaxel as an intraabdominal dwell. The median overall survival for the 49 patients was 92 months and the median progression-free survival was 17 months. The 3-year survival was 59% [42]. The National Cancer Institute of Italy enrolled 49 patients to undergo CRS and IPHC with cisplatin (25 mg/m²) and mitomycin C (3.3 mg/m²) or cisplatin (43 mg/l) and doxorubicin (15.25 mg/l) [45]. The overall median survival was not reached at the completion of the study and the progression-free survival was 40 months [45]. A phase II study from Lyon, France, recently reported 15 patients with DMPM who underwent CRS and IPHC with mitomycin C (0.5 mg/kg) and cisplatin (0.7 mg/kg) for 90 min [47]. The overall median survival was 47 months with 1-, 3- and 5-year survival of 72%, 49% and 37%, respectively [47].

Another important study, which was excluded from this review because of additional treatment interventions used, was reported by Taub et al. (R. N. Taub, M. E. Hesdorffer, M. L. Keohan et al., unpublished data) at Columbia University College of Physicians and Surgeons in New York, USA. The investigators carried out a prospective single-institution phase I/II trial on 27 patients with DMPM (R. N. Taub, M. E. Hesdorffer, M. L. Keohan et al., unpublished data). The treatment regimen consisted of an initial exploratory laparotomy with CRS and placement of indwelling intraperitoneal catheters; these were four intraperitoneal courses of doxorubicin (25 mg) alternating with four intraperitoneal courses of cisplatin (100 mg/m²). Four intraperitoneal doses of gamma interferon were followed by a second laparotomy with biopsy verification of complete response (no evidence of disease) or attempted resection of residual disease. IPHC with mitomycin C (10 mg/m²) plus cisplatin (75–100 mg/m²) and finally whole abdominal radiation was added to the plan of management. The overall median survival was 68 months with a 3-year survival of 67% (R. N. Taub, M. E. Hesdorffer, M. L. Keohan et al., unpublished data).

The histopathological classification of DMPM consists of epithelial, sarcomatoid and biphasic types. Yan et al. reported 37 patients (92%) with epithelial type and five patients (8%) with biphasic type. The survival of the biphasic type was relatively poor. Four of the five patients died within the first 6 months.
after the surgery. Other reports also documented the correlation between histopathology and survival outcomes [17, 37, 45].

An important consideration in a comparison of the efficacy of conservative management versus that of CRS plus PIC regards a possible selection bias for treatment by the combined management plan. There is no doubt that the results of treatment, as given in Table 1, which itemizes the results of traditional treatment as compared with those, in Table 4, which itemizes the results of combined treatment are very different. One possible explanation other than treatment effects is a selection bias for the combined approach. The literature does not provide information regarding the exclusion of patients from combined treatment who could not receive ‘optimal cytoreduction’. From our own institution, we can report that all patients except those judged to be in the terminal phases of their disease were evaluated, operated on, cytoreduced and given PIC. Data reported from our institution shows that over half of the patients had a peritoneal cancer index of 29 or above. Also, 17% of our patients showed sarcomatous or biphasic histology [35]. At least at the Washington Hospital Center, we cannot identify a selection bias for treatment using the combined approach. The only clinical feature consistently used to exclude patients from combined treatment was clinical evidence of systemic disease. Only very recently, within the year 2006 have exclusion criteria for patient selection in a combined treatment approach been utilized [37].

The morbidity and mortality of DMPM patients undergoing CRS and PIC seems to be comparable to other major surgical procedures for GI cancer. In general, after CRS and PIC, the morbidity ranges from 20% to 50% and mortality varies between 1% and 10% in most published series [55–60]. In the past, a senior author reported a prospective morbidity and mortality analysis in the first 60 patients who underwent CRS and PIC for peritoneal carcinomatosis [55]. The morbidity and in-hospital mortality rates were 35% and 5%, respectively. In 2003, the morbidity and mortality rates of 68 DMPM patients who underwent this treatment were 24% and 7%, respectively [35]. The recent updates included in the present study from various institutions showed similar morbidity and mortality rates [38, 42, 45, 47, 48] (T. D. Yan, M. Links, D. L. Morris, unpublished data). A morbidity rate of 25%–40% and mortality of 0%–8% may be acceptable in light of current standards for management of GI cancer, but can be reduced with improved patient selection, technical skills intraoperatively and postoperative care. Nevertheless, initiation of these treatments on an elective basis in patients with DMPM is not to be taken lightly. Using a radiologic test to select patients for complete cytoreduction would be of great help to eliminate patients who will have limited benefit from the combined treatment. In a recent study, a correlation was sought between the findings of the preoperative computed tomography and completeness of cytoreduction [61]. Data showed that the size of the tumor mass in the epigastric region and the interpretive radiologic findings of the small bowel/mesentery strongly correlated with the outcome of the surgery, i.e., adequate versus suboptimal cytoreduction [61].

Many unanswered questions remain regarding the surgical options in the management of DMPM. What can be stated with assurance is that this disease, which in the past was considered a preterminal condition, can now be treated with CRS and PIC with benefit in terms of long-term survival. Perhaps it is safe to indicate that this new treatment option, using combined therapy, is a new standard of care with which all other treatment options should now be compared. It is also important, however, to note that the results achieved by international experts in this field may not be replicated in routine clinical practice. In the current literature unfortunately there are limited data, but with increased recognition of this new treatment of DMPM more clinical evidence will be available.

The role of systemic chemotherapy in these patients remains to be settled. There are now Food and Drug Administration-approved treatment protocols using systemic chemotherapy [62]. How these are to be integrated into the combined therapy has yet to be determined. Currently, at the Washington Cancer Institute, patients who have a suboptimal cytoreduction with tumor nodules >0.5 cm remaining are recommended for systemic pemetrexed after their hospitalization has been completed. A well-designed, multi-institutional study would be potentially meaningful.

In conclusions, the clinical experience with DMPM in most centers is relatively small. This systematic review evaluated the current evidence for CRS and PIC for DMPM. Seven observational studies were available for assessment, which demonstrated an improved overall survival, as compared with historical controls, using systemic chemotherapy and palliative surgery.

acknowledgements

The authors thank Ilse Sugarbaker for editing the manuscript. T. D. Yan, a surgical oncology research fellow, is sponsored by the Foundation for Applied Research in Gastrointestinal Oncology and Medstar Research Institute.

references

34. Sugarbaker PH, Acherman YIZ, Gonzalez-Moreno S et al. Diagnosis and
treatment of peritoneal mesothelioma at the Washington Cancer Institute. Surg
35. Yan TD, Popa E, Brua EA et al. Sex difference in diffuse malignant
36. Yan TD, Brua EA, Carlo AG et al. Prognostic indicators for patients undergoing
cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse
cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse
testicular neoplasms—a prospective study of 70 consecutive cases. Ann Surg Oncol
(In press).
38. Yan TD, Yoo D, Sugarbaker PH. Significance of lymph node metastasis in
patients with diffuse malignant peritoneal mesothelioma. Eur J Surg Oncol
DCL: 10.1016/j.ejso.2006.05.009.
39. Ma KY, Barlett DL, Reed E et al. Continuous hyperthermic peritoneal perfusion
40. Park BJ, Alexander HR, Libutti SK et al. Treatment of primary peritoneal
mesothelioma by continuous hyperthermic peritoneal perfusion (CHPP). Ann Surg
41. Feldman LA, Libutti SK, Pengpang JK et al. Analysis of factors associated
with outcome in patients with malignant peritoneal mesothelioma undergoing
surgical debulking and intraperitoneal chemotherapy. J Clin Oncol 2003; 21:
4560–4567.
42. Deraco M, Casali P, Inglese MG. Peritoneal mesothelioma treated by induction
chemotherapy, cytoreductive surgery and intraperitoneal hyperthermic perfusion.
43. Nonaka D, Kusamura S, Baratti D et al. Diffuse malignant mesothelioma of
peritoneum: a clinicopathologic study of 35 patients treated locoregionally at
44. Deraco M, Nonaka D, Baratti D et al. Prognostic analysis of clinicopathologic
factors in 49 patients with diffuse malignant mesothelioma treated with
cytoreductive surgery and intraperitoneal hyperthermic perfusion. Ann Surg
45. Ghein D, Miltheus D, Oinsisky D et al. Surgery combined with peritoneectomy
procedures and intraperitoneal chemohyperthermia in abdominal cancers with
799–806.
46. Brigand C, Monnousse O, Mohamed F et al. Malignant peritoneal mesothelioma
treated by cytoreductive surgery and intraperitoneal chemohyperthermia: results of
47. Loggie BW, Fleming RA, McQuillen RP et al. Prospective trial for the treatment of
48. NHS Centre for Reviews and Dissemination. Undertaking Systematic Reviews of
Research on Effectiveness: CRD’s Guidance for those Carrying Out or
Reviews and Dissemination 2001.
50. Los G, Smals AG, van Vught MJH et al. A rationale for carboplatin treatment and
abdominal hyperthermia in cancers restricted to the peritoneal cavity. Cancer Res
51. van de Vaart PJ, van der Vange N, Zoetmulder FAN et al. Intrapерitoneal cisplatin
in advanced ovarian cancer: pharmacokinetics and cisplatin-DNA adduct formation in
53. Kuh HJ, Jang SH, Wenijs MG et al. Determinants of paclitaxel penetration and
accumulation in human solid tumor. J Pharmacol Exp Ther 1999; 290:
871–880.
in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery
and heated intraoperative intraperitoneal chemotherapy. Cancer 1996; 77:
2622–2629.
treatments with cytoreductive surgery and hyperthermic intraoperative
intraperitoneal chemotherapy using the Coliseum technique. Ann Surg Oncol


