Current Concepts in the Diagnosis and Management of Patients With Malignant Peritoneal Mesothelioma

Elizabeth E. Ginalis¹, Malini Patel¹ ², Claire Yue Li³, H. Richard Alexander ¹ ² ³ *

¹ Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA
² The Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA
³ Weill Cornell New York-Presbyterian Hospital, New York, New York, US

*Corresponding author: H. Richard Alexander, Chief Surgical Officer, Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA; Professor and Chief, Surgical Oncology, Department of Surgery, Rutgers Robert Wood Johnson Medical School, 195 Little Albany St., New Brunswick, NJ 08901. Tel: +17322357701; Fax: +17322358098; E-mail: r Richard.alexander@rutgers.edu

Abstract
Malignant peritoneal mesothelioma (MPM) is a malignancy that arises from the mesothelial lining of the abdominal cavity and largely manifests as a diffuse process. There are two hallmark features of MPM. First, MPM may progress and present itself diversely among patients. While some patients may endure a quick tumor progression that is refractory to seemingly successful initial therapeutic cytoreductive surgery, other patients may survive several years despite the presence of disease. Second, the disease usually progresses in the abdominal cavity with clinically relevant systemic metastases being rare and therefore patients suffer morbidity and mortality from loco-regional disease progression. When MPM disseminates outside the abdomen, it only occurs in the setting of advanced intra-abdominal disease. The majority of patients present with nonspecific signs and symptoms, which often results in a diagnosis of MPM when the condition is already fairly advanced. As the diagnosis is often made late, patients who are treated with only supportive care have a median survival of less than one year. The combination of systemic cisplatin with pemetrexed has an overall response rate of approximately 25%. However, as primary therapy, these agents have not been shown to meaningfully alter the natural history of the disease. Operative cytoreduction and regional chemotherapy administered as hyperthermic intraoperative peritoneal chemotherapy or early postoperative intraperitoneal chemotherapy has been found to improve survival in appropriately selected patients.

INTRODUCTION
Malignant peritoneal mesothelioma (MPM) is a malignancy that arises within the abdominal cavity. MPM is a rare cancer that makes up 15% to 20% of all mesothelioma diagnoses, which translates into approximately 600 to 800 new cases in the United States annually [1, 2]. In contrast to malignant pleural mesothelioma which affects males predominantly, MPM afflicts females slightly more often. The median age at diagnosis is approximately 63 years, although the age at presentation can vary widely [3]. The first described case of MPM was over 110 years ago when Miller and Wynn from Birmingham, England published a case report of a 32-year-old male miller who presented with weight loss and ascites.
At operative exploration, he was found to have a diffuse malignant process with numerous soft, friable tissue nodules of varying sizes. On microscopic analysis, the tumor cells were found to superficially infiltrate organs rather than arise from them. They also noted the lack of hematogenous or lymphatic spread of the cancer. They reasoned that this type of cancer remained localized to the abdomen rather than metastasizing distally, even in advanced stages. Five decades following this case, an additional 13 patients with MPM were reported and pathologically confirmed. These cases were reported in a series that described the pathologic features of MPM. Following this publication, the number of documented MPM cases rose in the medical literature. With increasing documentation of MPM, there was greater reporting of clinical symptoms and risk factors associated with the disease as well. In 1972, Moertel published a review of the MPM, which included 169 cases. In the 1980s, results of clinical trials and management plans targeted for patients with MPM were published. A variety of environmental risk factors are associated with the development of MPM. For years, the association between asbestos exposure and development of mesothelioma has been well defined. Asbestos workers have a lifetime risk of 10% for developing mesothelioma, with a latency period of approximately 20 years for MPM compared to 30-40 years for pleural mesothelioma. However, only 33% of MPM patients have a known history of asbestos exposure. Additional risk factors of MPM include radiation exposure and BRCA1-associated protein 1 (BAP1) gene mutation.

Clinical Presentation, Diagnosis, and Staging

Most patients with MPM initially present from 40 to 65 years of age. There is often a delay in diagnosis because of the nonspecific and gradually progressive nature of the disease and its symptoms, resulting in an average time to diagnosis of five months. Women are more commonly diagnosed with MPM and are often diagnosed at younger ages. MPM should be suspected in patients with clinical and radiographic evidence of a diffuse malignant process in the abdomen. Patients will typically present with vague complaints including diffuse abdominal pain, early satiety, decreased energy, and increasing abdominal girth which is usually due to ascites. Other symptoms include dyspnea, changes in bowel habits, or a palpable abdominal mass on physical examination. In some cases, patients will have the diagnosis made incidentally when undergoing a procedure for another purpose. Under those circumstances a careful review of the pathology and the extent of the abnormal findings is essential as some patients, usually woman, may have well-differentiated papillary peritoneal mesothelioma (WDPPM). This is an indolent or non-progressive condition, and patients can often be observed.

Figure 1: Computed Tomography Scan of the Abdomen in a 30-Year-Old Patient With MPM Showing Diffuse Upper Abdominal Ascites (Top Panel), an Omental Mass (Middle Panel, Arrow), and a Right Ovarian Mass (Bottom Panel, Arrow).
Typical radiographic findings include nodular thickening of the peritoneum, moderate to extensive ascites, bowel wall thickening, and omental caking or thickening. Extensive whole-body imaging is not indicated as the disease infrequently spreads extra-abdominally. If the upper images of a computed tomography (CT) or magnetic resonance study of the abdomen and pelvis do not show a pleural effusion, lower pleural thickening, or lower mediastinal adenopathy, then it is unnecessary to perform additional staging studies. However, a positron emission tomography scan may be useful when the diagnosis is uncertain, or the patient does not have the typical risk factors.

A definitive diagnosis is made pathologically with tissue biopsy. Tissue can be obtained via CT-guided core needle biopsy or laparoscopic biopsy. Fluid cytology is not recommended to diagnose MPM as it is frequently inconclusive and has a low yield [23]. Moreover, cytology cannot provide information regarding tissue invasion through the peritoneum into underlying stroma or fat, which is a histologic feature associated with aggressive tumor biology and decreased survival [24-26].

Tumor immunohistochemistry is essential for accurate diagnosis of MPM. However, there is not one marker that is specific for mesothelioma, and so several markers must be used. A panel of markers is required to distinguish MPM from more common tumors, including adenocarcinoma and peritoneal serous carcinoma. Positive antibody staining for at least two markers including cytokeratin 5/6, calretinin, and Wilms Tumor-1 (WT-1) as well as negative staining for at least two markers including carcinoembryonic antigen, Ber-Ep4, LeuM1, and Bg8 are recommended to confirm the diagnosis of MPM [24, 27]. Negative staining for paired-box gene 8 (PAX8) and loss of BAP1 may assist in differentiating MPM from ovarian carcinoma [13]. However, it is important to keep in mind that PAX8 stains positively in 15 to 20% of MPM samples, making the diagnosis challenging. Additionally, PAX8 staining is highly sensitive and specific for WDPPM [28]. MPM can be subdivided into three histologies: epithelioid, sarcomatoid, and biphasic (or mixed). Distinguishing the histological subtype is essential in prognosticating patients, as those with epithelioid histology carry a more favorable outcome than those with sarcomatoid or biphasic histologies [25].

The extent of tumor in the abdomen is scored using the peritoneal cancer index (PCI). A score of zero (absence of macroscopic tumor burden) to three (widespread tumor burden) is allocated to nine regions of the abdomen as well as four sections of small bowel and mesentery [29]. The total PCI score spans from 0 to 39, with a higher score reflecting greater disease. A tumor-node-metastasis (TNM) staging system has been described but is not broadly applied to patients with MPM [30]. The TNM staging system stratifies PCI scores into...
quartiles (1–10, 11–20, 21–30, >30) as a substitute for T-stages 1 to 4. N is used to delineate the absence or presence of metastasis to intra-abdominal lymph nodes. M describes the absence or presence of disease extending beyond the abdomen. Patients with T1 N0 M0 (stage I disease) have a 5-year survival of 87%. Patients with T2 N0 M0 or T3 N0 M0 (stage II disease) demonstrate similar 5-year survivals of 53%. The five-year survival rate for patients with T4, N1, or M1 disease (stage III disease) is 29%.

One study demonstrated that serum levels of cancer antigen (CA) 125 is prognostic and can be used in the surveillance for recurrence following treatment. However, it is not routinely used in selecting appropriate patients for cytoreductive surgery [31]. Similarly, serum mesothelin-related protein baseline levels have been shown to be elevated in 60% of patients and may be useful as a component of post-treatment surveillance if they are initially elevated [13]. Additionally, the BAP1 gene is frequently mutated in MPM, with one study reporting up to 80% of MPM tissues with loss of BAP1 protein expression [34]. It is also associated with an increased susceptibility for MPM. Studies have shown that BAP1 mutant mice were more likely to develop MPM following low-dose asbestos exposure, thus suggesting that patients with germline BAP1 mutations may be more susceptible to MPM in addition to other cancers [32, 33]. However, the clinical utility of BAP1 mutation analysis in patients or assessment of protein expression in tumors is not yet clearly described [34].

Patient Selection, Risk Stratification, and Biomarkers

In appropriately selected patients, cytoreductive surgery (CRS) and some form of peri-operative regional chemotherapy, usually hyperthermic intraperitoneal chemotherapy (HIPEC), is widely acknowledged as the best initial therapeutic intervention. There are several factors important in patient selection for CRS [16, 35-37]. Age greater than 60 years and male gender are independent adverse prognostic factors [17, 26, 38, 39]. Additionally, patients who present with symptoms of obstruction or weight loss may harbor infiltrative disease that is not amenable to complete cytoreduction. Pathologic features such as high tumor grade, high Ki-67, tumor invasion into stroma, and biphasic and sarcomatoid histology are associated with shortened survival. Radiographic features such as a high PCI (greater than 25), solid tumor infiltrating the mesentery, and extra-abdominal disease indicate a higher likelihood of incomplete cytoreduction and worse outcomes. Markedly elevated CA-125 is associated with worse clinical outcomes after CRS and HIPEC. Thrombocytosis at baseline (before treatment) is associated with an aggressive tumor biology [37]. In patients with baseline thrombocytosis who undergo a complete cytoreduction, rapid recurrence and early death from disease is common. All these factors should be weighed when considering a patient for operative cytoreduction. In general, males over 60 years of age, patients with biphasic and sarcomatoid (versus epithelioid) histology, and those with baseline thrombocytosis should be considered for non-operative management initially. Some patients are offered systemic chemotherapy initially, and, if the disease can be controlled with a three- to four-month course of treatment, then CRS and HIPEC can be considered.

Cytoreductive Surgery With Regional Chemo-therapy

CRS in combination with regional perioperative chemotherapy is currently the preferred therapy for MPM in appropriate cases. CRS involves surgical resection of disease with peritonectomy where there is visible disease (selective peritonectomy) or total parietal peritonectomy (systematic peritonectomy) (Figure 3) [40]. Regional perioperative chemotherapy is administered to address microscopic disease and improve therapeutic results. It is administered as either HIPEC or early post-operative intraperitoneal chemotherapy (EPIC). Cisplatin and mitomycin C are the most commonly used chemotherapeutic agents. Other options include cisplatin plus doxorubicin, cisplatin plus mitomycin, or carboplatin alone. Ideally, the administered agents should have demonstrated synergistic cytotoxicity when combined with hyperthermia. HIPEC is administered via large bore catheters that are placed within the peritoneal cavity using a closed technique connected to an extracorporeal recirculating perfusion circuit. Four to six liters of chemotherapy are warmed to a temperature of 42°C and circulated in the closed
abdominal cavity for 90 minutes. EPIC is usually administered on post-operative day one and continued daily for 5 to 7 days. The chemotherapy solution is placed for 23 hours and then drained for one hour before repeat administration. CRS with HIPEC or EPIC is associated with survivals ranging from 34 to 92 months [16, 38, 41]. A meta-analysis of 20 publications reporting on 1047 MPM cases managed with CRS showed a five-year actuarial overall survival of 42% [18]. 46% to 93% of patients had a complete or near-complete cytoreduction, with a median of 67%.

Table 1: Results of Selected Series of Cytoreductive Surgery and HIPEC for Patients With MPM

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>No.</th>
<th>Median Overall Survival, mo</th>
<th>Favorable Prognostic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yan, 2009</td>
<td>Multicenter interna-</td>
<td>405</td>
<td>53</td>
<td>Epithelioid histology</td>
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<td></td>
<td>tional review</td>
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<td>Negative LNs</td>
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<td>Optimal CCR</td>
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<td></td>
<td>Use of HIPEC</td>
</tr>
<tr>
<td>Alexander, 2013</td>
<td>Multicenter US review</td>
<td>211</td>
<td>38</td>
<td>Histologic grade</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Optimal CCR</td>
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<td></td>
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<td></td>
<td></td>
<td>Age &lt; 60 y</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Use of cisplatin</td>
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<tr>
<td>Baratti, 2013</td>
<td>Single institution</td>
<td>106</td>
<td>63</td>
<td>Low mitotic count (Ki-67)</td>
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<td></td>
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<td></td>
<td></td>
<td>Epithelioid histology</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Optimal CCR</td>
</tr>
<tr>
<td>Helm, 2014</td>
<td>SEER database</td>
<td>1047</td>
<td>N/A</td>
<td>Use of surgery</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Young age</td>
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<td></td>
<td>Optimal CCR</td>
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<td></td>
<td></td>
<td>Absence of operative complications</td>
</tr>
<tr>
<td>Magge, 2014</td>
<td>Single institution</td>
<td>65</td>
<td>46</td>
<td>Use of cisplatin</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Use of EPIC</td>
</tr>
<tr>
<td>Muira, 2014</td>
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<td>38</td>
<td>Lack of thrombocytosis</td>
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<td>Optimal CCR</td>
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<td>33</td>
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<td></td>
<td></td>
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<td>Low mitotic count (Ki-67)</td>
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<td>Gilani, 2018</td>
<td>Single institution</td>
<td>76</td>
<td>98</td>
<td>Optimal CCR</td>
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Abbreviations: CCR, completeness of cytoreduction; EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intra-operative peritoneal chemotherapy; LN, lymph nodes; N/A, not available; SEER, Surveillance, Epidemiology, End Results

Figure 3: Top Panel Shows Multiple Nodular Lesions Infiltrating the Omentum Without Involvement of the Serosa of the Colon
Bottom panel shows diffuse nodularity of the mesentery in a patient with MPM.
The results contrast favorably when compared to patients undergoing non-operative management with chemotherapy or supportive care. For example, in a series of 35 MPM patients in Turkey, the overall survival in patients who received palliative systemic chemotherapy or supportive care was 16 months [15].

Selected primary data from retrospective single-center institutional reviews and large multi-center reviews reporting patient results following CRS with HIPEC are presented in Table 1. In a recent analysis of 1591 patients from 1973 to 2006, they identified factors associated with shortened survival, including male gender, advanced age, high-grade (biphasic) histology, large burden of disease at presentation, and lack of operative resection [17]. Patients undergoing CRS showed a significant increase in overall survival. However, this finding was a likely a result of improved patient selection.

Recently, a retrospective study on 249 patients who underwent CRS and HIPEC with various chemotherapeutic agents was reported. The study found improved overall survival and progression-free survival when two combined chemotherapeutic agents, especially those with platinum-based regimens, were used for HIPEC compared to the use of only one agent [42]. Adjuvant normothermic intraperitoneal chemotherapy long-term (NIPEC-LT) is an additional treatment that can supplement MPM management with CRS, HIPEC, and EPIC. A recent study described a five-year survival of 75% in patients treated with CRS, HIPEC, and NIPEC, compared to 52% in patients managed with CRS, HIPEC, and EPIC and 44% in patients who received CRS and HIPEC. However, there was no statistically significant improvement in survival when EPIC was added to HIPEC. The addition of NIPEC-LT has shown to improve survival in this single institution study [41].

Two large multicenter retrospective studies including patients with MPM from both the United States and Europe reported actuarial median and 5-year overall survivals of 38 months and 41% in the United States study and 53 months and 47% in the European study (Figure 4) [16, 36]. Factors independently associated with improved outcomes were epithelioid histologic subtype, lack of lymph node metastases, optimal CRS, age younger than 60 years, HIPEC with cisplatin (versus mitomycin C), and administration of HIPEC. One study showed that patients who had a suboptimal cytoreduction (defined as a completeness of cytoreduction greater than 1), HIPEC regardless of chemotherapeutic agent did not show significant clinical benefit [16].

In a recent retrospective analysis of data from a dedicated peritoneal malignancy database of 1586 patients with MPM, 76 (4.8%) of patients underwent CRS. HIPEC was administered to 67 of those patients following CRS. Median overall survival and disease-free survival after CRS was 98 and 59 months, respectively. The Ki-67 proliferation index was found to be an independent predictor of decreased survival.

CRS and HIPEC-associated morbidity can be substantial and should be discussed with patients prior to treatment. Adverse events related to CRS commonly include intra-abdominal events such as fistula, bleeding, wound infection, prolonged ileus, bowel obstruction, and sepsis. At experienced centers, the morbidity and mortality risks are acceptable, with an operative mortality rate of 0-8% and serious morbidity rate of 10-45%. One study at a high-volume treatment center reported on complications that occurred in 65 cases following CRS and HIPEC [38]. The mean age was 54 years, median PCI was 12, optimal cytoreduction was achieved in 86% of patients, and median overall survival was 46 months, suggesting this was a representative cohort. The mean operating time was about 440 minutes, the estimated blood loss was 600 mL, and the median length of hospital stay was 12 days. Major postoperative morbidity occurred.
in 35% of patients, and the 60-day mortality rate was 6%. On multivariate analysis, postoperative sepsis was associated with decreased survival. In another study, complications in 380 patients from eight institutions who underwent CRS and regional perioperative chemotherapy were reported. Adverse effects including bowel-related complications (18%), respiratory complications (11%), renal complications (10%), hematologic toxicity (6%), and cardiac complications (3%). The operative mortality was 2%, and the average length of hospital stay was 22 days [36]. Other studies publish operative mortality rates of less than 2% [16, 35]. Overall, appropriate patient selection and clinical expertise in MPM treatment are crucial to optimize outcomes in patients managed with CRS and HIPEC.

Systemic Chemotherapy

In 1983, Antman et al., reported outcomes in 14 MPM patients with measurable disease managed with a regimen that included doxorubicin and found that 43% of patients showed a positive response to therapy [8]. The median survival in the responding patients was 22 months, compared to 5 months in the patients who did not respond. However, the toxicity associated with treatment was significant. Prospective single arm studies investigating pemetrexed-based chemotherapeutic regimens are also reported in the literature. Janne et al., reported outcomes of pemetrexed alone or in combination with cisplatin for 98 patients with surgically unresectable disease [44]. The response rates were not statistically different for patients who had not previously received chemotherapy compared to those who had previously received chemotherapy (25.0% and 23.3%, respectively). The patients who received the combination regimen had a median survival of 13 months and a favorable safety profile. The disease control rate was 71% with the combination therapy [45]. A second study evaluated the outcomes of pemetrexed and gemcitabine in patients with MPM. It showed generally similar results except that toxicity was marked higher than pemetrexed and cisplatin [46]. The median overall survival was 26.8 months, the median time to disease progression was 10.4 months, and the rate of disease control was 67%. However, 25% of patients failed to complete the scheduled therapeutic regimen. Of note, the study reported one treatment-related death. Because of the similar disease control rates in this study compared to patients receiving pemetrexed and cisplatin, this regimen is usually not used as first-line therapy due to the severe toxicities, which limit its clinical utility in the management of MPM. In the elderly, it is also reasonable to substitute carboplatin for cisplatin, which is better tolerated. An International Expanded Access Protocol examining patients with MPM noted similar response rates, time to progression, and one year overall survival in those who received pemetrexed plus cisplatin compared to those who received pemetrexed plus carboplatin [47].

A recent prospective randomized control trial in patients with pleural mesothelioma reported a statistically significant, but clinically minimal, 2.5-month increase in overall survival when bevacizumab was added to pemetrexed and cisplatin compared with the chemotherapy agents alone [48]. The role of bevacizumab in MPM is not yet understood.

The role of immunotherapy or check-point inhibition in MPM is under clinical evaluation. The monoclonal antibody avelumab, which targets the programmed death-ligand 1 (PD-L1), has been tested in a prospective clinical trial on patients with mesothelioma. The cohort had predominantly pleural mesothelioma, and a small proportion had MPM [49]. The overall confirmed response rate was modest at 9%, but more importantly the duration of response was 15 months, with higher responses in patients with tumors expressing PD-L1 (greater than 1%). This pattern of modest but durable responses to checkpoint blockade therapy has been observed across various malignancies. The double-blind, placebo-controlled phase IIb DETERMINE study examined the use of tremilimumab, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody in previously treated malignant mesothelioma. A total of 571 patients were enrolled, with peritoneal mesothelioma histology making up 4% of the cohort (26 patients). There was no statistical difference in overall survival between the treatment arm and the placebo arm. However, due to the small number of peritoneal mesothelioma patients included, it is difficult to make meaningful conclusions on subgroup analysis [50]. A recent report suggests that a higher proportion of MPM have PD-L1
expression compared to pleural mesothelioma and, therefore, the continued evaluation of checkpoint blockade, perhaps in combination regimens in patients with MPM, is indicated [51].

The advantages of neoadjuvant or adjuvant systemic chemotherapy with CRS and HIPEC is not well defined. Two retrospective studies failed to demonstrate any advantage to the addition of systemic chemotherapy before or after CRS and HIPEC [52, 53]. Generally, the decision to use chemotherapy in combination with CRS and HIPEC should be personalized. Instead, systemic chemotherapy may be considered for patients who are not medically optimized for immediate surgical management or whose histopathology is associated with a high risk of early recurrence and progression.

While it is commonplace to extrapolate data from malignant pleural mesothelioma trials, caution should be exercised in applying therapeutic principals broadly. A recent search on clinicaltrials.gov yielded a search of 77 trials for pleural mesothelioma, compared to 14 trials for peritoneal mesothelioma. Challenges undoubtedly exist in designing prospective trials specifically for MPM due to the relative rarity of its occurrence. Therefore, it is essential that this rarer form of mesothelioma is included in larger pleural mesothelioma trials.

CONCLUSION

CRS with regional intraperitoneal chemotherapy such as HIPEC is the preferred first-line therapy in appropriate patients with MPM. Performance status, probability of achieving a complete or near-complete cytoreduction, tumor histology, tumor distribution in the abdominal cavity, and baseline thrombocytosis are important factors that should be considered during patient selection for CRS and HIPEC. In experienced centers, procedure-related morbidity is similar to other oncologic abdominal operations. The use of systemic chemotherapy is considered in patients not suited for surgical therapy or in those at high risk of early disease recurrence. Identifying novel targets including immune checkpoint inhibitors are currently under preclinical and clinical testing [50, 54, 55].

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Not applicable.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS APPROVAL

Not applicable.

REFERENCES


