Principles of Surgical Management of Peritoneal Mesothelioma

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ABSTRACT

Malignant peritoneal mesothelioma (MPeM) is a rare malignancy and represents 5% to 30% of malignant mesothelioma cases. The primary curative therapy for MPeM is radical cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), with the strongest predictor of long-term survival being complete cytoreduction. There is a paucity of high-quality evidence available to guide management in MPeM; however, NCCN Guidelines for the management of MPeM were updated this year. In well-selected patients, 5-year overall survival exceeds 65%, but achieving optimal results requires careful preoperative evaluation and expert surgical management. Preoperative patient selection includes histology review and staging with cross-sectional imaging. Ideal candidates for curative intent surgery are those with epithelioid MPeM, a low peritoneal cancer index, and a good performance status. Contraindications to curative intent surgery include the sarcomatoid MPeM, distant metastases, extensive nodal metastases, and extensive small bowel serosal or mesentery involvement not amenable to complete cytoreduction. Those with biphasic histology, bicavitary disease, and metastatic lymphadenopathy may be considered for surgery following response to neoadjuvant therapy. CRS involves resection of all peritoneal disease, the extent of which varies case by case. Key aspects involve careful evaluation of all peritoneal surfaces, complete parietal peritonectomy and omentectomy, and evaluating suspicious abdominal lymph node basins. Once maximum cytoreduction is achieved, HIPEC is performed using a platinum-based perfusate. Postoperative protocols are recommended to optimize recovery and mitigate HIPEC-specific complications, namely chemotherapy-mediated nephrotoxicity and bone marrow suppression.

Malignant mesothelioma is a rare primary malignancy of the mesothelium arising in the pleura, peritoneum, pericardium, or tunica vaginalis. Peritoneal mesothelioma accounts for approximately 5% to 30% of all cases of malignant mesothelioma.1,2

Radical resection with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) remains the primary curative therapy for malignant peritoneal mesothelioma (MPeM), and the strongest predictor of long-term survival is complete removal of all visible disease, referred to as complete cytoreduction.3–7 In well-selected patients, 5-year overall survival (OS) approaches 68%.8 To achieve these optimal results, appropriate patient selection and expert surgical management is essential.9

Due to the rare nature of MPeM, there is a paucity of high-quality controlled trials pertaining to its management; thus, management is based on data from retrospective studies.10,11 Several national and international bodies have developed consensus statements on MPeM management with the goal of harmonizing therapeutic interventions,10,12 and an updated version of the NCCN Clinical Practice Guidelines on Oncology (NCCN Guidelines) for Mesothelioma: Peritoneal was published in December 2022.11

This article reviews currently available evidence on the surgical management of MPeM, outlining appropriate patient selection, preoperative planning, surgical technique for CRS and HIPEC, and postoperative considerations. Finally, we will touch on future perspectives for the management of peritoneal mesothelioma.

Patient Selection

Although detailed discussion of the preoperative workup for patients with MPeM is beyond the scope of this review, several key aspects of preoperative care for patients with MPeM are worth highlighting.

Diagnosis

Patients with MPeM present indolently with abdominal pain, distention, ascites, and weight loss, with a median time of 4 to 6 months between symptom onset and diagnosis.13,14 Treatment decisions for MPeM are highly dependent on an accurate tissue diagnosis, allowing differentiation between the more benign entities of
multicystic peritoneal mesothelioma (MCPM) and well-differentiated papillary peritoneal tumors (WDPPT) from MPeM.10,15 Furthermore, 3 subtypes of MPeM are recognized: epithelioid, biphasic (mixed), and sarcomatoid.11,16 Although ascites is frequently present in patients with MPeM, cytology has limited sensitivity, ranging from 30% to 75%, and is not recommended for the diagnosis.16–18

The International Mesothelioma Interest Group consensus statement emphasizes the importance of adequate biopsy, with the histologic diagnosis being based on both tissue morphology and immunohistochemistry findings.16 Such biopsies can be obtained at the time of diagnostic laparoscopy or via image-guided biopsy in the setting of a dominant mass.16,19

Epithelioid MPeM is the most common and least aggressive subtype, accounting for approximately 60% of cases, with disease frequently limited to the peritoneal cavity and less prone to lymphatic or hematogenous dissemination. Cytoreductive surgery (CRS) with HIPEC (CRS-HIPEC) is therefore an attractive treatment modality for these patients. In contrast, the sarcomatoid subtype accounts for 20% of cases and has a more aggressive disease course, prone to local invasion and spread beyond the peritoneal cavity. It has a universal poor prognosis with prompt recurrence following CRS-HIPEC and a median survival of <6 months, and is thus considered a contraindication to curative intent surgery.6,11 The biphasic subtype has features of both epithelioid and sarcomatoid mesothelioma, and accounts for approximately 20% of cases. Due to its sarcomatoid features, it behaves in a more aggressive manner than pure epithelioid mesothelioma; however, in carefully selected patients, long-term survival can be obtained with CRS-HIPEC.20

MCPM and WDPPT are relatively indolent forms of disease, but can become symptomatic; they are prone to local recurrence following CRS ± HIPEC, with some experts advocating observation alone.10,21

Staging
Once the diagnosis of MPeM is established, appropriate clinical staging is paramount; however, a universal staging system does not yet exist. The NCCN Guidelines recommend CT of the chest, abdomen, and pelvis at the time of diagnosis.11 Chest imaging helps rule out bicavitary disease involving both peritoneal and pleural surfaces, which is a relative contraindication to up-front surgery.12 It is also important to evaluate for metastatic lymphadenopathy, because it is associated with a poor prognosis and is present in 7% to 13% of patients.22

Dedicated abdominopelvic imaging guides surgical planning and prognostication and can be used to quantify the peritoneal tumor burden in the preoperative setting and determine anatomic resectability. The peritoneal cancer index (PCI) is a useful classification system for both the prognosis and operability of MPeM. It was designed to be used at the time of laparotomy prior to cytoreduction23,24; however, establishing the PCI score prelaparotomy is attractive because it can identify patients with unresectable disease, thereby avoiding a nontherapeutic laparotomy.25,26 Unfortunately, both MRI and CT often underestimate the PCI, although diffusion-weighted MRI may be superior to CT for determining PCI for secondary peritoneal malignancies.27–28 Despite this, CT-PCI score is prognostic in patients with MPeM, with PCI <20 associated with an improved OS,29 with 1-year survival rates of 59% versus 22% in patients with a PCI ≥20.30 Additionally, extent of ascites, which is not accounted for by PCI, can be determined on abdominal imaging. In one Finnish cohort study, the presence of ascites was associated with poorer median survival (7 vs 39 months).30

Thorough review of preoperative imaging enables optimal preparation for CRS and involvement of other subspecialty surgeons as needed for resection and reconstruction of key structures. Cross-sectional imaging allows identification of tumor implants in key areas that portend difficulty in achieving a complete cytoreduction despite a seemingly low PCI score. These features include tumor implants encasing the portal structures, disease in the lesser omentum, loss of the normal small bowel and mesenteric architecture, and encasement of the root of mesentery.31,32 One review from the United Kingdom found that 75% of patients in their cohort who had unfavorable features on CT underwent incomplete cytoreduction; conversely, no unfavorable sites were involved in 79% of patients undergoing complete cytoreduction.33

The Peritoneal Surface Oncology Group proposed a pathologic staging system for MPeM, based on the definitive PCI determined at laparotomy.34 Stage I refers to patients with a PCI ≤10 (T1), stage II includes patients with PCI 11–20 (T2) and 21–30 (T3), and stage III includes patients with PCI 30–39 (T4), any nodal disease (N1), or any distant metastases (M1). Interestingly, those with extensive peritoneal disease with PCI >30 but no distant metastases have similar survival to those with metastatic disease. This staging system nicely stratifies outcomes, with reported 5-year survival rates of 87%, 53%, and 29% for stages I, II, and III, respectively.34

Diagnostic Laparoscopy
For patients being considered for surgery, laparoscopy can further determine candidacy for complete cytoreduction and avoid nontherapeutic laparotomy.10,11

Laterza et al35 evaluated the role of laparoscopy specifically in MPeM, reporting 33 cases of patients who underwent CRS-HIPEC: at laparoscopy, 30 (91%) patients were deemed to have resectable disease, with complete cytoreduction achieved in 29. The 3 patients considered poor candidates for CRS at laparoscopy did not achieve a
complete cytoreduction. They concluded that the sensitivity and specificity of laparoscopy was 100% and 75%, respectively. To optimize the accuracy of laparoscopy, we strongly advocate that a surgeon familiar with peritoneal surface malignancies (PSM) perform the diagnostic laparoscopy to ensure accurate PCI calculation and assessment of all areas, including opening the lesser sac, completely running the small bowel, and inspecting the pelvis. In patients with inguinal hernias, it is important to assess the hernia sac. When thinking about future CRS, we favor placing midline trocars so that port sites can be resected at the time of laparotomy to minimize the risk of port-site recurrences.

### Principles of Cytoreduction

CRS is a standardized surgical procedure involving an ordered sequence of surgical maneuvers to evaluate for and resect all peritoneal disease. The extent of CRS varies depending on the type of PSM and extent of visible disease and involves parietal peritonectomies with the addition of visceral resections when indicated. For MPeM, CRS-HIPEC remains the only potentially curative treatment modality and offers the chance of long-term survival. Indeed, a recent analysis by the US HIPEC Collaborative, including 130 patients with peritoneal mesothelioma (all histologic subtypes included) who underwent CRS-HIPEC, reported a 67.8% 5-year OS and 89.7% conditional OS, which was superior to that of patients with appendiceal or colorectal cancer undergoing CRS-HIPEC.

A midline laparotomy is the preferred approach to CRS, allowing access to all quadrants of the peritoneal cavity. The PCI is calculated prior to beginning cytoreduction to evaluate resectability of disease. Importantly, a thorough assessment of the small bowel is key prior to beginning CRS, because extensive small bowel serosal or mesentery involvement is not amenable to complete cytoreduction, and further surgery is not warranted in such situations.

### Completeness of Cytoreduction Score

The completeness of cytoreduction (CC) score was developed to describe the extent of residual disease after maximal cytoreduction. A complete cytoreduction with no residual disease (CC-0) is the optimal outcome following CRS; however, near complete cytoreduction with a CC-1 score (residual disease ≤2.5 mm) is also acceptable for epithelioid MPeM. A large multi-institutional study suggested a 2% change in 5-year OS rates and no difference in median OS for patients with epithelioid MPeM undergoing CC-1 versus CC-0 resection. Similar oncologic outcomes between patients with CC-0 and CC-1 resections have been reported in other retrospective series as well. The low-volume disease remaining after CC-1 resection can be addressed by HIPEC, which penetrates a few millimeters. Thus, we agree with published consensus statements that the goal of cytoreduction should be to achieve at minimum a CC-1 score for epithelioid MPeM. In contrast, only a complete cytoreduction (CC-0) is of benefit in the setting of biphasic MPeM, and thus these patients must be carefully selected.

### Peritonectomy

Unlike secondary peritoneal malignancies in which a partial parietal peritonectomy (PPP) is recommended, for MPeM a complete parietal peritonectomy (CPP) is necessary to eradicate any microscopic involvement of the parietal peritoneum and to prevent recurrences. Baratti et al compared both peritonectomy approaches for mesothelioma with a case-control study: 30 patients underwent PPP and were matched to 30 patients undergoing a CPP. On multivariate analysis, CPP was an independent predictor of improved prognosis. Moreover, in half of patients undergoing CPP, histologic review identified disease involvement in regions without macroscopic involvement. In practice, we routinely perform CPP and anecdotally have observed the same findings as Barrati et al, that often grossly normal peritoneum can be found to be involved with peritoneal mesothelioma by the pathologist, thus validating this approach of CPP for peritoneal mesothelioma, which is also supported by international consensus guidelines.

### Omentectomy

Greater omentectomy is typically performed during CRS to remove omental tumor implants and is traditionally performed even in the absence of macroscopic omental disease. A recent single-institutional study evaluated the rates of occult histologic omental metastases (OHOM) in a cohort of 683 patients undergoing CRS with (n=580) and without (n=103) greater omentectomy; 12.5% of the omentectomy group had grossly normal appearing omentum. The cohort included 62 patients with mesothelioma, of which 56 (90.3%) underwent omentectomy. Overall, OHOM were identified in 31.9% of patients (2 of which had mesothelioma). Importantly, the omentectomy group had higher rates of CC-0/1 (97.3% vs 92.2%; P=.039). Thus, based on these data and personal experience, we routinely perform greater omentectomy for patients with MPeM undergoing CRS; it can be performed with low morbidity and, when performed correctly, does not add significant operative time or blood loss.

### Lymphadenectomy

Lymph node metastases are relatively uncommon (7%–13%) but are considered a very strong poor prognostic indicator in patients with MPeM. However, systematic lymphadenectomy is not routinely performed across all centers. There is lack of consensus on which
lymph node basins to include. In a study by Baratti et al,42 the iliac and paracolic nodes were the most frequently involved with disease. Lymph node groups that have been suggested for histopathologic assessment include the deep epigastric nodes, external and common iliac nodes, lymph nodes at the origin of the gastroepiploic vessels, and accessible mediastinal lymph nodes immediately superior to the diaphragm.10 The dissection of suspicious retroperitoneal lymph nodes and the sampling of nonsuspicous nodes could be considered during CRS to enhance the prognostic characterization of the patient. However, the level of evidence for this is poor and further studies are needed. In clinical practice, we advocate for preoperative evaluation of radiographic lymphadenopathy and histologic confirmation. Metastatic lymphadenopathy is such a poor prognostic factor, we use it as a relative contraindication to CRS and HIPEC and only selectively operate in this setting.

**Principles of HIPEC**

HIPEC involves the administration of a heated chemotherapy solution directly into the peritoneal cavity. Advantages of this approach include the direct contact of chemotherapy with residual tumor cells after CRS and minimization of systemic toxicity.7,43 Hyperthermia has a direct cytotoxic effect and increases the depth of penetration of chemotherapy.43,44 Combination of HIPEC with CRS for MPeM is a prognostic variable associated with improved patient survival.7

**Choice of Intraperitoneal Chemotherapy**

Platinum-based (carboplatin and cisplatin) agents are the preferred intraperitoneal chemotherapy for MPeM. A systematic review and meta-analysis including outcomes of 1,047 patients with MPeM treated with CRS-HIPEC37 noted that survival in those treated with cisplatin-based HIPEC (alone or in combination) was superior to survival of those treated with mitomycin C (MMC)–based HIPEC (expected 5-year survival, 49% vs 30%). Use of platinum agents is further supported by data from a multi-institution US study showing that cisplatin-based HIPEC resulted in improved outcomes compared with MMC; interestingly, no survival advantage of cisplatin over MMC was apparent with incomplete cytoreduction (CC-2/3).5 Thus, HIPEC should be omitted in the setting of residual disease >2.5 mm after CRS for patients with MPeM. Similarly, a small study from Creighton University Medical Center demonstrated improved survival with carboplatin compared with MMC as the HIPEC agent.45

The current preferred intraperitoneal chemotherapy is cisplatin alone or in combination, with cisplatin/doxorubicin the most commonly used combination therapy.7,10,41 Dosing regimens are beyond the scope of this review, but acceptable regimens have been outlined by the Chicago Consensus.12

**Iterative CRS-HIPEC**

In recurrent MPeM, patients with good general condition, resectable disease, and favorable prognostic profile (eg, young age, epithelioid subtype, time to recurrence >1 year, limited PCI), iterative CRS and HIPEC could be considered, and can provide similar progression-free survival rates compared with the index surgery.46 The rates of achieving CC-0/1 are inferior in the setting of redo surgery; however, acceptable long-term survival has been reported, with one study showing a median OS of 54 months following a second CRS-HIPEC procedure.47

**Postoperative Management**

Although CRS-HIPEC can be performed with a relatively low mortality,4 morbidity remains elevated, with the recent US HIPEC Collaborative study reporting a 57% complication rate and median length of hospital stay of 9 days.8 Moreover, use of high-dose cisplatin-based HIPEC is an independent predictor of postoperative complications.48 Local postoperative complications are specific to the extent of CRS performed, including visceral resections and bowel anastomoses.

Systemic toxicities unique to patients post-HIPEC that are important to recognize and can occur in up to 12% of patients49 include acute renal failure, bone marrow suppression, and pulmonary toxicity. The combination of cisplatin + doxorubicin HIPEC appears to confer the greatest risk of nephrotoxicity, approaching 16%.49 Renal protective strategies are used perioperatively to minimize the nephrotoxic effects of cisplatin; we routinely use perioperative hydration, avoid nephrotoxic agents (both medications and intravenous contrast agents), and use sodium thiosulfate at the time of HIPEC and for the following 12 hours postoperatively.19

Enhanced recovery after surgery (ERAS) protocols have been established for patients receiving CRS-HIPEC with the aim of standardizing and optimizing perioperative care. CRS-HIPEC can result in significant tissue trauma and subsequent systemic inflammatory response. Early reversal of this inflammatory cascade can enhance postoperative recovery and provides the basis for ERAS protocols. In 2020, ERAS Society recommendations were elaborated for CRS-HIPEC and are a useful tool to guide postoperative care. One limitation of these guidelines is the absence of high-level evidence to inform recommendations. Key aspects include the avoidance of routine nasogastric tube placement, early removal of urinary catheters, and optimization of postoperative analgesia. For the latter, we routinely use spinal anesthetics, administered immediately preoperatively; in our experience, these provide excellent pain relief for the first 24 hours postoperatively and have not resulted in a delay in urinary catheter removal or significant hemodynamic alterations. Early postoperative nutrition is important following these major surgeries, and in accordance with the ERAS Society guidelines, we typically begin oral nutrition within 24 hours of surgery.
with the ERAS guidelines, we advocate for omission of nasogastric tubes and initiating early oral intake as tolerated.

**Perioperative Therapy**

Perioperative therapy has been investigated as a method to improve survival and resectability among patients with MPeM. For patients with clearly resectable disease, namely epithelioid subtype; PCI <20; and a good performance status, systemic therapy is rarely indicated, and patients should proceed directly to surgery. Patients with borderline resectable disease with high-risk features may benefit from systemic therapy to improve resectability and test disease biology. High-risk patients include those with Ki-67 >90%, nodal metastasis, high tumor burden (PCI >20), biphasic disease, or bicavitary disease. Those exhibiting a good radiographic response can be considered for CRS-HIPEC.

Currently, only a small number of patients with MPeM have been treated in clinical trials with immunotherapy, and thus no definitive conclusion can be made about their efficacy. Response rates seem to be low and occur mainly in non-epithelioid histology. Perioperative immunotherapy with CRS and HIPEC has led to 5-year disease-free survival in at least one case of sarcomatoid MPeM. Immunotherapy is an exciting future direction for MPeM, and we look forward to the results of an ongoing clinical trial evaluating neoadjuvant chemotherapy with or without immunotherapy (ClinicalTrials.gov identifier: NCT05001880).

**Conclusions**

Due to the rarity of MPeM, there is a paucity of level 1 data to guide treatment decisions. Patient evaluation is directed toward selecting the most appropriate treatment paradigm, with most patients fitting into 1 of 3 categories: (1) those with extraperitoneal disease, clearly unresectable peritoneal disease, or poor performance status who are best treated with systemic chemotherapy or best supportive care; (2) those with borderline resectable localized disease, who may be considered for downstaging neoadjuvant therapy and repeat laparoscopy, prior to proceeding to CRS-HIPEC; and (3) those who are fit and have disease amenable to complete resection. The latter group are those best served by CRS and HIPEC.

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**References**


