Malignant peritoneal mesothelioma: a review

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Abstract: Mesothelioma is a malignancy of serosal membranes. It is most commonly encountered in the visceral pleura with the second most common location in the peritoneum. The diagnosis is very rare and has been linked to toxic exposure to industrial pollutants, especially asbestos. Malignant peritoneal mesothelioma (MPM) commonly presents with diffuse, extensive spread throughout the abdomen with rare metastatic spread beyond the abdominal cavity. Due to its rarity and nonspecific symptoms, it is usually diagnosed late when the disease burden is extensive. Because pleural mesothelioma is more common than MPM, most research has been on the pleural variant and extrapolated for MPM. While treatment advances have been made for MPM, the disease is universally fatal from either abdominal complications secondary to the spread of disease or starvation. Untreated, the life expectancy is less than a year. Cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC) has become the mainstay of therapy with systemic therapies still being developed. We will review the epidemiology of MPM and discuss diagnostic and treatment strategies.

Keywords: Peritoneal; mesothelioma; cytoreductive surgery (CRS); heated intraperitoneal chemotherapy (HIPEC)

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Introduction

Mesothelioma is a very rare malignancy of serosal membranes, including the pleura, peritoneum, pericardium, and the tunica vaginalis testes. The first reported case in the literature, described by Miller and Wynn, was of a 32-year-old male who presented with abdominal pain and ascites, and was found to have a diffuse intraperitoneal neoplastic process that was not amenable to surgical resection. He was treated symptomatically and passed away within a year (1). Due to its rarity, there are few prospective trials, though larger case series and research have advanced our knowledge.

Mesothelioma has been linked to toxic exposure to industrial pollutants, especially asbestos. The most common site is the visceral pleura, followed by the peritoneum. Because pleural mesothelioma is more common than malignant peritoneal mesothelioma (MPM), most research has been on the pleural variant. The assumption has been that mesothelioma in the peritoneum would be biologically similar to the pleura, but some differences have been found. MPM commonly presents with diffuse, extensive spread throughout the abdomen with rare metastatic spread beyond the abdominal cavity.

Epidemiology

Malignant mesothelioma is a rare entity, the vast majority of which arise from the pleura with MPM accounting for 7–30% of cases (2-5). The epidemiologic data on malignant mesothelioma varies widely across countries. The highest rates are reported in some industrialized countries like UK, Australia, and New Zealand, while some of the lowest reported rates are from Japan, Slovenia and other countries in central Europe. The highest incidence rate reported is from the UK at 3.6 and 0.7 cases per 100,000 people for

men and women respectively.

Meanwhile, the United States has an incidence in the middle range of about 1.94 and 0.41 per 100,000 for men and women respectively (5-7). In the U.S., from 2003 to 2008 there were over 3000 cases reported per year with a peak of 3,284 cases in 2005 and a 2.6% decrease per year since. Estimations suggest that there will be approximately 94,000 cases of pleural and 15,000 cases of peritoneal mesothelioma diagnosed between 2005 and 2050 in the U.S. (4). Of the 2,500 cases in men, 85% were diagnosed in the pleura and 7% in the peritoneum. Of the 700 cases in women, 73% were diagnosed in the pleura and 18% in the peritoneum (5). While there is a significant predominance of men diagnosed with pleural mesothelioma, of the 300–400 new cases of MPM a year, the prevalence between men and women is equal in the U.S.

Mesothelioma has been linked to industrial pollutants and mineral exposure. The most common carcinogen identified for pleural mesothelioma has been asbestos, with approximately 80% of cases linked to asbestos exposure (7,8). While asbestos is also the best defined risk factor for MPM, the link is weaker. Only 33–50% of patients diagnosed with MPM report any known prior exposure to asbestos (7,9). Time and duration of exposure do not directly correlate with disease development, with some long-term exposures yielding no disease while some short-term exposures leading to significant tumor burden. Gender as a risk is also inconsistent as approximately 23% of women reported asbestos exposure as a risk factor as compared to 58% of men (10-13). Other risk factors in pleural mesothelioma have included exposure to radiation as well as other minerals, such as erionite, thorium and mica. These other mineral-associated risks have only been reported in case reports so the relative risk for developing MPM has not been quantified (7,14,15).

Presentation

MPM is difficult to diagnose due to its vague, nonspecific symptoms. Patient presentation is quite variable due to the extent of tumor spread within the abdominal cavity. The most common initial complaint is abdominal distension, which is present in 30–80% of patients. Abdominal pain is the second most common symptom with 27–58% of patients presenting with this complaint (16-22). The pain is usually diffuse and nonspecific, though in rare instances the patient may present with an acute abdomen due to malignant bowel obstruction or perforation (23,24). Patients often also complain of early satiety, weight loss, and nausea. Other rare presentations include new onset hernia, fever of unknown origin, night sweats, and the occasional diagnosis found at laparoscopy (7,25).

Due to the nonspecific nature of these symptoms, diagnosis is often delayed. In one series, the average time of diagnosis from the onset of initial symptoms was approximately 4–6 months (16). Due to this delay in patient presentation and diagnosis, it is not surprising that almost all cases of MPM have some spread throughout the abdominal cavity. A patient with increasing abdominal distension with weight loss and loss of lean muscle should raise suspicion for malignant ascites and a possible peritoneal malignancy, so should undergo further workup.

Diagnosis

There is no specific imaging modality that is diagnostic for MPM. However, the widely accepted first-line modality is computed tomography (CT) scan, which is usually one of the first imaging studies obtained when a patient presents with abdominal pain and distension. The use of further imaging is rarely needed for staging unless clinically indicated, as extra-abdominal spread is rare.

On CT, MPM appears as a solid, heterogeneous, soft tissue mass with irregular margins that enhances with the use of intravenous (IV) contrast (26). MPM tends to be more expansive than infiltrative so diffuse distribution throughout the abdominal cavity should raise suspicion. The lack of a primary site with neither lymph node involvement nor distant metastases helps differentiate MPM from other intra-abdominal malignancies (27). Ascites is found in 60–100% of patients that are newly diagnosed (28,29). Other findings include caking, thickening or masses in the omentum, mesenteric nodules, peritoneal thickening, diaphragmatic involvement, scalloping of the intraabdominal organs such as the liver and spleen, and loculated ascites (30,31).

There are some studies which demonstrate that diffusion-weighted and dynamic gadolinium-enhanced MRI can more accurately estimate the disease burden of peritoneal disease, including MPM, but the usefulness for diagnostic purposes is not well defined (32). Similarly, PET and PET/CT are evolving imaging modalities that are being used more frequently in staging of cancers, but their value in evaluating and staging MPM is still unclear (27). Based on cross-sectional imaging, the differential diagnosis for MPM can include peritoneal carcinomatosis, serous peritoneal

carcinoma, ovarian carcinoma, lymphomatosis, and tuberculous peritonitis. Despite advances in imaging, there is ultimately no imaging finding that is specific for MPM.

Serum chemistry and markers have limited utility for diagnostic purposes in MPM. Most of the research on serum markers have been done in pleural mesothelioma, with some patients shown to have elevations in CA-125, alpha fetoprotein, CEA, mesothelin, osteopontin, and fibulin-3. Unfortunately, their sensitivities are too low to be used for diagnostic purposes (28,33-35). Levels of serum mesothelin-related protein (SRMP) have shown more promise, with a sensitivity of 60% (7,36). While not useful for diagnostic purposes in MPM, CA-125 and mesothelin have some promise for a marker of tumor response or surveillance. If initially elevated, serum CA-125 often normalizes to baseline levels after treatment and has been shown to correlate with post-treatment disease progression (33).

Histology/pathology

Because of the nonspecific nature of its symptoms, imaging findings, and serum markers, the definitive diagnosis of MPM is made by pathologic evaluation. Many patients present with ascites and cytologic examination of abdominal paracentesis fluid can sometimes yield a diagnosis. However, due to the low number of malignant cells in ascites and the significant cytologic diversity in tumor cells, cytologic analysis of ascitic fluid is often inconclusive and has a low diagnostic yield (7,21,37,38). Fine-needle aspiration of a tumor implant can yield a diagnosis using immunohistochemistry. However, due to variability in expression of tumor markers, the diagnostic accuracy increases with solid tumor samples (39). These can be obtained via a CT-guided core-needle biopsy or direct sampling during a diagnostic laparoscopy. The advantage of diagnostic laparoscopy is that direct visualization of the peritoneal cavity can help with diagnosis and direct further therapy. Additionally, if the patient has a pleural effusion, thoracentesis or video-assisted thoracic surgery (VATS) is indicated for evaluation of thoracic spread.

According to the World Health Organization (WHO), MPM is divided into three histologic subtypes: epithelioid, sarcomatoid, and biphasic/mixed. This division is relevant for both prognostic and therapeutic purposes. The epithelioid subtype is composed of cells that resemble normal mesothelial cells in a tubulopapillary or trabecular pattern with uncommon mitotic figures. The occasional presence of signet-ring cells and desmoplastic response can make this subtype difficult to distinguish from adenocarcinoma based solely on histologic appearance. The sarcomatoid subtype is composed of tightly packed spindle cells with the occasional presence of malignant osteoid, chondroid or muscular elements. The biphasic subtype is defined as containing both epithelioid and sarcomatoid components, with each contributing at least 10% of the overall histology (40).

The epithelioid subtype is the most common, making up approximately 75% of MPM and also has the best prognosis. Approximately 25% of MPM are biphasic while the sarcomatoid subtype is exceedingly rare. Both of these subtypes have a significantly worse prognosis, similar to the corresponding pleural mesothelioma variants (21,41-44). In one study, the median survival of patients with epithelioid subtypes of MPM was 55 months compared to 13 months for the biphasic subtype (45).

MPM can be difficult to diagnose based solely on histologic patterns, making immunohistochemical markers important in diagnosis. No single immunohistochemical marker is specific for MPM. Instead, panels of markers are used to differentiate MPM from other more common tumors that can have similar histologic features. MPM stains positive for EMA, calretinin, CK 5/6, WT-1, mesothelin, and antimesothelial cell antibody-1, and negative for carcinoma markers CEA, Ber-EP4, LeuM1, and Bg8 thyroid transcription factor-1, and B72.3. These markers help differentiate MPM from primary papillary serous carcinoma of the peritoneum, serous ovarian carcinomas, colorectal adenocarcinoma involving the peritoneum, and borderline serous tumors. The current recommendation is to use two mesothelioma markers and two carcinoma markers (43,46,47).

Staging

Morbidity and mortality in MPM is due to diffuse spread through the abdominal cavity. Isolated cases of localized MPM have been reported but these are extremely rare and found incidentally. While the biology of the disease is aggressive, MPM tends to remain confined to the abdominal cavity due to the limited hematogenous and lymphatic metastatic potential (48). Extra-abdominal disease can sometimes present as pleural effusions, trans-diaphragmatic extension, and extra-abdominal lymph node spread. These are rare presentations and usually occur with long-standing disease (49-53). Despite the extensive peritoneal spread, lymph node involvement is rare. Most suspicious-appearing

nodes are pathologically negative. Among patients that undergo cytoreductive surgery (CRS), 20–28% are found to have lymph node metastases (54,55).

Due to the infrequency of nodal and metastatic spread, MPM does not fit well into a typical TNM staging paradigm. A novel "TNM" staging system was proposed in 2011 by Yan and associates, based on extent of peritoneal disease burden (T), intra-abdominal nodal metastasis (N), and extra-abdominal metastasis (M) (51). The T stage is determined by calculating the peritoneal carcinomatosis index (PCI). PCI scores of 1–10, 11–20, 21–30, and 31–39 correspond to T stages of 1, 2, 3, and 4, respectively. Stage I disease included T1N0M0, stage II included T2–3N0M0, and stage III included T4N0M0 and any N/M positive disease. Corresponding 5-year survivals of 87%, 53%, and 29% were identified for stage I, II, and III disease respectively (51). This novel staging system allows better prognostic stratification.

Treatment options

Surgical therapy

Due to the rarity of MPM, with incidence rates in industrialized countries ranging between 0.5–3 and 0.2–2 cases per million for men and women, there have been no randomized controlled trials on the best treatment strategies (9). Most of the data has been based on retrospective reports of single-institution experiences. One of the first series describing the treatment of MPM was in 1983 by Antman and colleagues (56). Of 18 patients treated with CRS and doxorubicin-based systemic chemotherapy, 14 patients had measurable disease. Six of the 14 responded to treatment with a median survival of 22 months as compared to the 5 months median survival for the eight patients who did not respond to treatment.

Since that time, CRS and intraperitoneal chemotherapy has become the consensus standard first-line therapy for MPM. The peritoneal chemotherapy can either be delivered in the form of heated intraperitoneal chemotherapy (HIPEC) or early postoperative chemotherapy (EPIC), though most institutional reports have used HIPEC. The data for CRS-HIPEC for MPM has been largely based on single institution retrospective studies with two multi-institution studies. The median overall survival ranged from 30 to 92 months (48,54,57-62). This wide range likely reflects surgeon variability, patient selection, and treatment modality, as there is no agreed-upon standardized technique for HIPEC. Studies have shown that there is a learning curve for CRS-HIPEC and the completeness of cytoreduction (CCR) improves with experience.

Analysis of the largest multi-institutional registry of retrospective data for patients with MPM treated with CRS-HIPEC included 405 patients across 29 centers. The median overall survival was 53 months and the 5-year survival was 47% (54). Another multi-institutional study, combining the data for 211 patients from three U.S. centers, of MPM patients treated with CRS-HIPEC reported a median overall survival of 38 months with a 5-year survival of 41% (57). A recent meta-analysis of 20 studies that included 1,047 patients with MPM that underwent CRS-HIPEC showed a 5-year survival of 42% in the 67% of patient that achieved a complete or near complete cytoreduction prior to HIPEC (62).

CRS-HIPEC is not without its complications. It can lead to significant morbidity and mortality, but in experienced institutions, operative mortality was 0–8% and morbidity rates for serious complications was 10–45% (48,49,63). Myelosuppression is one of the common complications seen with HIPEC. Complications related to the laparotomy and CRS include wound infections, prolonged ileus, bowel obstruction, fascial dehiscence, urinary tract infections, sepsis, and fistula formation. Without treatment, median survival has been reported from less than 5 months to up to 12 months from the time of diagnosis (16). Therefore, despite these known issues with CRS-HIPEC, the gains are substantial, with median survival rates of at least 38 months and up to 92 months. CRS-HIPEC after recurrence has also been shown to be effective in a study that reported median overall survival of 54 months for those undergoing a second procedure compared to 77 months for those after initial CRS-HIPEC (64).

Systemic chemotherapy

Though the first-line treatment for MPM is CRS-HIPEC, not all patients are appropriate candidates for surgical intervention. Systemic chemotherapy is the alternative treatment for those that are ineligible or wish to pursue non-surgical management. Perioperative chemotherapy has also been used in patients who have high-risk histology or extensive disease, though the efficacy of perioperative chemotherapy is still being investigated.

Most studies of chemotherapeutic agents have been done for pleural mesothelioma, often excluding MPM. Despite some significant differences in biology between

disease sites, it has been assumed that the effectiveness of chemotherapeutic agents will be similar (65). A meta-analysis of initial trials of pleural mesothelioma showed that cisplatin was the most effective therapeutic agent. However, in 2003, Vogelzang and associates published the results of a phase III randomized trial that showed a median survival of 12.1 months with pemetrexed plus cisplatin, compared to 9.3 months in the cisplatin-only group (66). The pemetrexed group also had a longer time to disease progression (5.7 *vs.* 3.9 months) and a higher rate of objective clinical response (41% *vs.* 17%) when compared to the cisplatin-only group. This trial was the impetus for worldwide acceptance and FDA approval for the use of pemetrexed in the treatment of pleural mesothelioma in 2004. Pemetrexed is an antifolate that inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). Pemetrexed-based regimens are currently the first-line systemic chemotherapy in most institutions, though there is no consensus which complimentary agent, or agents, should be used to supplement pemetrexed.

The efficacy of pemetrexed alone or in combination with cisplatin for MPM was reported in two studies which showed that median survival for pemetrexed alone was 8.7 months compared to 13.1 months for patients who received cisplatin as well. The response rate was 26% and the disease control rate (stable + response) was 71.2% (67,68). These results were similar for chemotherapy-naïve patients compared to those previously treated with another agent. Pemetrexed was well-tolerated with low rates of grade 3 or 4 hematologic toxicity, primarily anemia reported in 2% and neutropenia reported in 1%. Grade 3 or 4 non-hematologic toxicities included dehydration (7%), nausea (5%), and vomiting (5%) (67,68). This trial depended on the investigators to report serious complications, so there is a chance that the rates were under-reported.

Replacing cisplatin with carboplatin has been showed to have similar efficacy, with 24% objective response and 76% disease control rate. Carboplatin tends to be tolerated better than cisplatin so this regimen has been proposed for palliative and older patients (69). The use of gemcitabine with pemetrexed for unresectable MPM was studied as a subset of one of the largest prospective studies treating pleural mesothelioma. This study showed a 15% response rate, 50% disease control rate, 10.4-month time to disease progression, and median survival of 26.8 months (70). Due to the toxicity, only 75% of patients completed the planned course. The toxicity with the inferior disease control rate limits the utility of this regimen as a first-line therapy for MPM. Other drug combinations, including cisplatin with irinotecan, gemcitabine with cisplatin/carboplatin, and vinorelbine alone, have been studied in pleural disease and their efficacy in MPM is as yet unknown (69,71,72). Currently, the data supports pemetrexed with cisplatin/carboplatin as the first-line chemotherapy regimen with other drug combinations reserved for second-line therapy.

The use of systemic chemotherapy in those patients undergoing CRS-HIPEC is controversial. A study in 2009 by Yan and associates showed a trend toward improved survival in those that received pemetrexed chemotherapy along with CRS-HIPEC. However, this difference of 76 *vs.* 53 months was not found to be significant (54). A more recent study by Kepenekian and colleagues in 2016 investigated the use of perioperative systemic chemotherapy in MPM patients who underwent CRS-HIPEC (73). On multivariate analysis, neoadjuvant chemotherapy was independently associated with worse outcomes, with a 5-year overall survival of 40% compared to 67%, 62%, and 56% in those that had adjuvant, perioperative, and no chemotherapy, respectively. This study suggests that neoadjuvant chemotherapy should be avoided if upfront CRS-HIPEC is a viable option. While not statistically significant, there was also a trend towards improved survival in those that received perioperative or adjuvant chemotherapy *vs.* those that only underwent CRS-HIPEC.

Molecular therapy

With only modest gains achieved with systemic chemotherapy, there is growing research on molecular pathways that can be manipulated in the treatment of MPM. Again, most of the research identifying relevant molecular pathways has been in pleural mesothelioma, but targetable pathways in MPM are being identified. No improvement in progression-free or overall survival for pleural mesothelioma was seen with the addition of angiogenesis-inhibitor bevacizumab to gemcitabine and cisplatin (74,75). Epidermal growth factor receptor (EGFR) is overexpressed more in MPM than pleural mesothelioma, so despite poor results for tyrosine kinase inhibitors targeting EGFR in pleural mesothelioma, the effectiveness in MPM with EGFR mutations is still being investigated (76,77). Tremelimumab, a monoclonal antibody that targets the cytotoxic T-lymphocyte antigen 4 (CTLA4), was studied as a second-line therapy for both pleural and peritoneal mesothelioma (78). There appears

to be some promise as a second-line regimen after failure of more traditional chemotherapy with response and disease control rates of 7% and 31% respectively and a median progression-free survival of 6 months. Additionally, preliminary research suggests that there may be a role for targeting phosphatidylinositol-3-kinase and mammalian target of rapamycin (P13K/mTOR) signaling pathways with phase I and II trials underway (79,80).

There is significant ongoing research trying to identify pertinent molecular pathways in MPM, including mesothelin, the EGFR and vascular endothelial growth factor (VEGF) pathways, as well as inhibitors of histone deacetylase and focal adhesion kinase (FAK). Much of this research has focused on pleural mesothelioma, because it is the more prevalent form of this rare disease. However, with the differences in biology of the disease between sites, it is important to continue to look at targets specific to MPM.

Prognosis

Some of the predictive factors for overall survival in patient with MPM have been identified as histologic type (49,54,58,81) and grade (49,57), CCR (49,54,57), PCI (49,81), age (49,57), involvement of lymph nodes (54,58), and the use of cisplatin as one of the agents during HIPEC (57,59). Individual studies have also identified sex, mitotic rate (58), GLUT-1 expression (82), and pre-operative CA-125 (81) as predictors of survival.

One of the most consistent factors in predicting survival in MPM has been the histologic type. It is well-established in pleural mesothelioma that sarcomatoid and biphasic subtypes have significantly worse outcomes than the epithelioid subtype. Similar findings have been reported in multiple series for MPM as well. Yan *et al.* [2009], Baratti *et al.* [2013], and Schaub *et al.* [2013] all demonstrated that the epithelioid subtype is a favorable prognostic factor for survival while those with sarcomatoid and biphasic subtypes have a worse prognosis (54,61,81,83). Schaub *et al.* [2013] and Alexander *et al.* [2013] both further sub-categorized the epithelioid subtype to include those with significant solid component as a marker for worse outcomes (57,81). Magge *et al.* [2014] showed that there may be no benefit gained from CRS-HIPEC in the sarcomatoid and biphasic groups, with a median survival of 10.5 *vs.* 51.5 months for those with a more favorable histology (49).

Dedrick and associates showed in 1978 that the depth of penetration of intraperitoneal chemotherapy is about 3 mm, which led to the acceptance that a complete (CCR 0) or near-complete (CCR 1) cytoreduction is required to make HIPEC effective (84). Therefore, it is not surprising that achieving a complete or near-complete cytoreduction is a favorable prognostic factor compared to incomplete cytoreduction (CCR 2/3) (48,57,61). In a series by Yan *et al.* [2009], the median survival was 94, 67, 40, and 12 months for CCR 0, 1, 2, and 3, respectively, further demonstrating the need for a complete cytoreduction (54). Magge *et al.* [2014] showed similar results with median overall survival of 56.7 months in those that got a complete cytoreduction (CCR 0/1) as compared to 7.4 months in those with an incomplete (CCR 2/3) cytoreduction (49).

Stage was identified as a prognostic factor by Yan *et al.* [2011] when they created a novel staging system for MPM based on PCI, lymph node involvement and extra-abdominal metastatic spread (51). Outcomes from numerous studies have supported this finding, with Schaub and colleagues creating a novel nomogram for predictive survival that was partly based on the PCI ranges that were essentially the same as the staging system proposed by Yan and associates (81). Additionally, Magge *et al.* [2014] found similar finding with a lower pre-CRS PCI predictive of increased overall survival (49). Yan *et al.* [2009] showed that patients with positive lymph nodes had a median survival of 20 *vs.* 56 months for patients without positive nodes (54). This data strengthens the finding by that same group in 2006 which showed survival of 6 months in lymph node-positive patients *vs.* 59 months in lymph node-negative patients (85). This finding was also found in 2013 by Baratti and associates (58).

Age has been identified in multiple studies as a predictive factor in survival. Magge *et al.* [2014] showed that patients older than 65 years had poor median overall survival of 17 months compared to 85.6 months in those ≤65 years of age (49). Other studies have reaffirmed that older age is a negative predictive factor, though the age studied has varied from study to study. Two studies found that age <60 years was a favorable factor and one study showed that age <53.7 years was favorable (48,57,58).

Because of the variability of HIPEC protocols between institutions, there is no consensus on the best chemotherapy agent to be used. Mitomycin-C was one of the first agents used but two studies have shown that cisplatin, either alone or in combination with other agents, has resulted in better overall survival (57,59). Blackham and associates [2010] showed better 1-, 2-, and 3-year survival with the use of cisplatin *vs.* mitomycin, with a median survival of 40.8 *vs.* 10.8 months in the cisplatin

group *vs.* the mitomycin group (59). Another study by Shetty *et al.* [2014] showed 1- and 5-year survivals of 72.3% and 27.3% respectively for the mitomycin group *vs.* 89.7% and 62.5% in the carboplatin group (86). A large meta-analysis confirmed these findings of the superiority of cisplatin over mitomycin in HIPEC (62).

Female sex has been consistently shown to be a predictor of improved survival in univariate analysis (57,87,88). However, on multivariate analysis, only one study showed that sex is a factor in predicting survival (88). Cao *et al.* [2012] showed that overall 1-, 3-, and 5-year survival rates for female patients were 89%, 76%, and 68%, respectively, compared with 77%, 50%, and 39% in male patients. This difference remained significant on multivariate analysis (88). It has been postulated that the disease process is different between the sexes with men presenting with more extensive peritoneal spread and less favorable histological patterns. This trend has been studied in pleural mesothelioma with similar findings of female sex as a favorable predictive factor for overall survival.

The use of EPIC, sometimes in conjunction with HIPEC, has seen varied results in studies. Yan *et al.* [2009] found that the use of EPIC did not change survival and other studies have shown similar results (54). However, a meta-analysis by Helm and colleagues showed that EPIC did improve outcomes (62).

A novel nomogram was developed by Schaub and associates in 2013 which can be used to predict survival in patients with MPM. They found that the three most important factors that predict overall survival are the detailed histologic type (epithelioid w/<10% solid, epithelioid w/>10% solid, biphasic/sarcomatoid), pre-operative PCI score (≤10, 11–19, >19), and pre-operative CA-125 (≤16, 17–71, >71) (81). Epithelioid histology with minimal solid components, preoperative PCI ≤10, and preoperative CA-125 ≤16 predicted the best overall survival rates. Biphasic or sarcomatoid subtypes, preoperative PCI >19, and preoperative CA-125 >71 predicted poor survival.

Discussion of treatment algorithm

The first imaging modality for patients with suspected MPM should be a CT with oral and IV contrast. Tumor markers of mesothelin, SRMP, CA-125, alpha fetoprotein, and CEA should be sent to help with the diagnosis. If there is concern for MPM, samples should be obtained by paracentesis, fine needle biopsy, core needle biopsy, or laparoscopy. Solid tumor samples via core needle biopsy or laparoscopy have better diagnostic yields. Laparoscopy is also useful to help identify the extent of disease burden and peritoneal spread in order to determine if a complete cytoreduction can be achieved (89). Pathologic review should include an immunohistochemical panel which includes at least two mesothelioma markers and two carcinoma markers. Once a diagnosis is confirmed, treatment should be initiated.

The treatment algorithm for MPM is based on the performance status (PS), usually determined by using the Eastern Cooperative Oncology Group (ECOG), histologic type, and a determination of the ability to achieve a complete (or near complete) cytoreduction during surgery. Some specific radiographic criteria have been used as selection factors in determining whether a peritoneal surface malignancy would be amenable to complete cytoreduction, and therefore benefit from CRS-HIPEC. Findings of segmental obstruction of the small bowel or tumor nodules >5 cm diameter on the small bowel surface or directly adjacent to the mesentery of the jejunum or ileum predict a lower likelihood of achieving complete cytoreduction, and therefore a poor outcome from CRS-HIPEC (90,91).

Those with disease that appears amenable to complete cytoreduction, no signs of a metastatic disease, epithelioid subtype, and good PS should undergo CRS-HIPEC. This first-line treatment can lead to excellent improvement in survival that is worth the risks associated with CRS-HIPEC. While cisplatin has been shown to be superior in a number of studies, no randomized controlled trials have shown that mitomycin is inferior. Therefore, while cisplatin may be the superior agent, the use of mitomycin is still acceptable. Furthermore, there is no significant evidence that EPIC is superior to HIPEC at this time. While neoadjuvant chemotherapy may play a role in more advanced disease and borderline-resectable disease, at this time the first choice should be CRS-HIPEC. The role of adjuvant, or perioperative chemotherapy, is still under investigation, but should be considered as there are trends in studies that demonstrate possible survival benefit.

Patients with biphasic and sarcomatoid subtypes do not have the same survival benefit from CRS-HIPEC when compared to those with epithelioid subtype. In these patients, the decision for CRS-HIPEC *vs.* definitive systemic chemotherapy is more debatable. With reported median survivals of less than 12 months for these subtypes, and the significant morbidity and mortality of CRS-HIPEC, a discussion of using systemic chemotherapy should be initiated.

For those that are not eligible for CRS-HIPEC, systemic chemotherapy should be used. The most effective agent for MPM has been pemetrexed, with either cisplatin or carboplatin. Failure to obtain disease control should prompt a switch to another regimen such as cisplatin with irinotecan, gemcitabine with cisplatin/carboplatin, or vinorelbine alone. Another alternative for second-line systemic treatment is the use of a molecular agent, such as tremelimumab. All of these second-line therapies are still under investigation and enrollment in clinical trials could be beneficial.

The nomogram created by Schaub and associates is a good starting point when discussing outcomes with the patient (81).

Conclusions

MPM is a very rare disease of peritoneal surfaces which is diagnosed less frequently than the pleural variant. Advances have been made in treatment, with CRS-HIPEC as first-line therapy in those with favorable factors. While systemic chemotherapy has been shown to be effective, further advancements in systemic therapy are likely to be found in targeting molecular pathways. Investigations into this treatment modality are underway and are promising for providing better survival for this disease which is currently ultimately fatal due to its aggressive extensive peritoneal spread.

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Footnote

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