12 Mesothelioma and Miscellaneous Disease Processes

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Introduction

Peritoneal surface disease (PSD) disseminates from a wide range of tumors, most commonly including colorectal, appendiceal, ovarian, gastric, and neuroendocrine neoplasms. Mesothelioma, however, is an unusual malignancy of the serosal membrane itself, with potential involvement including the pleura, peritoneum, pericardium, and tunica vaginalis testes. First described over a century ago by Miller and Wynn [1], malignant peritoneal mesothelioma (MPM) is a rare cancer, with an estimated incidence of approximately 400 new cases per year in the United States [2]. MPM typically presents with diffuse peritoneal studding and/or ascites with uncommon spread beyond the abdomen. Unlike its more common pleural counterpart, most research on MPM includes single-institution case series or multi-institutional cohort studies, with no randomized controlled trials.

Another rare form of PSD includes carcinomatosis from a urachal origin. Although challenging to differentiate from other intra-abdominal mucinous tumors, evolving pathologic methods used to classify tumor origin and multiinstitution collaborations have helped elucidate the pathophysiologic characteristics and prognosis of urachal PSD. This chapter reviews the diagnosis, treatment options, and prognosis of MPM and urachal sources of PSD.

Epidemiology

Mesothelioma is a relatively uncommon disease, with an incidence in the United States of 1.94 and 0.41 cases per 100,000 for men and women, respectively [3, 4]. The vast majority of mesothelioma arises from the pleura, with only 7–30% of cases arising from the peritoneum [3–6]. There is an equal distribution of MPM among men and women, in contrast to pleural mesothelioma, where there is a significant predominance of men diagnosed with disease [3, 4]. Mesothelioma has been linked to radiation [7], infection with simian virus 40 [8], and mineral exposure, specifically erionite [9], but the most common and well-known carcinogen remains asbestos exposure [10, 11]. However, unlike pleural mesothelioma where asbestos exposure accounts for approximately 80% of cases [10, 12], MPM is less associated with asbestos (if at all), and patients present at a younger age [13–15]. In patients with MPM, only 33–50% report any prior asbestos exposure [10, 11], and time and duration of exposure do not correlate with the development of disease [16]. Due to the rarity of MPM, risk of developing MPM due to exposure to other minerals or

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pollutants has not been well quantified. It is noteworthy that ferruginous (asbestos) bodies have not been found in any pathologic specimens from resections of MPM at our institution.

Presentation and Diagnosis

MPM is typically diagnosed between 40 and 65 years of age [17] and often presents with vague, nonspecific symptoms that can be quite variable depending on the extent and distribution of disease throughout the peritoneum. Patients most commonly complain of increasing abdominal distension and abdominal pain, and in the majority of patients, the increase in abdominal girth is due to ascites [18, 19]. Abdominal pain is generally diffuse and nonspecific, although occasionally a palpable mass or malignant bowel obstruction can be found [19, 20]. Early satiety, weight loss, and nausea are also common complaints. Occasionally, MPM is discovered incidentally during laparoscopy for other indications [21]. Because of the nonspecific presentation of MPM, diagnosis is often significantly delayed. Average time from onset of symptoms to diagnosis is 4–6 months [22]. Not surprisingly, most patients have diffuse disease throughout the abdomen by the time of diagnosis; however, hematogenous and nodal metastases are rare occurrences [23].

Diagnosis of MPM first begins with a thorough history and physical examination, with careful attention to asbestos and chemical exposures. Potential physical examination findings may include a protuberant abdomen with a fluid wave or palpable mass. Serum chemistry and tumor makers have a limited role. CA-125 may be elevated, but this is nonspecific for diagnosis and best used as a marker for disease recurrence or progression [24, 25].

The most common modality used in detecting MPM is contrast-enhanced CT scan. MPM appears as a contrast-enhancing, heterogeneous, solid, soft-tissue mass in the peritoneum or omentum [26, 27]. It often lacks a distinct primary site as well as lymph node involvement or extra-abdominal metastasis, which may help to differentiate it from other malignancies [28]. Peritoneal thickening, omental caking, and scalloping of solid organs indicative of tumor infiltration are often discovered [27], and ascites is present in over 60% of patients (Fig. 12.1) [29, 30]. If the disease infiltrates the small bowel mesentery, the mesentery may have a pleated appearance while the mesenteric vessels have an uncharacteristically straight course [31]. Late findings of MPM include small bowel obstruction and replacement of mesenteric fat by solid tumor (Fig. 12.2) [32].

Recent studies suggest that compared to CT imaging, diffusion-weighted and dynamic contrast-enhanced MRI more accurately assesses the extent of disease or peritoneal cancer index

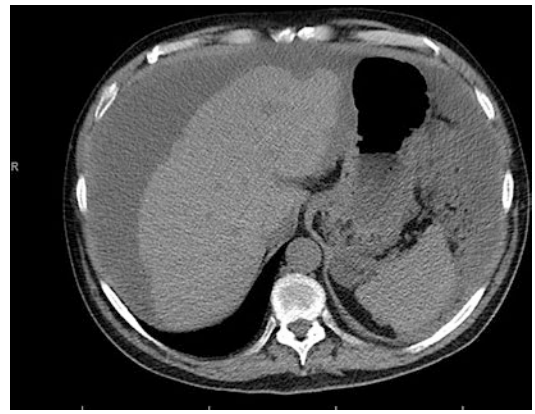

Fig. 12.1 CT scan

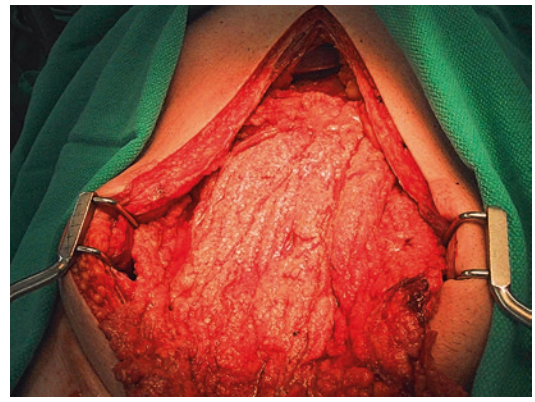

Fig. 12.2 Extensive epithelioid malignant peritoneal mesothelioma involving the omentum

(PCI) in patients with PSD [33]. In patients undergoing CRS, the PCI was correctly predicted by MRI in 88% of patients [33]; however, only one of these patients had MPM. Likewise, CT-PET has an evolving role in cancer staging, but its value in imaging MPM is limited in our experience and remains unclear [28].

To definitively diagnose MPM, pathologic evaluation is required. As the majority of patients present with ascites, it is tempting to send this fluid for cytologic examination. However, due to the low number of malignant cells in ascites, analysis of ascitic fluid has a low diagnostic yield and is often inconclusive [10, 19, 34]. Even if diagnostic paracentesis is suggestive of MPM, a pathologic specimen is still required for immunohistochemical staining to confirm a diagnosis. Fine-needle aspiration of peritoneal implants can confirm a diagnosis, but for improved accuracy, the preferred diagnostic modality is core-needle biopsy or direct tissue sampling by diagnostic laparoscopy [35]. Diagnostic laparoscopy also offers the advantage of direct visualization of the abdominal cavity with improved assessment of tumor burden, as CT scans often underestimate the volume of disease [28]. If undertaken, it is incumbent upon the surgeon to define the extent of disease as well as to obtain tissue sufficient for accurate pathologic analysis.

MPM is divided into three histopathological subtypes: epithelioid, sarcomatoid, and biphasic. Approximately 75% of MPM is epithelioid, 25% is biphasic, and sarcomatoid is rare and associated with very poor outcomes [36]. Histologically, epithelioid MPM cells resemble normal mesothelial cells in a tubulopapillary or trabecular pattern with rare mitotic figures [31, 37]. Because of occasional signet ring cells and desmoplastic response, it can be difficult to distinguish from adenocarcinoma [38]. In contrast, sarcomatoid MPM has tightly packed spindle cells with malignant osteoid, chondroid, or muscular elements. As the name suggests, the biphasic subtype contains both epithelioid and sarcomatoid cellular components, with each contributing to at least 10% of the overall histology [31, 37].

Because cellular histology is often similar to other tumors, immunohistochemical staining plays an important role in the diagnosis of MPM. No single marker is specific for MPM, but panels of antibodies are used to differentiate MPM from other tumors with similar cellular features, such as papillary serous carcinoma of the peritoneum, serous ovarian carcinoma, colorectal adenocarcinoma of the peritoneum, and borderline serous tumors [16]. MPM stains positive for cytokeratin 5/6 (CK 5/6), calretinin, vimentin, epithelial membrane antigen (EMA), Wilms tumor 1 (WT-1), mesothelin, and antimesothelial cell antibody-1 [39–41]. Negative staining for CEA, Ber-EP4, thyroid transcription factor 1 (TTF-1), PAX-2, LeuM1, Bg8, and B72.3 supports the diagnosis of MPM. Current histopathologic recommendations include using two mesothelioma markers and two carcinoma markers for diagnosis [39–41].

Pathologic characteristics of MPM are also prognostic even within the epithelioid group. We have found that histomorphologic features of the epithelioid subtype of MPM convey strong prognostic information [38]. Specifically, using nuclear features and mitotic rate, the epithelioid MPM cases can be divided into low- and high-risk groups with significantly different 5-year survival rates after CRS/HIPEC of 57% versus 21% survival at 5 years. The utility of expert pathologic review of these cases cannot be understated.

Staging

Due to its unusual natural history with diffuse spread throughout the abdomen and rare nodal or extra-abdominal metastatic spread, MPM does not logically fit into typical Tumor-Node-Metastasis (TNM) staging systems. The 8th edition of the AJCC staging manual has a staging system for pleural mesothelioma, but it does not have a staging system for MPM [42]. To address this issue, a novel TNM staging system was proposed by Yan and colleagues [43]. In this system, T was assigned based on the extent of disease burden quantified by intraoperative PCI and divided into four subgroups: T1 (PCI 1–10),

T2 (PCI 11–20), T3 (PCI 21–30), and T4 (PCI 31–39). Node status (N) was assigned based on the presence (N1) or absence (N0) of positive lymph nodes on histopathology of surgical specimens. Any extra-abdominal metastasis discovered on preoperative imaging was assigned M1. Stage I disease included T1N0M0, stage II included T2–3N0M0, and stage III included T4N0M0 and N1 or M1 disease [43]. Using this staging system, 5-year survival for stages I, II, and III disease was 87%, 53%, and 29%, respectively [43].

Treatment

MPM is an aggressive disease, and without treatment, it is uniformly fatal, with an estimated survival of 6–16 months from time of diagnosis [22, 44]. Due to its rarity, there are no randomized controlled trials evaluating the best treatment strategies. Recommendations for therapy are based on single-institutional cohort studies and retrospective data from multiinstitutional registries and include systemic chemotherapy, immunotherapy, and surgical resection.

Systemic Chemotherapy

Most of the data on systemic therapy for MPM is extrapolated from experience with pleural mesothelioma. Early trials of systemic chemotherapy for MPM used a doxorubicin-based regimen and demonstrated a measurable response in only 43% of patients [45]. Of those who responded, median overall survival (OS) was 22 months; median OS for those with stable or progressive disease was 5 months [45]. Since that time, a randomized clinical trial demonstrating longer median OS, longer disease-free progression, and higher rate of clinical response using pemetrexed plus cisplatin in treatment of pleural mesothelioma has prompted further study in MPM [46].

Efficacy of pemetrexed alone or in combination with cisplatin on surgically unresectable MPM was reported by Janne et al. [47] They found a median survival of 13.1 months for patients who received combination pemetrexed and cisplatin, compared to 8.7 months for those who received pemetrexed alone. Additionally, they showed the response rate by RECIST criteria for patients who received the combination was greater than for patients who received pemetrexed alone (30% versus 19%, respectively), and all patients with a complete response received the combined treatment. Pemetrexed was well tolerated, with low rates of grade 3 or 4 toxicities. These results established pemetrexed in combination with cisplatin as first-line systemic chemotherapy for MPM.

Other chemotherapeutic drug combinations have also been investigated. Campbell and colleagues studied carboplatin instead of cisplatin in combination with pemetrexed and demonstrated a similar efficacy, with a 24% objective response rate and 76% disease control rate [48]. As carboplatin is often better tolerated than cisplatin, they proposed the use of carboplatin in older patients and for palliation. Gemcitabine in combination with pemetrexed was investigated as part of a larger study for pleural mesothelioma, but results were dismal [49]. Due to toxicity, only 75% of patients completed the planned treatment, and response rate and disease control rate were inferior to that of platinum-based regimens. As a result, pemetrexed in combination with a platinum agent remains first-line systemic treatment.

A trial reported at the European Society of Medical Oncology meeting from the Francophone trials group evaluated the utility of adding bevacizumab to pemetrexed and platinum for pleural mesothelioma [50]. That study found that adding bevacizumab increased the median OS from 2.7 months to nearly 19 months. As a result, this three-drug regimen has become the current standard for MPM at our, and many other, centers.

Immunotherapy

Similar to other malignancies, immunotherapeutic approaches are being considered in MPM. Tremelimumab, an anti-CTLA-4 agent, was studied as a second-line agent in patients with MPM who progressed on a platinum-

based regimen [51]. A modest benefit was shown, with a median OS of 10.7 months and median progression-free survival of 6.2 months. Investigations targeting epidermal growth factor receptor (EGFR) and phosphatidylinositol-3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathways are underway [52–55].

Surgical Resection

Operative therapy provides the mainstay for treatment of MPM. A study of patients treated in the USA and recorded in the National Cancer Database (NCDB) found that only 50% of MPM patients underwent CRS, and CRS/HIPEC offered the best survival [56]. Other studies have shown prolonged survival in well-selected patients, with studies demonstrating a median survival of 34–92 months and 5-year survivals of 29–59% [17, 19, 21, 56–64]. There is a wide range of surgeon variability and CRS/HIPEC technique, although the overall goal of resecting all intra-abdominal disease is the same. Our techniques have been published in detail elsewhere, but are briefly outlined below [65].

At our institution, prior to CRS/HIPEC, we first confirm a histologic diagnosis of MPM with a pathologic second opinion. Patients with the sarcomatoid variant are not candidates for the procedure; however, the biphasic and epithelioid cases are [36]. Exclusion criteria for resection include comorbid conditions that significantly decrease functional status, extra-abdominal metastasis, poor performance status (ECOG >2), or a tumor burden so extensive on preoperative imaging or diagnostic laparoscopy as to preclude an R2a resection or better [58, 65]. Although laparoscopic resection is possible with a PCI less than 10 in some cases, this is not commonly encountered with MPM. Anesthesia is secured with arterial line monitoring, and nasogastric and urinary catheters are routinely placed. If the patient has significant pelvic disease volume or a complex history of prior surgery, we arrange for temporary external ureteral stents to be placed at the outset of the case to facilitate retroperitoneal dissection. A wide prep including the lower chest is performed, and antibiotics and venous thrombosis prophylaxis are routine. We start with a midline laparotomy incision to thoroughly explore the abdomen and proceed to quantify the PCI. We perform a routine supracolic omentectomy and resection of all gross disease. Peritoneal stripping and resection of intra-abdominal organs are performed only as indicated by the presence of visible disease. Small tumor implants on the small bowel or mesentery are treated with electrofulguration or ultrasonic surgical aspiration if they are too numerous or diffuse to be removed with small bowel resection.

Following CRS, we use a closed abdomen HIPEC technique and perfuse with cisplatin according to the National Cancer Institute (NCI) described protocol with sodium thiosulfate given intravenously [59]. Due to a paucity of trials and comparison studies, there is no standardized HIPEC technique, and a variety of chemoperfusion regimens are currently used. Brigand et al. in France report using cisplatin and mitomycin as a combined chemoperfusion, with overall 1-, 3-, and 5-year survivals of 69, 43, and 29%, respectively [60]. At the National Cancer Institute in Milan, Deraco et al. reported a combined chemoperfusion regimen of cisplatin plus mitomycin, or cisplatin plus doxorubicin with a 5-year survival of 57% [61]. Other large cancer centers report HIPEC combined with early postoperative intraperitoneal chemotherapy (EPIC). At the NCI, Feldman et al. report cisplatin-based HIPEC with 5-fluorouracil and paclitaxel EPIC between postoperative days 7 and 10 [59], and the Washington Cancer Institute reports combined cisplatin and doxorubicin HIPEC, with the same regimen plus paclitaxel for EPIC on postoperative days 1–5 [2].

The large variability in treatment regimens for MPM is due to the paucity of comparative studies examining outcomes of the various chemoperfusion regimens [58, 61]. In their series, Deraco et al. found no statistically significant difference between cisplatin plus mitomycin versus cisplatin plus doxorubicin on OS or progression-free survival (PFS) [61]. In a study conducted at our institution, Blackham et al. compared DFS, PFS,

event-free survival (EFS), and OS in patients who underwent HIPEC with mitomycin versus cisplatin [58]. Prior to 2004, we perfused with 30–40 mg/m^2 of mitomycin; however, based on data from the NCI, we began using cisplatin in 2004. When comparing survival with cisplatin or mitomycin perfusion, we demonstrated a statistically significant OS benefit at 1, 2, and 3 years in patients perfused with cisplatin (80% vs. 47%, 80% vs. 47%, and 80% vs. 42%, respectively) [58]. Median OS survival for cisplatin and mitomycin was 40.8 months and 10.8 months respectively, although this difference did not reach statistical significance. DFS, PFS, and EFS showed a trend of better outcomes for those perfused with cisplatin, but likely due to the small number of patients in the study and shorter follow-up period of the cisplatin cohort, these differences were not significant.

Precision Medicine

Using tumor DNA to identify actionable genetic mutations for use in adjuvant treatment is an emerging strategy in precision oncology. At our institution, work is underway to develop microengineered 3D tumor organoids from fresh-tissue specimens to provide patient-specific models with which treatment optimization can be performed in vitro prior to initiation of adjuvant therapy. Specifically, Mazzocchi and colleagues have demonstrated the viability of this organoid platform in tumor specimens resected from two patients with MPM [66]. They showed the results of in vitro chemotherapy on the organoids mimicked the response to chemotherapy observed in the patients themselves. Moreover, they identified a specific genetic mutation in one patient which conferred susceptibility to a nonstandard treatment, and further confirmed its effectiveness in tumor regression [66]. Although a limited study, the results are promising for a personalized treatment strategy in MPM, and potentially other diseases.

Prognosis

Due to the rarity of the disease, the best data on MPM following CRS/HIPEC stem from large single-institution studies, multiinstitutional registries, and national databases, which are summarized in Table 12.1. The largest multiinstitutional registry of patients with MPM treated with CRS/HIPEC included 8 international institutions during a 10-year period and accrued 405 patients [23]. The median OS was 53 months, and 1-, 3-, and 5-year survival rates were 81%, 60%, and 47%, respectively. Epithelioid subtype, absence of lymph node metastasis, CC0/CC1 resection, and HIPEC itself were independently associated with improved survival. The overall complication rate was 46%, of which 31% were grade 3 or 4 complications, and perioperative mortality was 2%. Another multiinstitutional study with patients from three US institutions included 211 patients and demonstrated a median OS of 38.4 months with a 5-year survival rate of 41% [62]. Independent predictors of survival included age, sex, histology, resection status, and chemoperfusate. A similar perioperative mortality rate (2.3%) and complication profile were found.

More recently, a meta-analysis that included 20 studies and 1047 patients found a median OS ranging from 19 to 92 months, median PFS of 11–28 months, and median DFS from 7.2 to 40 months [63]. OS at 1 and 5 years was 84% and 42%, respectively. There was a wide range of morbidity (8.3–90%) and mortality (0–20%), however, likely related to the steep learning curve in some reporting institutions. A recent study of national trends using the NCDB identified 1514 patients with MPM, 216 (14%) of which underwent CRS/HIPEC [56]. Their median OS was 61 months, compared to those who underwent CRS with systemic chemotherapy (52 months), CRS alone (21 months), systemic chemotherapy alone (17 months), and observation (6 months). Independent predictors of survival included age, gender, insurance status, histology, and CRS/HIPEC. Due to limitations of the database, resection status and stage were not included in

Table 12.1 Reported survival outcomes of patients with peritoneal mesothelioma

Author (year of publication)	Study type	*N*	Subtype	PCI	CC score	Perfusion technique	Agent	Median OS, months	5-Year OS
Brigand et al. [60] (2006)	Single institution	15	Epithelial/ biphasic		0–3	HIPEC	Cisplatin, mitomycin	35.6	28.9%
Deraco et al. [61] (2006)	Single institution	49	Epithelial/ biphasic	22 (mean)	0–3	HIPEC	Cisplatin and mitomycin/ doxorubicin		57%
Feldman et al. [59] (2003)	Single institution	49	Multiple			HIPEC and EPIC (POD 7 and 10)	Cisplatin (HIPEC); 5-FU and paclitaxel (EPIC)	92	59%
Yan et al. [2] (2007)	Single institution	100	Epithelial/ biphasic		0–3	HIPEC and EPIC (POD 1–5)	Cisplatin and doxorubicin (HIPEC); cisplatin, doxorubicin, paclitaxel (EPIC)	79	50%
Blackham et al. [58] (2010)	Single institution	34	Epithelial/ biphasic		R0-R2a (22), R2b-c (12)	HIPEC	Mitomycin (30–40 mg)	10.8	
							Cisplatin (250 mg/m^2)	40.8	
Yan et al. [23] (2009)	Multiinstitutional data registry	405	Epithelioid/ biphasic/ sarcomatoid	20 (mean)		Variable	Variable	53	47%
Helm et al. [63] (2012)	Review	1047	Multiple	19 (median)	0–3	Variable	Variable	19–92	42%
Verma et al. [56] (2018)	Retrospective database	216	Multiple					61	52%
Magge et al. [66] (2014)	Single institution	65	Epithelial/ biphasic	12 (mean)	CC 0/1 in 86%	HIPEC	Mitomycin (93.8%) or cisplatin (6.2%)	46.2	39%
Votanopoulos et al. [36] (2018)	Multiinstitutional data registry	34	Biphasic	18 (median)	0			6.8 years	50.2%
					1			2.8 years	41.6%
Alexander et al. [62] (2013)	Multiinstitutional data registry	211			CC 0/1 in 52.6%	Variable	Variable	38.4	41%

the analysis. However, it seems clear that CRS combined with chemotherapy either via HIPEC or systemically is associated with the best outcomes [56].

Histologic subtype of MPM has remained one of the most consistent factors in predicting survival. Multiple studies have demonstrated that the epithelioid subtype confers a more favorable OS (51.5 months) [67] compared to sarcomatoid and biphasic subtypes (10.5 months) [23, 67–69]. The sarcomatoid subtype carries such a dismal prognosis that most centers, including ours, consider it a contraindication to CRS/HIPEC, as there is no proven survival benefit [67]. Recent work by Votanopoulos et al., however, has demonstrated that for the biphasic subtype, long-term survival can be achieved in patients with a complete cytoreduction (CC-0) and HIPEC [36]. The previously nihilistic view of the biphasic subtype likely stemmed from its rarity and traditional practice to group it with the sarcomatoid subtype. Median OS for biphasic subtypes with a CC-0 resection was 6.8 years, but dropped off steeply with an incomplete resection (2.8 years for CC-1 resection). This study demonstrated that the biphasic subtype should not be considered an absolute contraindication to CRS/HIPEC as long-term survival can be attained with a complete cytoreduction.

The completeness of cytoreduction or resection status has also been well established as an independent predictor of survival in patients with MPM who undergo CRS/HIPC. In the largest analysis by Yan et al., the CC score had a statistically significant impact on survival, with a median OS of 94, 67, 40, and 12 months for CC 0, 1, 2, and 3, respectively [23]. Alexander and colleagues had similar findings, showing that patients with a CC of 2 or 3 had nearly twice the risk of death compared to those with a CC of 0 or 1 (HR 1.81, $p = 0.02$) [62]. In biphasic cohorts, survival depends so greatly on resection status that even a CC 1 resection has a shorter survival by 4 years [36]. Thus, at many institutions, if a complete or near complete cytoreduction cannot be obtained, CRS/HIPEC is considered contraindicated. However, there is potential value in controlling malignant ascites with HIPEC even if complete CRS is not achievable [70, 71].

Both age and gender have been shown to affect survival in patients with MPM. Although the age division varies between studies, multiple institutions report improved outcomes in patients less than 65, 60, 54, and 50 and decreasing survival with advanced age [23, 56, 59, 62, 67, 72]. Magge et al. demonstrated a median OS of 17 months in patients over 65 years of age, compared to 85.6 months in patients less than 65 [67]. Male sex is also an indicator of poor survival in some studies [23, 62]. A median OS of 119 months has been shown in women, as compared to a 36-month median OS in men [23]. The improved survival outcomes in women are found in pleural mesothelioma as well, causing speculation that men generally present with more disease spread and less favorable histology [16].

Staging systems, by definition, should include factors prognostic for survival. With the creation of a novel TNM staging system for MPM, Yan and colleagues identified seven prognostic factors previously shown to impact survival: age, gender, histologic subtype, CC score, PCI, and lymph node metastasis [43]. As age, gender, and histologic subtype were intrinsic and not affected by disease progression, and CC score could only be determined postoperatively; only PCI, nodal status, and extra-abdominal metastasis were included in the staging system. Previous studies demonstrated a median OS of 119 months for patients with a PCI less than or equal to 20, but an only 39-month survival if the PCI was greater than 20 [23]. Likewise, Magge et al. demonstrated that preoperative PCI was predictive of OS [67]. Although a rare finding, patients with nodal metastasis had an OS of 20 months, as compared to 56 months in patients without nodal metastasis. The poor prognosis of involved lymph nodes was also confirmed by Baratti and colleagues, who found that pathologically negative nodes were independently correlated with increased OS [73]. The presence of extra-abdominal metastases as a poor prognostic indicator is not surprising, as this is true of all intra-abdominal malignancy. In their study, Yan et al. included 12 patients with disease that penetrated the tendinous portion of the diaphragm. Despite resection of extra-abdominal disease in all cases, the median OS of 20 months

was poor and significantly less than patients with no metastatic disease [23].

In order to provide an assessment tool for clinicians, Schaub and colleagues developed a nomogram for MPM that predicts survival [69]. Their nomogram uses histologic subtype, estimated preoperative PCI, and serum CA-125 levels to determine estimates of 3- and 5-year survival. In this model, patients with epithelioid subtype, preoperative PCI less than or equal to 10, and serum CA-125 of less than or equal to 16 have the best 3- and 5-year OS, approaching nearly 100%, while patients with sarcomatoid or biphasic subtype, PCI of greater than 19, or CA-125 of greater than 71 have a poor estimated 3- and 5-year OS. Intermediate survival is estimated for patients with combinations of subtype, PCI, and CA-125 in between these extremes. The authors intended for clinicians to use the nomogram in the office as a quick reference, so they may better evaluate patients with MPM who are potential candidates for CRS/HIPEC.

Miscellaneous Diseases

The urachus is tubular structure that extends medially to connect the bladder to the allantois during embryonic development. The lumen gradually degenerates throughout fetal development and ultimately becomes the median umbilical ligament in adults. If the lumen of the urachus fails to close completely, this may lead to various disease processes, including malignant transformation [74]. Urachal carcinoma is an overall rare disease, as is pseudomyxoma peritonei (PMP), a clinical condition involving extensive spread of intraperitoneal mucin. Not surprisingly, urachal-derived PMP is, thus, exceedingly rare, with only 20 case reports in the English literature [75–77]. Not all peritoneal metastases from urachal carcinoma result in PMP [78, 79].

Diagnosing urachal carcinoma-derived peritoneal metastases can be challenging not only due to the rarity of the disease but also due to the difficulties in differentiating it from other more common primaries. Clinical presentation and histologic grade are variable, but most authors agree that urachal-derived PMP more closely resembles the pathophysiology of PMP of appendiceal origin, rather than that typical for urachal carcinoma [75]. In contrast to urachal adenocarcinoma, urachal-derived PMP rarely causes nodal metastasis or hematogenous-derived distant metastases, and local recurrence is more likely [75]. Currently, three criteria are used for diagnosis: midline mass on preoperative CT scan, mucosuria from the persistent connection between the urachal remnant and bladder, and elevated serum CA 19–9 [77].

Because of its similarities to PMP of appendiceal origin, CRS/HIPEC has emerged as the optimal treatment strategy for urachal-derived PMP. In the largest published series of urachal-derived PMP, a prospectively maintained, multicenter international registry identified 36 patients who underwent CRS/HIPEC over a 23-year period at 14 specialized centers [77]. There was a male predominance (66.7%) with a median age of 43 years. Half received preoperative chemotherapy, and the median PCI was 8.5 (range 1–33). An open HIPEC technique was used in 63.9% of patients, with various chemoperfusion agents and combinations. A macroscopic complete resection (CC-0/CC-1), including resection of the urachus and typically partial cystectomy, was achieved in 86.1% of patients, and 11.5% had lymph node involvement. There was a 37.9% rate of major complications, but no perioperative deaths.

Liu et al. had similar findings in their series of nine patients treated at one specialty hospital in Japan [76]. The median age of their cohort was 48 years, but they found a female predominance (55.6%). The median PCI was 10 (range 2–33), and all patients underwent HIPEC with an open technique with mitomycin and cisplatin chemoperfusion. All patients had a complete cytoreduction, and there was no lymph node involvement in any patients. No grade 3 or 4 complications were reported, but one patient had a urinary leak and another had a pancreatic fistula postoperatively, both of which resolved with nonoperative management.

Mercier and colleagues reported a median OS of 58.5 months, with a median DFS survival of 60.5 months [77]. Liu et al. found a median DFS of 27.5 months [76]. Mercier and colleagues found

that resection status was the only significant predictor of survival, with a 53.9% 5-year survival for patients with a CC-0/CC-1 resection, and no 3- or 5-year survivors with a CC-2 or CC-3 resection [77]. Although patients with a PCI greater than 14 trended toward worse OS compared to those with a PCI less than or equal to 14, this difference was not significant. Higher PCI did significantly affect DFS, however, with those with a higher PCI being 15 times more likely to recur. Lymph node involvement was also not associated with poor OS, but it was a significant factor in DFS.

Conclusions

MPM and urachal carcinoma with peritoneal metastases or PMP are both rare diseases typically localized only to the abdominal cavity with low potential for lymphatic or extra-abdominal metastases. CRS/HIPEC has provided the mainstay of treatment for both diseases, demonstrating long-term survival especially in patients with favorable subtypes, low PCIs, and complete cytoreductions. Treatment strategies will continue to be refined as more data emerge regarding intraperitoneal perfusion options and adjuvant systemic therapies. As targeted molecular therapies continue to evolve, a multimodal strategy is likely to involve both a surgical and systemic approach.

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