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Peritoneal Mesothelioma

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Opinion statement

Malignant peritoneal mesothelioma (MPM) is an aggressive neoplasm that rapidly spreads within the confines of the abdominal cavity to involve most accessible peritoneal and omental surfaces. Current treatment options are unsatisfactory, and new approaches are needed. Recent publications have reported improved survival with an intensive loco-regional treatment strategy including cytoreductive surgery (CRS) along with hyperthermic intraperitoneal chemotherapy (HIPEC). We have noted at our institution prolonged survival in selected patients after intensive multimodality treatment. Our most recently reported trial included initial laparatomy with omentectomy, resection of peritoneal implants, and placement of bilateral peritoneal Portacath; repeated courses of intraperitoneal chemotherapy with doxorubicin, cisplatin, and interferon gamma; second-look laparotomy; and intraoperative hyperthermic perfusion with mitomycin and cisplatin, followed by whole abdominal radiation. To date there have been no universally accepted treatments for MPM. Unless referred to a specialty center, patients are routinely treated with pemetrexed and cisplatin which has been shown to increase survival in pleural mesothelioma.

Introduction

Approximately 250 cases of malignant peritoneal mesothelioma (MPM) are diagnosed per year, which represents 10–20% of all mesothelioma diagnosed in the United States. The median age of diagnosis is 65–69 years. Males account for approximately 54.7%, while females account for 45.3%, affecting females according to the surveillance, epidemiology, and end results (SEER) database. In females, the ratio of pleural to peritoneal tumors is about 2:1 [1]. There is a clear relationship between mesothelioma and asbestos exposure. In particular, heavy exposure to airborne asbestos fibers has been associated with peritoneal mesothelioma [2–4]. Other risk factors thought to contribute to the development of mesothelioma include infection with the simian tumor virus (SV 40) through contaminated polio vaccine administered between the years 1955 and 1963 [5], prior radiation exposure [6], and chronic peritonitis [7].

The usual presenting symptoms include pain, ascites, weight loss, increasing abdominal girth, and/or an abdominal mass. Poor prognostic factors include leukocytosis, thrombocytosis, and persistent fevers [8–11]. Biopsy of the affected tissue is necessary to confirm the diagnosis of malignant mesothelioma. Tumors may show epithelial, sarcomatous, or biphasic histology. It is not uncommon to find the three subtypes within a single tumor with sarcomatoid observed in 25% of the cases, though pure sarcoma-

toid is rarely observed. The most predominant subtype epithelial displays growth patterns described as tubular, papillary (most common) diffuse, and deciduoid [12]. Researchers from Wake Forest University have recently reported no differences were observed in the staining of markers in pathologic samples of pleural and peritoneal malignant mesothelioma with the exception of epidermal growth factor receptor. Ninety-two percent of peritoneal tumors demonstrated 3+ or 4+ immunoreactivity as against 33% in pleural mesothelioma ($P = 0.0004$). The battery of immunohistochemical markers examined in 24 peritoneal and 9 pleural mesotheliomas were: cytokeratin, AE 1/2, Calretinin, c-kit/CD117, desmin, epidermal growth factor receptor, estrogen receptors, progesterone receptors, MIB-1, and cleaved caspase-3 [13].

Epithelial mesothelioma does not usually invade solid organs but in most cases is found to infiltrate the omentum. The disease usually remains confined to the abdomen and multiple sites are reported throughout the peritoneum. At the time of surgery, small numerous or confluent nodules (1–5 mm) may be found upon the peritoneal surfaces, as well as malignant ascites. The sarcomatoid subtype tends to be more infiltrative and grows more rapidly. In advanced stages, involvement of the pleural cavity and distant metastatic disease may be seen [14]. Though there is no accepted staging system for MPM, the Peritoneal Cancer Index (PCI) is often used at the time of surgery to describe extent of disease as well as predict the likelihood of a complete surgical debulking [15, 16]. Computed tomography (CT) scans can identify large tumors at crucial anatomic sites and are useful in determining suitability for cytoreductive surgery (CRS) but are less useful in quantifying mesenteric thickening, ascites, and peritoneal studding. Positron emission tomography (PET) can be useful in identifying metastatic spread prior to planned surgical procedure and is still being investigated [16–18].

The median survival of untreated patients in most series is 9–18 months, although more recently, subgroups with different 2-year survivals have been identified according to specific parameters, completeness of cytoreduction, and mitotic count, whereas those for progression-free survival were performance status and mitotic count [19].

Soluble mesothelin-related peptide (SMRP) is a potential marker identified in both serum and effusions of patients with pleural mesothelioma. Its role in early diagnosis for high risk patients is under investigation, and correlation with MPM is yet to be defined [20]. The small number of patients with MPM makes it difficult to conduct clinical trials of sufficient power to analyze response rates or to assess the true benefit of treatment. Complete surgical resection is usually not feasible and has not been shown to prolong survival. Radiation therapy cannot be given alone in sufficient doses to eradicate peritoneal disease [21, 22]. The initial excitement associated with the approval of pemetrexed and cisplatin has subsided, and the work of finding improved treatment options continues. Trials of multimodality therapy incorporating debulking surgery, intraperitoneal chemotherapy, and in some series whole abdominal radiation have resulted in long-term survival of a few selected patients [19, 23–25].

Treatment

Diet and lifestyle

- There is no evidence to date that modification of lifestyle or diet has a role in the development or management of MPM. Occupational, nonoccupational, direct, or second-hand exposure to asbestos remain the principal etiologic factor in the development of MPM. Proper protective gear should be used when handling asbestos-contaminated products. Protective respiratory masks as recommended by National Institute for Occupational Safety and Health (NIOSH) should be worn when airborne particles are suspected or verified.

Surgery

- As a single entity, surgery is of benefit in palliation of small bowel obstruction. There is a clear role for paracentesis to evacuate large volume ascites [26].

- The Columbia strategy for DMPM differs conceptually from most investigators who currently combine surgery with intraperitoneal chemotherapy for this disease. Other protocols generally employ a single aggressive surgical procedure with intensive intraoperative and early postoperative chemotherapy. The Sugarbaker technique employs surgical cytoreduction with peritonectomy and visceral resection in an attempt to eradicate pertioneal implants. Perioperative intraperitoneal chemotherapy is then used as a chemical cytoreduction to eradicate residual cancer cells and small implants [22]. In our operative experience of over 100 patients with MPM, we have sought to use regional chemotherapy in a manner that is more analogous to traditional systemic chemotherapy by exposing the malignant cells to repeated doses of chemotherapy over a much longer schedule. The strategy is designed to expose more cells to drug at a vulnerable period in the cell cycle rather than focusing on several days in the perioperative period. The Columbia procedure includes an omentectomy and removal of all visible disease nodules 0.5 cm in thickness. Peritoneal surfaces or loops of bowel with superficial miliary nodules of mesothelioma would not be stripped or resected, but would be left for later extirpation with intraperitoneal chemotherapy. Two Portacath peritoneal access catheters are tunneled through the abdominal wall to prevent leakage of the peritoneal chemotherapy solution. Thus, whereas most groups compress the intraperitoneal chemotherapy into a 1–10-day period, our protocol delivers chemotherapy repeatedly over 18 weeks. Although each of the surgical procedures in our approach is less aggressive than total peritonectomy, two laparotomies are required, thereby exposing the patients to the risks, discomfort, and convalescence required for two abdominal operations. Even so, as can be seen in Table 1, combining the morbidity and mortality of both operations compares favorably to the single more intensive strategy.

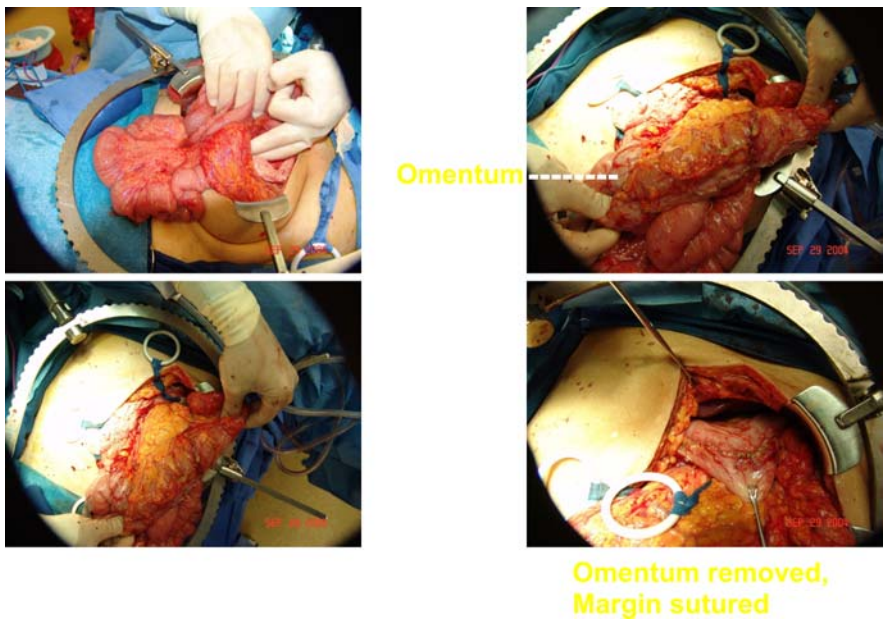

Table 1. Surgical treatment of peritoneal mesothelioma

Investigator	*N*	Surgery	Unresectable disease (%)	Chemotherapy	Postoperative chemotherapy	Second-look [exploratory laparotomy] surgery	Perioperative Adverse events (Gr III-IV)	Mortality	Survival (years), % 1 year	3 years	5 years	Median overall survival (months)
Hesdorffer (2008) (Prospective Phase II [23])	27	Exploratory laparotomy, omentectomy, cytoreduction, mediport	11%	IPHP mytomycin/ cisplatin IP	IP doxorubicin × 4, cisplatin × 4, gamma IFN × 4	Following IP chemotherapy (3 months)	8/27	0	1	1	1	70
Deraco (2006) [19]	48	Exploratory laparotomy, omentectomy, cytoreduction	NA	IPHP mitomycin/ cisplatin v doxorubicin cisplatin	No	No	Surgical 15%, hematological, 12%	0	NA	NA	57 31, PFS	39.3, PFS
Feldman (2003) [10]	48	Exploratory laparotomy, tumor resection or debulking, omentectomy (50%), organ resection (29%)	NA	Continuous hyperthermic perfusion, cisplatin 250 mg/m^2 for 90 min	Single IP dose of 5FU/paclitaxel 7–10 days postop.	No	25% (18 surgical complications in 12 patients); neutropenia, hyperamylasemia	NA	86	59	59	92
Yan (2007) [34] (consecutive patients)	70	Exploratory laparotomy, cytoreductive surgery [periontectomy, splenectomy, omentectomy, colonic anastomosis: 35%, permanent ostomy: 24%]	NA	Hyperthermic intraoperative intraperiotneal chemotherapy, cisplatin 50 mg/m^2 and doxorubicin 15 mg/m^2 for 90 min	IP paclitaxel, 20 mg/m^2 per day × 5 days	No	Grade III morbidity rate 27% (30 grade III events in 19 pts.), Grade IV morbidity 14% (13 events in 10 patients)	0	82	57	49	59
Brigand (2006) (identified from prospective database) [35]	15	Cytoreductive surgery [omentectomy, cholecystectomy, peritonectomy, intestinal anastomosis, antrectomy: 1 pt]	NA	Hyperthermic intraoperative intraperitoneal chemotherapy, cisplatin 0.7 mg/kg, mitomycin 0.5 mg/kg for 90 min	No	No	Grade III complications 40% (2/15 secondary to IPHC)	0	69	43	28	36
Costamagna (2003) [36]	24	"Radical surgery"	21%	Hyperthermic intraperiotneal perfusion (closed technique), MMC + CDDP (3 pts), doxorubicin + CDDP (15 pts), dox alone (1 pt)	No	1 reop.	Postoperative morbidity 26%	Operative mortality 11%	50	13	8	40

PFS—progression-free survival.

Radiotherapy

- A single modality has not been shown to be effective in peritoneal mesothelioma, but long-term survival has been reported when incorporating radiation into a multimodality approach have been [23, 27, 28].

Systemic treatment

- In 2004, the FDA approved the Combination of Alimta (pemetrexed) and Cisplatin based on the results of a multicenter randomized trial comparing Alimta and Cisplatin to Cisplatin plus a placebo. A total of 448 patients from 19 countries participated in this trial, the largest trial ever conducted in malignant mesothelioma. Overall survival was more for the combination, 12.1 months, than for cisplatin alone, 9.3 months [29••].
- An analysis of the expanded access program which included peritoneal mesothelioma reported activity in this subgroup of patients as well [30••].
- Treatment: Pemetrexed 500 mg/mg every 21 days plus cisplatin 75 mg/m^2 every 21 days [29••].
- Contraindications: Renal insufficiency (creatinine clearance <45 mL/min), neuropathy, sensory hearing loss, inability to be compliant with folic acid repletement.
- Main drug interactions: Cisplatin may lower anticonvulsant drugs in plasma to subtherapeutic levels. Pyridoxine may antagonize the chemotherapeutic effects of cisplatin.
- Main side effects: Mucositis, leukopenia, neutropenia, neuropathy, rash, nausea, and emesis.
- Special points: Concurrent use of NSAIDS should be avoided during therapy. Folic acid repletion should continue for 21 days post-discontinuation of pemetrexed.

Selected combination regimens reporting activity in malignant mesothelioma

Gemcitabine plus cisplatin

- Gemcitabine, 1000 mg/m^2, days 1, 8, 15 plus cisplatin, 100 mg/m^2, day 1 (28-day cycle) [31].
- Contraindications: Renal insufficiency (creatinine clearance less than 45 mL/min), neuropathy, sensory hearing loss.
- Main drug interactions: Gemcitabine acts synergistically with cisplatin. No drug interactions for gemcitabine have been recognized. Cisplatin may lower anticonvulsant drugs in plasma to subtherapeutic levels.
- Main side effects: Anemia, leukopenia, and thrombocytopenia may be seen with gemcitabine. Renal toxicity (decreased creatinine clearance) may occur after repeated doses of cisplatin. Neuropathy and hearing loss (due to cisplatin) may occur. Weakness and fatigue are common side effects for both agents.
- Special points: Treatment is palliative.
- Carboplatin AUC 5, day 1 plus Gemcitabine 1000 mg/m^2, days 1, 8, 15 (21-day cycle) [32].
- Contraindications: Adjust dose of carboplatin for renal insufficiency.
- Main drug interactions: Carboplatin can potentiate the renal effects of nephrotoxic drugs.

- Main side effects: Leukopenia, thrombocytopenia, anemia, flu-like symptoms, myalgias, fever, edema, rash
- Special points: Treatment is palliative.
- Vinorelbine 25 mg m^2 weekly and Cisplatin 100 mg m^2 every 4 weeks [33].
- Contraindications: Cisplatin may lower anticonvulsant drugs in plasma to subtherapeutic levels. Pyridoxine may antagonize the chemotherapeutic effects of cisplatin. No contraindications reported with vinorelbine.
- Main drug interactions: Bronchospasm and shortness of breath can develop when vinorelbine is administered with mitocycin. Cisplatin may lower anticonvulsant drugs in plasma to subtherapeutic levels.
- Main side effects: Leukocytopenia nausea, neurotoxicity, illeus.
- Special points: Treatment is palliative.
- Intraperitoneal chemotherapy: Following a recent Phase III study in Ovarian Cancer, treatment of peritoneal carcinomatosis with intraperitoneal chemotherapy was declared the standard of care by the National Cancer in 2006. This has been adopted by those surgeons treating peritoneal mesothelioma. To date, no regimen has proved superior to the others but all have demonstrated improved survival statistics compared to historical controls.

Specific multimodality procedures

Combined resection, intraperitoneal chemotherapy, and whole abdominal radiation [23]

- Debulking surgery, followed by 12 instillations of intraperitoneal chemotherapy, second planned surgery with a heated perfusion of cisplatin and mitomycin, followed by whole abdominal radiotherapy.
- Therapies: intraperitoneal chemotherapy doxorubicin 25 mg total dose × 4 doses, cisplatin 100 mg/m^2 × 4 doses, IFN Gamma 9 million units twice weekly × 1 week, and then 30 million units once weekly × 3, heated chemotherapy with mitomycin (10 mg/m^2) and cisplatin (100 mg/m^2) in 2 L of normal saline at a temperature of 41°C perfused intraperitoneally for 60 min via suprahepatic inflow and pelvic outflow catheters connected to a recirculating circuit with a roller pump and heater/exchanger. Patients completing intraperitoneal chemotherapy and second-look surgery were then scheduled for radiotherapy. This consisted of 3000–3080 cGy total dose to the abdomen and pelvis with kidney blocks placed to anterior and posterior portals after 1400–1550 cGy. No other transmission blocks were used.
- Results: The median overall survival was 70 months with a 3-year survival of 67% (95% confidence interval, 46–81%). Fourteen patients have died of their disease with a median time to death of 17 months (range, 0.4–71 months) after consenting to treatment. Seven patients are alive without evidence of disease with a median follow-up of 90 months (range, 71–110 months), and six are alive with disease with a median follow-up of 86 months (range, 70–106 months). The regimen was well tolerated.
- Complications: There were no patients with Grade III or IV hematological toxicities, two patients with Grade III ototoxicity, and three patients with Grade III gastrointestinal toxicity.

Prognostic analysis of clinicopathologic factors in 59 patients with diffuse MPM treated with CRS and intraperitoneal hyperthermic perfusion [19].

- Therapies: At the completion of CRS with intestinal anastomosis using a closed abdomen technique, the temperature was maintained at 42.5°C. CDDP at 25 mg m^2/L and mitomycin c 3.3 mg/m^2/L or CDDP 43 mg/L plus doxorubicin 15.25 mg/L. Volume of persuade was approximately 3.5 L of body surface area. Forty-nine patients were treated using this technique.
- Results: At a mean follow-up of 20.3 months (range, 1–89 months), the 5-year OS and PFS were 57% and 31%, respectively. The median PFS was 39.7 months (95% confidence interval, 26.8–52.6 months).
- Complications: 15% of patients experienced a Grade III complication. The more significant of these complications included intestinal fistula, gastric perforation, pneumonia, pulmonary embolism, and pancreatic fistula.

Analysis of factors associated with outcome in patients with MPM undergoing surgical debulking and intraperitoneal chemotherapy [10••]

- Surgical debulking and intraperitoneal chemotherapy with a heated perfusion of cisplatin followed by intraperitoneal paclitaxel and five fluorouracil.
- Therapies: At the conclusion of the debulking procedure, the peritoneal cavity was warmed to a median temperature of 41°C, and cisplatin mixed in 1 L of 0.9% sodium chloride solution was added to the perfusate at a median dose of 250 mg/m^2. Perfusion was continued for 90 min. Thirty-five patients were treated on a protocol that included chemotherapy given as a single intraperitoneal dose between 7 and 10 days after the operation of FU 800 mg/m^2 and paclitaxel 125 mg/m^2.
- Results: At a median potential follow-up of 28.3 months, median actuarial PFS is 17 months and actuarial OS is 92 months. Factors associated with improved PFS and OS by the Cox proportional hazards model were a history of previous debulking surgery, absence of deep tissue invasion, minimal residual disease after surgical resection (OS only), and age younger than 60 years (OS only).
- Complications: Two patients required reoperation for fascial dehiscence or gastric perforation. The mean time between surgery and resumption of a regular diet was 8.5 days (range, 3–38 days). Thirteen percent of patients had Grade III or greater neutropenia in a time course consistent with an effect of paclitaxel and FU. Hyperamylesemia was observed in four patients (8%) but was not associated with symptoms of pancreatitis.

Morbidity and mortality assessment of cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma—A prospective study of 70 consecutive cases [34]

- Following a cytoreduction with peritonectomy and visceral resection with perioperative intraperitoneal chemotherapy cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2), a temperature of approximately 42°C in 3 L of 1.5% dextrose peritoneal dialysis solution was maintained during the instillation of perfusate.

- Results: The median follow-up period was 35 months (range, 1–89 months). All patients were followed until the last time of contact or death. The overall median survival was 59 months (range, 1–89 months).
- Complications: The perioperative mortality rate was 3%. The Grades III and IV morbidity rates were 27% and 14%, respectively. Primary colonic anastomosis ($P = 0.028$), more than four peritonectomy procedures ($P = 0.015$), and duration of the operation of more than 7 hours ($P = 0.027$) were the risk factors for Grade IV morbidity.

Peritoneal Mesothelioma Treated by Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemotherapy: Results of a Prospective Study [35]

- Following a cytoreduction with peritonectomy and visceral resection using the Sugarbaker technique, 4–6 L of isotonic dialysis fluid was circulated at a flow rate of 500–700 mL/min and heated to achieve an intraperitoneal temperature between 42°C and 42.5°C. Mitomycin c (.5 mg/kg) and cisplatin (.7 mg/kg) were administered intraperitoneally.
- Results: The overall median survival for this group of 14 patients with malignant mesothelioma was 35.6 months. The median survival was 37.8 months for patients treated with a CC-0 or CC-1 resection, whereas it was 6.5 months for those treated with a CC-2 or CC-3 resection (diameter of residual nodules >2.5 mm; $P < .001$). Of the original 15 patients, one was found to have nonmalignant multicystic mesothelioma and was excluded from survival analysis.
- Complications: Of the 15 patients treated under this protocol, two were reported to experience a Grade III toxicity. One patient developed a superficial wound necrosis, probably because of extravasation of chemotherapeutic perfusate during IPHC. Another patient experienced acute renal failure that resolved with intravenous rehydration.

Treatment of peritoneal mesothelioma using cytoreduction and intraperitoneal hyperthermic chemotherapy [36]

- Cytoreductive surgery and hyperthermic antiblastic peritoneal perfusion was performed by the original "semi-closed" technique, using MMC+CDDP in 3 patients, CDDP + doxorubicin in 15 patients, and only doxorubicin in 1 patient.
- Results: Of the 24 patients treated under this regime, operative mortality was 11% and postoperative morbidity was 26%. Four patients are DOD (4 patients are DOD at 2, 2, 20 and 40 months; 5 patients are AWD at 15, 15, 25.34 and 72 months); and 8 patients are NED at (1, 12, 13, 16, 20, 20.47 and 81 months); and 8 patients are NED (81, 47, 2 at 20 months, 16, 13, 12 months, 1 patient recently operated). The median survival is 40%.
- The results cited above are two of many centers involved in the management of MPM. Survival statistics have improved using the combination of surgical debulking coupled with intraperitoneal chemotherapy. Reported results are encouraging as survival has been greatly improved using these approaches.

Emerging therapies

- Several novel approaches utilizing immunotherapy, new chemotherapeutic agents, and targeted agents are currently under investigation for malignant mesothelioma. Though none of these approaches are

specifically for those with MPM, one would expect that if efficacy is observed in pleural mesothelioma those with MPM would also benefit.

- New trial utilizing MORAb-009, a chimeric antimesothelin monoclonal antibody, is currently under investigation in malignant mesothelioma. Mesothelin, an antigen normally present on mesothelial cell, is highly expressed in malignant mesothelioma. It is normally present on cells lining the pleura, peritoneum, and pericardium. Other agents under investigation targeting mesothelin are CRS207 and SS1P [37, 38].
- Taxalog, a newly developed oral taxane, has demonstrated activity in taxane-resistant tumors including malignant mesothelioma. A Phase II study has recently been started in multiple centers for malignant mesothelioma based on promising Phase I results as well as preclinical data in mesothelioma cell lines [39].
- Vorinostat, a histone deacetylase inhibitor, is a novel class of therapeutic agents that inhibits deacetylate histones and other proteins involved in the regulation of gene expression and cell cycle progression. Based on promising results in a Phase I study, Vorinostat is currently being tested against placebo in a large national and international intergroup trial [40].
- The role of immune therapy is under investigation and also holds promise for improving survival in mesothelioma. Vaccines as well as gene therapy trials are currently being conducted and promising results have been reported based on Phase I data in malignant mesothelioma [41–43].
- Vascular endothelial growth factor, platelet derived growth factor, and epidermal growth factor receptors are known to be highly overexpressed in malignant mesothelioma. Numerous trials are currently being conducted using cytotoxic drugs that target these receptors either as single agents or in addition to chemotherapeutic agents [44–48].

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