

Intra-abdominal manifestations of pleural mesothelioma

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Abstract: Malignant pleural mesothelioma is a disease characterized by persistent and progressive disease within the hemithorax. However, after aggressive local-regional treatment using surgery, regional chemotherapy, radiation therapy, and systemic chemotherapy, metastases outside of the pleural space may become the chief obstacle to long-term survival. One possible direction of cancer dissemination is direct extension through the hemidiaphragm into the peritoneal space by the disease itself or as a result of diaphragm resection. In those patients who have isolated progression of disease within the peritoneal space, evaluation of their clinical condition using prognostic indicators is essential. Patients with a limited extent of disease and favorable radiologic findings by CT should be considered for cytoreductive surgery using peritonectomy procedures and perioperative combined intraperitoneal and systemic chemotherapy. Although few patients with pleural to peritoneal disease extension have been treated, some favorable long-term results suggest that selected patients should be thoroughly evaluated for disease control within the abdominal and pelvic space.

Keywords: Malignant peritoneal mesothelioma; hyperthermic intraperitoneal chemotherapy (HIPEC); cytoreductive surgery; intraperitoneal chemotherapy; peritonectomy; concerning radiologic features; sarcomatoid mesothelioma; diaphragm resection

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Introduction

The majority of patients with treated or untreated pleural mesothelioma die as a result of disease persistence and progression within the thoracic cavity. Causes of death are most commonly an increasing extent of disease that causes progressive respiratory failure, pneumonia, or heart failure often with arrhythmias. Secondly, the disease progression within the mediastinum and chest wall produces an unrelenting pain syndrome which leads to cachexia. Finally, poor nutrition from dysphagia caused by tumor progression of the esophagus is common (1). However, in approximately one-third of patients, the disease penetrates the hemidiaphragm directly and may disrupt bowel function. Alternatively, in surgically-treated patients the disease may be disseminated into the abdomen at the time of diaphragm resection. These extrathoracic manifestations of the disease very often occur late in the course of the disease process. Approximately two-thirds of the patients will, at the time of death, have distant metastases with

the most frequently involved organs being liver, adrenal gland, kidney, contralateral lung. When distant metastases do occur, they are predominantly of the sarcomatous histological type.

Intra-abdominal disease as a result of direct extension through the hemidiaphragm

Although unusual, direct extension of pleural mesothelioma through the hemidiaphragm to seed the peritoneal space can occur at the time of initial diagnosis of pleural disease. More frequently, direct extension occurs in patients with non-surgical management of the pleural mesothelioma allowing invasion of the chest wall and diaphragm with the resulting dissemination within the peritoneal space. A second mechanism for disease extension into the peritoneal space comes about as a result of diaphragm resection and the peritoneal contamination from dislodged mesothelioma cells or emboli into the peritoneal space. Whatever the cause of the dissemination process, patients with peritoneal

Table 1 Selection of patients for treatment of peritoneal metastases of pleural mesothelioma

Clinical features suggesting a favorable outcome for use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal metastases from pleural mesothelioma

- (I) General medical condition compatible with survival and recovery from the procedure
- (II) Clinical information regarding the peritoneal metastases compatible with a complete or near complete cytoreduction from contrast-enhanced CT
 - (i) Relative sparing of the small bowel and colon
 - (ii) Absence of disease outside the abdomen/pelvis
 - (iii) If hepatic metastases are present, they are limited, compatible with wedge resection.
 - (iv) Absence of disease within the porta hepatis
- (III) With a high-grade malignancy, a low or moderate peritoneal cancer index
- (IV) Symptomatic patient

Clinical features suggesting cytoreductive surgery and hyperthermic intraperitoneal chemotherapy should not be recommended

- (I) Poor performance status
 - (II) Rapid progression of a high-grade disease process
 - (III) Low likelihood of a response to perioperative chemotherapy
 - (IV) One or more concerning radiologic features by CT
 - (V) Prior abdominal or pelvic radiation therapy
 - (VI) Local control of the pleural mesothelioma is unlikely
 - (VII) Asymptomatic from peritoneal metastases
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involvement should be evaluated for possible favorable outcome from additional intraperitoneal surgical or regional chemotherapy interventions. In patients where combined surgical and regional chemotherapy treatments have achieved local control within the chest cavity, intra-abdominal surgery and regional chemotherapy treatment options should be considered (2,3). In patients who do not have local control within the pleural space, the treatment options are limited to systemic chemotherapy or best supportive care.

Patients with control of disease in the initially involved hemithorax, no extension to the opposite thoracic cavity, and no known metastatic disease other than in the peritoneal space should be considered for cytoreductive surgery and hyperthermic perioperative chemotherapy for disease control within the peritoneal space. Bidirectional adjuvant normothermic chemotherapy (BANC) within the peritoneal space may also be considered (4).

Table 1 presents the clinical features that suggest a favorable versus a low benefit outcome when cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

(HIPEC) are used to treat peritoneal metastases. With some modifications, these same criteria for selection of patients for treatment by CRS and HIPEC apply not only to gastrointestinal and gynecologic cancer patients but also those who have peritoneal extension of pleural mesothelioma. Patients having an aggressive thoracic surgery, hyperthermic combined intraperitoneal and intrathoracic perioperative chemotherapy and then systemic chemotherapy may have a reduced performance status suggesting that they are at high risk for abdominal surgery. Also, this additional abdominal surgery may not be compatible with a complete recovery back to a reasonable quality of life.

The CT scan of abdomen and pelvis contrast-enhanced with both oral and intravenous contrast can be of great help in patient selection. The CT should show relative sparing of the small bowel and colon, an absence of disease outside of the abdomen and pelvis, an absence of liver metastases unless they are compatible with a wedge resection, and an absence of large volume disease within the porta hepatis. With pleural mesothelioma, a high grade malignancy, the CT peritoneal cancer index (CT-PCI) should be in the low

Table 2 Surgical technology to achieve a complete response

Peritonectomy procedure
Anterior parietal
Right subphrenic
Left subphrenic
Pelvic
Omental bursa
Mesenteric
Visceral resections
Greater omentum
Spleen
Uterus and ovaries
Rectosigmoid colon
Right colon
Lesser omentum
Stomach

range, certainly less than 20 (5-7).

Clinical features that suggest cytoreductive surgery and HIPEC should not be recommended include a poor performance status, rapid progression of the disease from chest into the peritoneal space with a short free interval, one or more of the concerning radiologic features, and question of control of the primary disease in the hemithorax. If the clinical features suggest a favorable outcome and no contraindications to an aggressive approach, the cytoreduction with HIPEC should be presented to the patient as a treatment option.

Cytoreductive surgery

The surgical technology required for a favorable outcome with pleural mesothelioma extending into the peritoneal space do not differ significantly from the surgical technology required to treat peritoneal mesothelioma. As shown in *Table 2*, this involves a series of five peritonectomy procedures and several visceral resections. All visible evidence of disease is to be removed surgically if prolonged disease control within the peritoneal space is to be achieved.

Perioperative chemotherapy as a planned part of the surgical procedure, a warm chemotherapy solution is used to wash the peritoneal surfaces following the peritonectomy



Figure 1 Administration of heated intraperitoneal chemotherapy. After the placement of tubes, drains, and temperature probes the skin edges are elevated onto the rim of a self-retaining retractor using a running suture. A plastic sheet incorporated into the sutures covers the abdomen and prevents splashing or loss of chemotherapy aerosols into the environment. A slit in the plastic sheet allows the surgeon's hand access to the abdomen and pelvis. His continuing activity guarantees that all abdominal surfaces will have access to uniform doses of heat and chemotherapy. A smoke evacuator pulls the air beneath the plastic cover through a charcoal filter to prevent any aerosols from gaining access to the operating room environment.

procedures and visceral resections. Optimally, an open hyperthermic chemotherapy treatment prior to the completion of intestinal anastomoses, repair of seromuscular tears, and prior to closure of the abdomen will occur (*Figure 1*). This minimizes the possibility for tumor entrapment within suture lines or the abdominal closure (8).

Perioperative chemotherapy

There are two different HIPEC regimens that have been used in peritoneal mesothelioma patients and are appropriate for these patients with pleural mesothelioma metastatic to the peritoneal space. Selection of one treatment over the other may be influenced by molecular tumor profiling.

In general, those patients who seem to have had a response to cisplatin are treated with the chemotherapy regimen presented in the top portion of *Figure 2*. This

Height: _____ ft Weight: _____ kg BSA: _____ m²
 _____ in _____ lbs

1 Cisplatin, doxorubicin, ifosfamide plus Mesna

a) Add cisplatin _____ mg (50 mg/m²) to 2 liters of 1.5% dextrose peritoneal dialysis solution. Add doxorubicin _____ mg (15 mg/m²) to same 2 liters of 1.5% dextrose peritoneal dialysis solution.
For intravenous (IV) administration:

b) Add ifosfamide _____ mg (1300 mg/m²) to 1 liter 0.9% sodium chloride. Begin continuous IV infusion over 90 minutes simultaneously with IP chemotherapy.

c) Add mesna disulfide _____ mg (260 mg/m²) to 100 ml 0.9% sodium chloride to be given IV as a bolus 15 minutes prior to ifosfamide infusion.

d) Add mesna disulfide _____ mg (260 mg/m²) to 100 ml 0.9% sodium chloride to be given IV as a bolus 4 hours after ifosfamide infusion begins.

e) Add mesna disulfide _____ mg (260 mg/m²) to 100 ml 0.9% sodium chloride to be given IV as a bolus 8 hours after ifosfamide infusion begins.

f) Send all the above to operating room # _____ at _____ o'clock on _____ (Date) for a 90-minute treatment.

2. Gemcitabine
For intraperitoneal (IP) administration:

a) Add gemcitabine _____ mg (1000 mg/m²) to 2 liters of 1.5% dextrose peritoneal dialysis solution.

b) Send the above to operating room _____ at _____ o'clock for 60-minute irrigation.

3. Melphalan
For intraperitoneal (IP) administration:

a) Add Melphalan _____ mg (50-70 mg/m²) to 2 liters of 1.5% dextrose peritoneal dialysis solution.

b) Send the above to operating room # _____ at _____ o'clock on _____ (Date) for 60-minute irrigation.

Figure 2 Three options for intraoperative chemotherapy for peritoneal mesothelioma.

is a 90-minute hyperthermic intraperitoneal treatment with cisplatin, intraperitoneal doxorubicin, and systemic ifosfamide plus mesna. In those patients who are thought to be resistant to cisplatin, hyperthermic intraperitoneal gemcitabine is recommended. This is a one-hour heated chemotherapy treatment with a single chemotherapy agent, gemcitabine. Alternatively, in patients who seem to have drug resistance to both cisplatin and gemcitabine, intraperitoneal melphalan has been shown to be of benefit.

Results of treatment

The number of patients treated to date is too few to make judgments regarding the efficacy of this approach and the prolonged benefit that may result. There is no doubt that patients who have peritoneal mesothelioma with direct extension into the pleural space may have long-term survival (9). This is conditional upon an aggressive approach to treatment of the direct extension of peritoneal mesothelioma into the pleural space. Of course, peritoneal mesothelioma is, for the most part, a much less aggressive disease process than pleural mesothelioma.

Rare manifestations of hematogenous metastases from pleural mesothelioma within the abdomen

In almost all patients who have peritoneal manifestations of pleural mesothelioma, this extension comes about through a direct and full-thickness invasion of the hemidiaphragm. Then cancer seeding occurs and is distributed by the normal peritoneal fluid around the abdomen and pelvis in a characteristic fashion. However, there are case reports of hematogenous metastases from pleural mesothelioma to abdominal and pelvic sites. The clinician should be aware that hematogenous metastasis, especially from biphasic or sarcomatoid pleural mesothelioma, is a real possibility. In *Table 3*, the clinical manifestations of hematogenous metastases from pleural mesothelioma are listed (10-15). For the most part, these metastases are to the highly vascularized portions of the gastrointestinal tract, the small bowel, stomach, and a single patient with colonic metastases. Also reported is a single patient with isolated pancreatic metastases from malignant pleural mesothelioma. The clinician taking care of pleural mesothelioma patients

Table 3 Manifestations of hematogenous metastases of pleural mesothelioma to the abdomen or pelvis

Author (reference)	Year	Histologic type	Metastatic site	Symptoms/signs
Chen (10)	2008	Sarcomatoid	Duodenum	Bleeding
Lin (11)	2009	Biphasic	Pancreas	Pain
Gocho (12)	2010	Biphasic	Jejunum	Perforation
Sibio (13)	2011	NA	Colon	Bleeding
Falkenstern-Ge (14)	2013	Epithelioid	Periumbilical	Palpable mass
Navarro García (15)	2015	Epithelioid	Jejunum	Perforation

must be aware that metastatic disease within the abdominal viscera may lead to a perforation or bleeding of the gastrointestinal tract which requires emergency surgical intervention.

In summary, patients with direct extension of pleural mesothelioma into the peritoneal space may be considered for CRS and HIPEC. Disease control within the thorax, an absence of systemic metastases, and a mesothelioma distribution within the abdomen and pelvis compatible with a complete cytoreduction are the selection factors to be applied. Standard of care would indicate HIPEC to be a part of this intervention.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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