

## SURGICAL BIOLOGY FOR THE CLINICIAN

# Peritoneal mesothelioma: current understanding and management

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Mesothelioma is an asbestos-related tumour. Mesothelioma in the thorax occurs on the pleura and is known as pleural mesothelioma. It is the more common form of mesothelioma, accounting for 70% of cases. The other form occurs in the abdomen. It accounts for much of the remaining 30% and is known as peritoneal mesothelioma. Early diagnosis of peritoneal mesothelioma is often difficult because the early symptoms are often overlooked as being a benign ailment of the gastrointestinal tract. Therefore, diagnosis often occurs at an advanced stage when disease is widespread throughout the peritoneal cavity. Treatment approaches have evolved in the last decade from systemic chemotherapy and palliative surgery to aggressive cytoreductive surgery and perioperative intraperitoneal chemotherapy. This has led to a marked increase in survival among patients who were once classified as “preterminal.” We update on the current understanding of peritoneal mesothelioma from a clinical perspective in hope that greater clinician awareness will promote best practice management of this condition.

Le mésothéliome est une tumeur liée à l'exposition à l'amiante. Lorsqu'il se forme au niveau de la cage thoracique, le mésothéliome se développe sur la plèvre et prend le nom de mésothéliome pleural. Il s'agit de la forme de mésothéliome la plus répandue, puisqu'il représente 70 % de tous les cas. L'autre forme se manifeste dans l'abdomen : on parle alors de mésothéliome péritonéal. C'est la forme que prend une bonne partie des 30 % de cas restants. Il est souvent difficile de diagnostiquer tôt le mésothéliome péritonéal parce que ses premières manifestations passent dans bien des cas à tort pour de banales malaises digestifs. On établit donc souvent le diagnostic alors que la maladie s'est déjà propagée à toute la cavité péritonéale. Les approches thérapeutiques ont évolué depuis une dizaine d'années, passant de chimiothérapies systémiques et chirurgies palliatives à des chirurgies cytoréductrices et des chimiothérapies périopératoires intrapéritonéales. Ces mesures ont permis de faire augmenter nettement la survie chez des patients que l'on jugeait à une époque en phase « préterminale ». Nous faisons ici le point sur les connaissances cliniques actuelles relatives au mésothéliome péritonéal dans l'espoir de sensibiliser davantage les médecins à ces approches et de promouvoir ainsi une prise en charge optimale de la maladie.

**M**esothelioma is a rapidly progressing, asbestos-related tumour. This tumour was once rare and is now showing an increasing incidence worldwide<sup>1</sup> following the vast mining of asbestos, which peaked in the 1970s.<sup>2</sup> Presently, although asbestos-related activities have been curtailed in most countries, the enormous historical production and use of asbestos in the form of various building materials and commercial products have resulted in millions of people being exposed to asbestos and a proportion of them now having asbestos-related diseases. In Canada, mining and exporting asbestos to developing countries is still ongoing.<sup>3</sup>

The diagnosis of mesothelioma occurs in the fourth to sixth decade of life. There is a preponderance toward the male sex.<sup>4</sup> This is thought to be caused by occupational exposure to asbestos. In Canada, there is a rising trend in the number of men receiving diagnoses of mesothelioma each year. In 2003, there were 344 diagnoses recorded, a marked increase from 153 diagnoses recorded

in 1984.<sup>3</sup> A Scottish study reported that the cost of hospital care associated with the treatment of 100 patients who died of asbestos-related mesothelioma in 2000 was £942 038.<sup>5</sup> This is an enormous amount for any health care system.

Mesothelioma arises from serosal surfaces, mainly in the pleura (70%) and peritoneum (30%). Other rarer locations include the tunica vaginalis of the testis and pericardium.<sup>6</sup> This article focuses on current concepts in peritoneal mesothelioma and provides clinicians with an increased awareness of this condition.

### ETIOLOGY

Asbestos is the primary carcinogen implicated in the pathogenesis of peritoneal mesothelioma. Although there is much debate as to how asbestos fibres enter the abdomen, current studies have found a strong association between peritoneal mesothelioma and asbestos exposure.<sup>7</sup> Furthermore, extensive research has been conducted to study the carcinogenic effects of asbestos fibres and their role in tumorigenesis.

First, irritation of the peritoneum by asbestos fibres is thought to induce a chronic inflammatory process whereby the mesothelial cells lining the peritoneum undergo repeated cycles of damage and repair. When this occurs, there is a release of cytokines such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and reactive oxygen species from the inflammatory reaction. In vitro studies of cultured human mesothelioma cells exposed to asbestos have demonstrated its cytotoxic effect.<sup>8,9</sup> However, this cytotoxic effect is negated by TNF- $\alpha$ , which acts by activating the nuclear factor- $\kappa$  B (NF $\kappa$ B) translocation and activation pathway.<sup>8</sup> Nuclear factor- $\kappa$  B activation increases cell survival by inducing cellular proliferation and inhibition of apoptosis. This favours tumorigenesis.<sup>8,10</sup> Reactive oxygen species generated from phagocytic cells such as macrophages and neutrophils lead to damage of DNA content in cells, which increase the susceptibility of genetic instability and alterations in oncogenes and tumour suppressor genes.<sup>11,12</sup>

Second, asbestos fibre interferes with the mitotic process by disrupting the mitotic spindles. This may potentially cause chromosomal instability, aneuploidy and other forms of chromosomal damage that underpin the development of mesothelioma.<sup>13-15</sup>

Third, the ferritin heavy chain in iron has been demonstrated to work as an antiapoptotic protein against asbestos and oxidative stress, contributing to resistance of apoptosis of mesothelioma cells.<sup>16</sup> Iron also works as a catalyst in the formation of reactive oxygen species whose effects have been described previously.<sup>17</sup>

Lastly, asbestos induces phosphorylation of the mitogen-activated protein kinases and extracellular signal-regulated kinases 1 and 2 and elevates expression of early response proto-oncogenes (*FOS* or *JUN* or activator protein 1 family members) in mesothelial cells thereby causing persistent

kinase-mediated signalling, which leads to persistent mesothelial cell proliferation.<sup>18,19</sup>

In addition to asbestos being implicated in the molecular carcinogenesis, an infective component is thought to play a role. Simian vacuolating virus 40 (SV 40), a DNA virus that is a polyomavirus found in both monkeys and humans, has been implicated as a cofactor in the formation of mesothelioma.<sup>20</sup> It is found in malignant cells and reactive mesothelial cells but not in normal adjacent tissues or in lung cancers.<sup>21</sup> It is thought that SV 40 exerts its oncogenic effect by blocking tumour suppressor genes. However, all this is still unclear, leaving asbestos as the one certain cause of peritoneal mesothelioma.

### CLINICAL PRESENTATION

Patients with peritoneal mesothelioma tend to have a heavier exposure to airborne asbestos fibres.<sup>22</sup> The latent period between asbestos exposure to disease onset averages about 20–30 years. This is shorter than that of pleural mesothelioma, which has a latent period of 30–40 years.<sup>23</sup> A study performed at the Washington Cancer Institute, a leading centre in the treatment of peritoneal mesothelioma, showed that patients typically present with either abdominal pain (33%) or increasing abdominal girth (31%). Other symptoms include new onset hernia in 12%, increased abdominal girth and pain in 5%, with the remaining 19% having a variety of other clinical symptoms such as anorexia, dyspnea, fever and abdominal mass.<sup>24</sup> Owing to the heterogeneity of these clinical symptoms, patients often do not recognize their sinister nature until late. At an advanced stage, patients may experience acute problems such as bowel obstruction, perforation or severe ascites, which require emergency surgery. Occasionally though, the diagnosis of peritoneal mesothelioma is made incidentally during abdominal/pelvic palpation or laparoscopy performed for another reason.

Peritoneal mesothelioma behaves in a similar way to other peritoneal surface cancers. These include pseudomyxoma peritonei of the appendix, ovarian cancer, colorectal cancer and peritoneal sarcomatosis. Therefore, patients with these peritoneal surface cancers would present in a similar fashion, adding to the diagnostic woes related to the associated vague presenting clinical symptoms. A number of paraneoplastic syndromes have also been reported with peritoneal mesothelioma, in particular, hematological disorders such as thrombocytosis, venous thrombosis,<sup>25</sup> paraneoplastic hepatopathy and a wasting syndrome.<sup>26</sup>

### DIAGNOSIS

The diagnostic work-up for a patient who is suspected to have peritoneal mesothelioma is analogous to that for an intra-abdominal cancer. Work-up includes a standard set of noninvasive tests comprising routine laboratory tests,

serum tumour markers and computed tomography (CT) scans of the chest, abdomen and pelvis.

Routine laboratory tests are often not useful in the diagnosis of peritoneal mesothelioma. Useful tumour markers in the diagnosis and monitoring of peritoneal mesothelioma are CA 125 and CA 15-3. Among these, CA 125, which is commonly elevated in peritoneal surface cancers and in ovarian cancer, has been shown to be the most useful, having a diagnostic sensitivity of 53.5%.<sup>27</sup> The diagnostic sensitivity of CA 15-3, which is commonly elevated in breast cancer is 48.5% and is occasionally used in peritoneal mesothelioma. Other tumour markers such as CA 19-9 and CEA have virtually no role as tumour markers for peritoneal mesothelioma; CA 19-9 is commonly elevated in gastric and pancreatic cancer (3.8%), and CEA is commonly elevated in colorectal cancer (0%).<sup>27</sup> However, they may be used to provide additional information when trying to exclude other tumours of gastric, pancreatic and colonic origin. Serum mesothelin-related protein (SMRP) and osteopontin are novel markers that are showing promising potential for use as potential markers.<sup>28,29</sup> Serum mesothelin-related protein is shown to be elevated in 71% of patients with mesothelioma; however, it is also elevated in ovarian cancer. Therefore, SMRP is useful in detecting peritoneal mesothelioma and ovarian cancer, but its usefulness in distinguishing them is poor.<sup>28</sup> The sensitivity and specificity of osteopontin are 84.6% and 88.4%, respectively, which is quite promising.<sup>29</sup> At present, these markers are still subjected to further research and are not routinely available. However, there is potential for biomarker combination to improve the diagnostic sensitivity and specificity.

Findings on CT scans are also nonspecific. They may demonstrate the involvement of the abdominal wall with the presence of ascites, omental caking, enlarged lymph nodes and abdominal or pelvic masses. This information is typical of numerous cancers of the abdominal and pelvic viscera. Therefore, it is not specific in the diagnosis of peritoneal mesothelioma. However, it provides us with useful information to assess the extent of the disease and assist in decision-making about treatment.

After this series of noninvasive tests, invasive tests are needed. Endoscopy and colonoscopy are commonly performed to exclude an intraluminal lesion in the stomach (gastric cancer) and bowel (colon cancer). It may also be common practice in some institutions to tap ascitic fluid for cytology. However, this procedure yields a low diagnostic potential owing to the high cytological diversity of malignant cells and the low number of malignant cells that are present within the fluid.

In our unit, laparoscopy is used to assess and stage patients with peritoneal surface cancers. Similar to the use of biopsy and cytology, this procedure should be performed with extreme caution because the risk of abdominal wall seeding of the tumour may adversely affect the outcome of an otherwise potentially curable disease.

Notwithstanding this limitation, if an adequate cytological sample is obtained, immunohistochemistry studies using calretinin or Wilm tumour 1 antigen (WT1) can identify mesothelial tissue and epithelial membrane antigen (EMA) to accurately identify the primary origin of the tumour. In experienced hands, the diagnosis can be made in about 80% of patients.<sup>4</sup>

## HISTOPATHOLOGY

Mesothelioma occurs in 3 main histologic forms: epithelioid, sarcomatoid or biphasic.<sup>6,30</sup> Epithelioid mesothelioma is the most common. The biphasic subtype shows a mixture of both epithelioid and sarcomatoid features and is seen in about 25% of patients. The pure sarcomatoid subtype is rare, with only 32 cases reported in the literature since 2006.<sup>30</sup> There are also other rarer varieties of mesothelial neoplasm that bear some resemblance and have archetypical features of the epithelioid subtype. These include benign adenomatoid tumour and the borderline tumours such as well-differentiated papillary mesothelioma and multicystic mesothelioma.<sup>6</sup>

Epithelioid tumours grow in 4 different patterns: tubular, papillary, diffuse and decidual.<sup>30</sup> The most common is the papillary type, which often coexists with other patterns, most commonly the tubular pattern.<sup>31</sup> The cells in the tubular and papillary patterns are of cuboidal appearance with little to moderate amounts of eosinophilic cytoplasm. Cytological atypia is typically mild.<sup>31</sup> Sarcomatoid tumours have a diffuse storiform and fascicular pattern and are characterized by severe cytological atypia and brisk mitotic activity. Areas of necrosis are often seen within the tumour.<sup>31</sup> Biphasic tumours consist of epithelioid and sarcomatoid components characterized by moderate to severe cytological atypia.<sup>31</sup>

Malignant peritoneal mesothelioma is characterized by positive staining for the following immunohistochemical markers: EMA, calretinin, WT1, cytokeratin 5/6, anti-mesothelial cell antibody-1 and mesothelin. Mesotheliomas can be distinguished from other serious carcinomas of the peritoneum (e.g., ovarian carcinoma, colorectal adenocarcinoma and borderline serious tumours) using calretinin, cytokeratin and thombomodulin stains. Electron microscopy is useful in situations when immunohistochemistry is unable to provide conclusive answers. It allows the detection of ultrastructural features such as tall and thin microvilli on the cell surface, which help the diagnostic process.<sup>30</sup> Because sarcomatoid tumours do not possess any microvilli, electron microscopy is of limited use in visualizing tumours of the sarcomatoid variety.<sup>30</sup>

## TREATMENT

At present, treatment approaches vary in each institution. Common methods include palliative surgery, systemic

chemotherapy, intraperitoneal chemotherapy and cytoreductive surgery with perioperative intraperitoneal chemotherapy.

Agents commonly used in systemic chemotherapy regimes include various combinations of cisplatin, irinotecan, cyclophosphamide, doxorubicin, dacarbazine, gemcitabine and pemetrexed. Prior to 2003, most institutions relied on evidence from smaller phase II studies and treated patients with cisplatin and gemcitabine. This yielded a median survival of 6–9 months.<sup>32</sup> Since then, larger trials have ensued, and most recently, it has been shown that the combination of cisplatin and pemetrexed leads to a median survival of 12–14 months.<sup>33,34</sup> However, although encouraging, these results still indicate that treatment of peritoneal mesothelioma with systemic chemotherapy still leads to a median survival of only about 1 year. This is similar to patients who are treated with a palliative approach.<sup>35</sup> Therefore, its effectiveness as a first-line treatment is questionable. Nonetheless it is still a useful option for patients who are not suitable surgical candidates.

Intraperitoneal chemotherapy involves surgical insertion of a Tenckhoff catheter to allow local administration of chemotherapy into the abdomen. When intraperitoneal cisplatin was used as a sole treatment for peritoneal mesothelioma, the results were similar to those with treatment using systemic chemotherapy, with a median survival of 9 months.<sup>36</sup> Therefore, it is not without basis to claim that the nonsurgical approach to treatment is futile given the poor response to treatment and the poor median survival associated with treatment.

Current research has shown that aggressive cytoreductive surgery using Sugarbaker's peritonectomy procedures<sup>37</sup> followed by perioperative intraperitoneal chemotherapy, which is now regarded as the standard practice of other peritoneal surface cancers, has been shown to dramatically improve survival.<sup>38</sup> Perioperative intraperitoneal chemotherapy involves hyperthermic intraperitoneal chemotherapy and early postoperative chemotherapy. Previously, the dissemination of a gastrointestinal tumour from a local site into the peritoneum was viewed as a metastatic spread. Patients with peritoneal dissemination were treated with a palliative intent. However, surgical oncology has evolved from treating just primary tumours to include the metastatic spread of tumours. Cytoreductive surgery and perioperative intraperitoneal chemotherapy are useful in treating peritoneal dissemination as they allow the removal of the diseased peritoneum hence achieving adequate cytoreduction. Adding a perioperative intraperitoneal chemotherapy allows improved drug delivery to residual tumour cells after cytoreductive surgery. Heating the perfusate provides a synergistic effect with the chemotherapy agent and enhances cytotoxicity. This treatment is now considered to be effective in treating selected patients with peritoneal carcinomatosis from appendiceal cancer, pseudomyxoma peritonei, colorectal cancer, gastric cancer, ovarian cancer

and peritoneal mesothelioma and abdomino-pelvic sarcoma.

A MEDLINE search for studies evaluating the use of cytoreductive surgery and perioperative intraperitoneal chemotherapy in peritoneal mesothelioma suggests a median survival of 28–35 months (Table 1).

Peritonectomy involves a midline laparotomy for maximal visualization of the abdomen and pelvis. Based on the tumour burden in the various regions, a peritoneal cancer index is scored.<sup>44</sup>

Perioperative intraperitoneal chemotherapy has been shown to be a useful prognostic indicator for peritoneal surface cancers. Studies of colorectal and appendiceal cancers with peritoneal carcinomatosis showed that higher perioperative intraperitoneal chemotherapy scores were associated with a poorer prognosis.<sup>45</sup> Interestingly though, a recent study investigating prognostic factors for peritoneal mesothelioma found that, although perioperative intraperitoneal chemotherapy may have a role as a prognostic indicator, after multivariate analysis mesothelioma nuclear size was the only independent factor associated with an improved survival after cytoreductive surgery and perioperative intraperitoneal chemotherapy.<sup>46</sup> Nonetheless, intraoperative assessment of perioperative intraperitoneal

**Table 1. Median survival reported in studies evaluating cytoreductive surgery with hyperthermic intraperitoneal and/or early postoperative chemotherapy for mesothelioma**

Study	Year	Treatment	Median survival, mo
Sebbag et al. <sup>39</sup>	2000	CRS, HIPEC, EPIC (cisplatin and doxorubicin)	31.0
Loggie et al. <sup>40</sup>	2001	CRS, HIPEC (mitomycin)	34.2
Deraco et al. <sup>41</sup>	2003	CRS, HIPEC (cisplatin and mitomycin OR cisplatin and doxorubicin)	28.0
Feldman et al. <sup>42</sup>	2003	CRS, HIPEC (cisplatin and doxorubicin) EPIC (5FU and paclitaxel)	28.3
Brigand et al. <sup>43</sup>	2006	CRS, HIPEC (cisplatin and mitomycin)	35.6
Yan et al. <sup>38</sup>	2007	CRS, HIPEC Systematic review of published and unpublished data from 7 observational studies	34–92

CRS = cytoreductive surgery; EPIC = early postoperative chemotherapy; HIPEC = hyperthermic intraperitoneal chemotherapy.

**Box 1. Peritonectomy procedures**

1. Abdominal exposure
2. Greater omentectomy and splenectomy
3. Peritoneal stripping from beneath the left hemidiaphragm
4. Peritoneal stripping from beneath the right hemidiaphragm
5. Dissection beneath the tumour through Glisson's capsule
6. Removal of tumour from beneath the right hemidiaphragm, from the right subhepatic space and from the surface of the liver, lesser omentectomy, cholecystectomy and stripping of the omental bursa
7. Pelvic peritonectomy



chemotherapy before cytoreduction is standard practice in peritonectomy.

Once the peritoneal cancer index is scored, cytoreductive surgery is performed. This involves the removal of all visible tumours on the surface of any viscera and the total removal of the diseased peritoneum (Box 1).

On completion of cytoreductive surgery, hyperthermic intraperitoneal chemotherapy is performed. Chemotherapy is administered for 90 minutes at 46°C to achieve an intra-abdominal temperature of 42°C. This heated form of administering chemotherapy in the abdomen allows greater concentration of the drug where it is required. Heating this perfusion helps kill cancer cells with little or no effect on normal cells, making the cytotoxic effects of the chemotherapy agent more effective, and softens the tumour nodules so that penetration of the chemotherapy into the tumour nodule is enhanced.<sup>37</sup>

After hyperthermic intraperitoneal chemotherapy, drains are placed into the abdomen and thorax and a Tenckhoff catheter is inserted in the abdomen to allow further instillation of chemotherapy during the early post-operative period.<sup>37</sup>

Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is now well regarded as a novel treatment option for patients with peritoneal mesothelioma and achieves a median survival of about 30 months. As this is an aggressive surgical approach associated with morbidity and mortality, the prolonged survival must be weighted carefully against potential risks.<sup>47</sup> If treatment is to be beneficial, it should only be offered to carefully selected patients with a good performance status, low volume of peritoneal disease and an absence of extra-abdominal metastases.<sup>48</sup>

The learning curve associated with cytoreductive surgery and perioperative intraperitoneal chemotherapy outcomes of patients who were treated over a period of about 10 years were reported in 2 studies (one of which was from our unit).<sup>49,50</sup> Results from these 2 studies showed a demonstrable improvement in survival, morbidity and mortality over time. Our own unit has performed over 250 peritonectomies with a mortality of 2% in the last 4 years.<sup>49</sup> This is attributed to improvement in patient selection, surgical techniques and intraperitoneal chemotherapy regimes. Studies evaluating quality of life after cytoreductive surgery and perioperative intraperitoneal chemotherapy have reported postoperative complications that affect short-term recovery; however, in the long term, patients experienced improved survival and quality of life.<sup>51-53</sup>

## CONCLUSION

Although peritoneal mesothelioma is a progressive and fatal cancer, novel treatment approaches using peritonectomy procedures have demonstrated survival benefits. To reduce its occurrence and associated morbidity and mor-

tality, avoiding asbestos exposure as a primary prevention approach is of utmost importance. However, it is important to bear in mind that, should an individual with a history of asbestos exposure present with nonspecific gastrointestinal complaints, an aggressive approach to investigation is needed to exclude this fatal condition. Aggressive surgical treatment involving cytoreductive surgery and perioperative intraperitoneal chemotherapy should be considered the standard of care for all patients with peritoneal mesothelioma.<sup>54</sup>

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