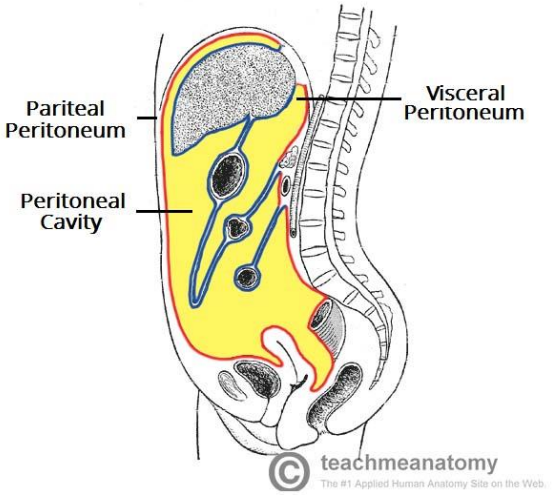
Cancer Association of South Africa (CANSA)

Fact Sheet
on
Peritoneal Mesothelioma

Introduction

The peritoneum is thin membrane that lines the abdominal and pelvic cavities, and covers most abdominal viscera. It is composed of layer of mesothelium supported by a thin layer of connective tissue.



[Picture Credit: Peritoneum]

Although ultimately one continuous sheet, two types of peritoneum are referenced:

- Parietal peritoneum is that portion that lines the abdominal and pelvic cavities. Those cavities are also known as the peritoneal cavity.
- Visceral peritoneum covers the external surfaces of most abdominal organs, including the intestinal tract.

Isaza-Restrepo, A., Martin-Saavedra, J.S., Velez-Leal, J.L., Vargas-Barato, F. & Riveros-Dueñas, R. 2018.
Background: Despite its complexity, the peritoneum is usually underestimated in classical medical texts simply as the surrounding tissue (serous membrane) of the gut. Novel findings on physiology and morphology of the peritoneum and mesothelial cell exist but they are usually focused or limited to Continuous Ambulatory Peritoneal Dialysis research and practice. This review aims to expose, describe and analyze the most recent evidence on the peritoneum's morphology, embryology and physiology.
Materials and Methods: A literature review was performed on Pubmed and MEDLINE. With no limit of publication date, original papers and literature reviews about the peritoneum, the peritoneal cavity, peritoneal fluid, and mesothelial cells were included (*n* = 72).
Results: Peritoneum develops in close relationship to the gut from an early period in embryogenesis. Analyzing together the development of the primitive gut and the surrounding mesothelium helps understanding that the peritoneal cavity, the mesenteries and other structures can be considered parts of the peritoneum. However, some authors consider that structures like the mesenteries are different to the peritoneum. The mesothelial cell has a complex ultrastructural organization with intercellular junctions and apical microvilli. This complexity is further proven by the large array of functions like selective fluid and cell transport; physiological protective barrier; immune induction, modulation, and inhibition; tissue repair and scarring;

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preventing adhesion and tumoral dissemination; cellular migration; and the epithelial-mesenchymal transition capacity.
Conclusion: Recent evidence on the anatomy, histology, and physiology of the peritoneum, shows that this structure is more complex than a simple serous membrane. These results call for a new conceptualization of peritoneum, and highlight the need of adequate research for identifying clinical relevance of this knowledge.

Peritoneal Mesothelioma
Just like pleural mesothelioma, peritoneal mesothelioma is caused by exposure to asbestos. When someone ingests microscopic asbestos fibres, the tiny sharp particles get embedded in the lining of the abdomen (peritoneum). Over a course of 20 to 50 years, the fibres in the peritoneum cause mutations in the surrounding healthy mesothelial cells. Constant genetic damage makes these cells cancerous, forming tumours on the peritoneum.

Peritoneal mesothelioma, sometimes called abdominal mesothelioma or diffuse malignant peritoneal mesothelioma, is a rare asbestos-related cancer. It is a form of mesothelioma that develops in the lining of the abdominal cavity (known as the peritoneum). It accounts for about 15 – 20 percent of all mesothelioma cases diagnosed throughout the world.

The peritoneal form is the second-most common form of the disease, and while almost always fatal, it has a more favourable prognosis than other types of mesothelioma. New treatments, particularly cytoreductive surgery and HPIEC, a heated chemotherapy wash, have extended survival times, with many patients living with the disease for seven years or more.

Incidence of Peritoneal Mesothelioma
The outdated South African National Cancer Registry (2014) does not provide any information regarding the incidence of Peritoneal Mesothelioma.

Le Stang, N., Bouvier, V., Glehen, O., Villeneuve, L. FRANCIM network, MESOPATH Referent National Center, Galateau-Sallé, F. & Clin, B. 2019.
BACKGROUND: Peritoneal malignant mesothelioma is a rare disease for which few population-based studies are available. The aim of this study was to describe the evolution of the incidence and survival of peritoneal malignant mesothelioma in France between 1989 and 2015, using data derived from the French network of cancer registries.
METHODS: Age world-standardized incidence rates and overall survival were calculated using data from 16 French cancer registries. Log-linear Poisson regression analysis was used to estimate the average annual percentage change in incidence rates. Overall survival was performed using age-adjusted Cox proportional hazards model.
RESULTS: In French men, the incidence has increased quietly over the reporting period from 0.07 to 0.10 with a maximum of 0.16 per 100,000 persons-years in 2001-2003. For women, the increase in incidence has been lower than for men over the period 1989-2015, ranging from 0.04 to 0.11. A better prognosis was associated with a diagnosis made after 2000 (HR = 1.76; p = 0.013), the epithelioid histological type (p = 0.003), and the fact of being a woman, which has a 5-year risk of death half that of men (HR = 0.55; p = 0.001), regardless of age, diagnosis period or histology.
CONCLUSION: Our results are similar to those currently available for other countries. In France, peritoneal mesothelioma remains a rare and fatal cancer with a small increase in the incidence rate

since 1989 and a median survival of 1 year; it seemed to develop equally in women and men over this period of time.

Cause of Peritoneal Mesothelioma

The development of Peritoneal Mesothelioma is as follows:

- Swallowed asbestos fibres travel from the digestive system to the peritoneum.
- Inhaled asbestos fibres travel via the lymphatic system to the peritoneum.
- Once fibres are in the peritoneum, they irritate the cells.
- The irritated cells begin to thicken the peritoneal lining.
- Excess abdominal fluid builds up.
- Over time, tumours begin to form on the damaged peritoneum.

Signs and Symptoms of Peritoneal Mesothelioma

A patient with peritoneal mesothelioma may not experience symptoms early on. If symptoms are evident, they may be mistaken for other illnesses. One common symptom in many peritoneal mesothelioma patients is fluid pockets called ascites, which often cause the stomach region to bulge outward.

Other symptoms include:

- Abdominal Pain
- Loss of Appetite
- Blood Clots
- Fatigue
- Fluid Build-up (Ascites)
- Nausea
- Abdominal Swelling
- Fever or Sweating
- Tissue Lumps in the Abdomen
- Anaemia
- Seizures
- Bowel Problems

In most cases, peritoneal mesothelioma does not spread to the lungs. It has been shown to spread to the other abdominal areas, such as ovaries, liver, or intestines. This metastasis often causes it to become discovered and sometimes misdiagnosed. Symptoms of stomach pains or ascites sometimes results in a misdiagnosis of hernias or a simple stomach ache (King, Bhagwandin & Labow, 2017).

Diagnosis of Peritoneal Mesothelioma

Mesothelioma is a malignancy of serosal membranes. It is most commonly encountered in the visceral pleura with the second most common location in the peritoneum. The diagnosis is very rare and has been linked to toxic exposure to industrial pollutants, especially asbestos. Malignant peritoneal mesothelioma (MPM) commonly presents with diffuse, extensive spread throughout the abdomen with rare metastatic spread

beyond the abdominal cavity. Due to its rarity and nonspecific symptoms, it is usually diagnosed late when the disease burden is extensive.

Because the symptoms of malignant peritoneal mesothelioma are often similar to those of other diseases, diagnosis can be difficult. A peritoneal mesothelioma diagnosis will usually start with imaging tests, like CT scans and x-rays, and blood tests to rule out more common diseases and other forms of cancer, like adenocarcinoma and ovarian cancer.

The most important step is the biopsy, which is currently the only way to confirm a peritoneal mesothelioma diagnosis. A doctor will take a fluid or tissue sample for analysis to confirm the cancer, as well as identify cell type and how the mesothelioma may progress.

Chapel, D.B., Churg, A., Santoni-Rugiu, E., Tsujimura, T., Hiroshima, K. & Husain, A.N. 2019.
"The pathologist plays a central role in the diagnosis and management of malignant mesothelioma, including definitive tissue-based diagnosis in conjunction with clinical and radiographic data; diverse ancillary studies of diagnostic, prognostic, and predictive importance; and research efforts to better define the pathobiology of mesothelioma and develop novel clinical applications. The pivotal role of pathology in care of mesothelioma patients was on display at the recent meeting of the International Mesothelioma Interest Group (iMig) in Ottawa, Canada. This review summarizes the key findings of the "Molecular Pathways and Diagnosis in Malignant Mesothelioma" plenary session, including a large multi-institutional validation of a composite nuclear grading system for pleural mesothelioma, including incorporation of tumor necrosis as an additional independent prognostic factor; the correlation between nuclear grading in small biopsies and paired resection specimens in pleural mesothelioma; a multi-institutional study of important clinical and pathologic prognostic factors in peritoneal mesothelioma; the diagnostic role of HEG1 immunohistochemistry as a highly sensitive and specific marker of mesothelial lineage; the prevalence and diagnostic significance of MET protein overexpression in mesothelioma, as well as the correlation between MET protein overexpression and MET gene amplification; and the prognostic role of EZH2 protein overexpression in mesothelioma, together with data indicating an important pathogenic role for EZH2 in mesothelioma tumorigenesis. Special consideration is given to the convergence of diagnostic, prognostic, and predictive tools and their role in guiding highly personalized patient-centered management, and to the translation of novel research findings to practical techniques for routine pathologic practice."

Liu, X.H., Wu, H., Huang, Y.F., Zhang, G.Y. & Xu, M.H. 2019.
Objective: To reduce the misdiagnosis rate of ascites and improve the diagnosis rate of malignant peritoneal mesothelioma.
Methods: From May 2008 to May 2018, in Xiangya Hospital of Central South University,the clinical data of malignant peritoneal mesothelioma misdiagnosed as tuberculous peritonitis were retrospectively analyzed.
Results: (1) Among the 6 patients, they were male; the age of onset was 42-70 (52±9.57) years old, and there was no history of asbestos exposure. (2) All cases with abdominal pain or abdominal distension were there and the course of disease was more than 1 month to more than 2 years. (3) In all patients,the nature of ascites was exudate; ADA was higher than normal value and below 45 U/L; LDH value in ascites was higher than 200 U/L (83.3%); mesothelioma was considered in ascites cytology in 1 case. (4) Laparoscopic biopsy was performed in 2 cases and B-ultrasound guided biopsy in 4 cases; Among them, malignant peritoneal mesothelioma diagnosed by pathology. (5) In Immunohistochemical positive markers, MC was the most sensitive (100%), followed by CR (67%), CK-Pan (67%), Ki-67 (67%) and EMA (67%). (6) Two patients received treatment with operation, abdominal hyperthermic perfusion and postoperative systemic chemotherapy.

Conclusions: (1) Malignant peritoneal mesothelioma should be considered in middle-aged and aged male patients with unexplained ascites and early laparoscopy or laparotomy for diagnosis. (2) ADA and LDH level in ascites are significant in differentiating tuberculous peritonitis from malignant peritoneal mesothelioma. (3) Immunohistochemical positive marker MC may be a potential specific marker for malignant mesothelioma. (4) The survival time of patients is improved by comprehensive treatment such as operation and chemotherapy.

Treatment of Peritoneal Mesothelioma

Patients diagnosed with peritoneal mesothelioma most often receive cytoreductive surgery with heated intraperitoneal chemotherapy (HIPEC). This combination of treatments is also generally known as a multimodal therapy.

Cytoreducitve Surgery is a procedure surgeons use to remove mesothelioma tumours that are in and around the abdominal cavity. A surgeon removes any visible signs of cancer. The surgeon may also remove nonessential organs affected by mesothelioma. The procedure itself is highly complex and can take up to 10 hours to complete.

Heated Intraperitoneal Chemotherapy (HIPEC) is a heated mixture of chemotherapy drugs introduced into the abdominal cavity shortly after the cytoreductive surgery is completed. The goal of HIPEC is to kill any microscopic traces of mesothelioma that may remain after surgery.
The mixture of drugs is typically heated to a temperature of 104 – 107^{o}C and circulated inside the abdominal cavity for a maximum of 2 hours. This allows the chemotherapy enough time to be absorbed into the microscopic cancer cells and increases the cancer-killing effectiveness of the drugs.

HIPEC may be given once, shortly after the surgical procedure, or as many times as the surgeon sees fit in the weeks following the surgery. One recent study reported that patients who receive repeated HIPEC after a single cytoreductive surgery experienced a longer survival time (approximately 80 months) than those who only received it once (27.2 months).

A Paracentesis involves the use of a needle or catheter to remove the build-up of fluid in the abdominal cavity. This procedure is mainly used to relieve any discomfort or pain caused by symptoms of peritoneal mesothelioma.

Levý, M., Boublíková, L., Büchler, T. & Šimša, J. 2019.

“Malignant mesothelioma is a highly malignant disease that most often occurs in the pleura of the thoracic cavity, followed by the peritoneum, pericardium, or tinea vaginalis testis. Malignant peritoneal mesothelioma (MPM) accounts for 10-15% of all mesotheliomas. The most significant risk factor for MPM is exposure to asbestos. There is no specific symptomatology, and imaging (computed tomography) and histopathology are crucial for diagnosis. There are no generally accepted guidelines for radical treatment of MPM. Previously, the prognosis of MPM patients was poor, with survival of up to 1 year. However, median survival of patients who are suitable candidates for radical therapy is currently 3-5 years. A combination of cytoreductive surgery (CRS) and hyperthermic perioperative chemotherapy (HIPEC) is recommended in selected patients, while chemotherapy alone has insufficient efficacy. Systemic chemotherapy remains the only treatment option for patients who are unsuitable for CRS and HIPEC. In selected patients scheduled for or currently undergoing CRS and HIPEC, surgery may be performed in combination with systemic chemotherapy in the neoadjuvant or adjuvant setting; however, the benefit is unclear. There are no recommendations for follow-up of MPM

patients after radical surgery. Existing guidelines for the pleural form (e.g., those issued by the European Society for Medical Oncology) do not specify the frequency or method of investigation. In the absence of specific serum markers, only CA 125 and mesothelin are generally available. Imaging methods include ultrasonography, computed tomography, and magnetic resonance imaging."

Ali, Y.M., Sweeney, J., Shen, P., Votanopoulos, K.I., McQuellon, R., Duckworth, K., Perry, K.C., Russell, G. & Levine, E.A. 2019.

INTRODUCTION: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) is an accepted treatment for peritonealmesothelioma. In this study, we evaluated QOL after HIPEC for peritoneal mesothelioma.

METHODS: This was a prospective study performed after HIPEC for peritoneal mesothelioma between 2002 and 2015. Patients completed QOL surveys, including the Short Form-36 (SF-36), Functional Assessment of Cancer Therapy + Colon (FACT-C), Brief Pain Inventory (BPI), and Center for Epidemiologic Studies Depression Scale (CES-D) preoperatively and at 3, 6, 12, and 24 months postoperatively.

RESULTS: Overall, 46 patients underwent HIPEC for peritoneal mesothelioma and completed QOL surveys. Mean age was 52.8 ± 13.8 years and 52% were male. Good preoperative functional status was 70%. Median survival was 3.4 years, and 1, 3, and 5-year survivals were 77.4, 55.2, and 36.5%, respectively. CES-D score decreased at 3 months postoperatively, but increased at 24 months ($p = 0.014$); SF-36 physical functioning scale decreased at 3 months but returned to baseline at 12 months ($p = 0.0045$); and the general health scale decreased at 3 months, then improved by 6 months ($p = 0.0034$). Emotional well-being ($p = 0.0051$), role limitations due to emotional problems ($p = 0.0006$), social functioning ($p = 0.0022$), BPI ($p = 0.025$), least pain ($p = 0.045$), and worst pain ($p < 0.0001$) improved. FACT-C physical well-being decreased at 3 months but returned to baseline at 6 months ($p = 0.020$), and total FACT-C score improved at 6 months ($p = 0.052$).

CONCLUSION: QOL returned to baseline or improved from baseline between 3 months and 1 year following surgery. Despite the risks associated with this operation, patients may tolerate HIPEC well and have good overall QOL postoperatively.

Kyziridis, D., Hristakis, C., Kalakonas, A., Vaikos, D., Pallas, N., Karamveri, C., Kyriakopoulos, V. & Tentes, A.A. 2019.

PURPOSE: Peritoneal mesothelioma is a rare disease that remains confined to the peritoneal surfaces for long. Cytoreductive surgery (CRS) combined with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) is the most effective treatment and complete cytoreduction is the most significant prognostic indicator of long-term survival. This study attempted to present the results of CRS in combination with hyperthermic intraperitoneal chemotherapy in patients with peritoneal mesothelioma and identify the prognostic indicators of survival.

METHODS: The files of patients with peritoneal mesothelioma were retrospectively reviewed. Morbidity, hospital mortality, recurrences, and the sites of recurrence were recorded. Survival and recurrence were correlated to performance status, age, extent of peritonealdissemination, tumor grade, tumor volume, and completeness of cytoreduction.

RESULTS: From 2005-2017, 29 patients underwent 33 cytoreductions for peritoneal mesothelioma. Hospital mortality and morbidity were 3% and 27.3% respectively. The median and 8-year survival were 66 and 62% months, respectively. The completeness of cytoreduction was the single prognostic indicator of survival, and the tumor grade the single prognostic indicator of recurrence.

CONCLUSION: CRS combined with HIPEC is the therapeutic strategy that may provide long-term survival.

Salo, S.A.S., Ilonen, I., Laaksonen, S., Myllärniemi, M., Salo, J.A. Rantanen, T. 2019.
BACKGROUND: Malignant peritoneal mesothelioma (MPeM) is a rare type of cancer with a poor prognosis. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) have been shown to improve survival. Treatment and survival of patients with MPeM have not been previously studied in Finland.
MATERIALS AND METHODS: The data consisted of all patients diagnosed with MPeM during years 2000-2012 in Finland, including cancer notifications, death certificates and information about asbestos exposure.
RESULTS: Among 50/94 (53.2%) patients treated for MPeM, 44/50 (88.0%) were treated palliatively, 4/50 (8.0%) with radical surgery and chemotherapy, and 2/50 (4.0%) with CRS plus HIPEC. Five-year survival was 50.0% for those treated with CRS plus HIPEC and 75.0% for those treated with radical surgery and chemotherapy. Radical surgery with chemotherapy was associated with significantly longer survival compared to radiation (p=0.008), chemotherapy and radiation (p=0.043), surgery, chemotherapy and radiation (p=0.039), and palliative surgery (p=0.009).
CONCLUSION: Treatment of MPeM is heterogenic in Finland. CRS plus HIPEC, and radical surgery with chemotherapy seem to increase the survival. Patients considered candidates for radical surgery should be sent to specialized centers for further assessment.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

Although clinical trials for peritoneal mesothelioma are not as abundant as those for pleural mesothelioma, researchers are studying whether immunotherapy combined with chemotherapy could play a bigger role in controlling the cancer by boosting the body's immune system.

For additional information, please visit: www.sanctr.gov.za/

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