Original Article

# Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Mesothelioma

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## Abstract

**Introduction: Peritoneal mesothelioma is a rare neoplasm. Due to the limited understanding of its biology and behaviour, peritoneal mesothelioma poses a diagnostic and management challenge. The management of peritoneal mesothelioma has been controversial; systemic chemotherapy, palliative surgery and cytoreductive surgery (CRS) with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) have been described. Materials and Methods: This study shares our experience with cytoreductive surgery and HIPEC for 5 out of the 6 cases of peritoneal mesotheliomas treated surgically, at a single institution in Singapore over the past 2 years. Computed tomography (CT) scans, positron emission tomography (PET)-CT scans and tumour markers were performed preoperatively but were not conclusive for the disease. All 6 cases presented to the Department of Surgical Oncology at National Cancer Centre Singapore, were diagnosed by histology of intraoperative biopsies. The combination of aggressive cytoreductive surgery and HIPEC was performed in 5 patients, with abandonment of procedure in 1 with extensive disease, who was treated with systemic chemotherapy instead. Results: Median duration of surgery, median length of hospital stay, and median follow-up duration were 7.04 hours, 11 days, and 15 months respectively. One postoperative morbidity relating to chemical peritonitis required exploratory laparotomy with good outcome. There were no mortality. All patients are alive at the last follow-up with no evidence of recurrences at 4 to 31 months from the time of their surgery. Conclusion: Peritoneal mesothelioma is a rare disease that requires early diagnosis and can be effectively treated by CRS and HIPEC in selected group of patients.**

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**Key words: Intraoperative chemotherapy, Mesotheliomas, Peritonectomy**

## Introduction

Mesothelioma is a rare and aggressive tumour that predominantly affects serous surfaces of organs. It was first described in 1908 by Miller and Wynn. The overall prevalence is 1 to 2 cases per million worldwide, with an estimated incidence of 200 to 400 new cases annually; 65% to 70% arise in the pleura, 20% to 30% in the peritoneum, and 1% to 2% in the tunica vaginalis testis, and pericardium. It is a rare neoplasm with a median survival of 6 to 12 months.

### *Diagnosis*

Peritoneal mesothelioma is often diagnosed when the disease is in advanced stage. This is often because its presentation is non-specific such as abdominal pain, weight loss or ascites. Occasionally, the diagnosis is made incidentally during laparoscopy for another condition, for example at laparoscopic appendicectomy, and diagnostic laparoscopy for the investigation of abdominal pain. Macroscopically, it is distinguished by multiple whitish tumour nodules that may unite to form plaques, masses or layers to cover the whole peritoneal surface. It is often associated with the presence of free intraperitoneal fluid.

Computed tomography (CT) is valuable for detection, characterisation, and staging. On CT, peritoneal mesothelioma appears as solid, heterogeneous, enhancing soft-tissue masses. Its growth pattern tends to be expansive as opposed to infiltrative. However, the CT scan findings are

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often non-specific and inadequate to establish a diagnosis.

A high index of suspicion is required and definitive diagnosis of peritoneal mesothelioma depends on histological and immunohistochemical examination. Analysis of ascites has a low diagnostic potential.

*Management*

The management of peritoneal mesothelioma has been controversial. Systemic chemotherapy, palliative surgery and cytoreductive surgery (CRS) with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) have been described, with no definite benefit established by any one of the treatment modalities. In this report, we share our experience of CRS and HIPEC for peritoneal mesothelioma at a single institution in Singapore over the past 2 years.

## Materials and Methods

This study reports 6 cases of peritoneal mesothelioma presented to the Department of Surgical Oncology, National Cancer Centre of Singapore, between June 2008 and September 2010. Five patients successfully underwent CRS and HIPEC, whilst 1 was found to have extensive disease on laparotomy. Of the 6 patients, 5 were female and 1 was male.

The first patient was a 33-year-old Chinese female who underwent a laparoscopic ablation of endometriosis in July 2003. Intraoperatively, peritoneal nodules were noticed and biopsied. The histology was reported to be papillary mesothelial proliferation, with no malignancy found. Four years later, she underwent a laparoscopic myomectomy, during which peritoneal lesions were again seen. Biopsies of the lesions were taken, and the histology showed malignant mesothelioma of epitheloid type. She had no previous asbestos exposure. A CT scan was performed, that did not reveal any peritoneal nodules or ascites, but showed mild prominence of both collecting systems and ureters, with no obstructing lesions. Tumour markers were normal. She was referred to the Department of Surgical Oncology, and underwent CRS, which involved stripping of bilateral paracolic and subdiaphragmatic peritoneum, omentectomy, appendicectomy, total hysterectomy and bilateral salpingo-oophrectomy (THBSO), and HIPEC with cisplatin uneventfully, and continued to have early postoperative intraperitoneal chemotherapy (EPIC) for 5 days. On postoperative day 3, she was noted to have a left pleural effusion that was managed with the insertion of a chest tube. This was removed on postoperative day 7, with resolution of the effusion. She was discharged well on postoperative day 10, and continued her follow-up in the outpatient clinic at 3 monthly intervals for 6 months and subsequently 6 monthly intervals. Annual CT scans of her abdomen and pelvis was performed. She was last seen in the clinic 31 months from her operation date, with a normal CT and tumour markers.

The second patient was a 28-year-old Indonesian female who underwent an open appendicectomy for presumptive appendicitis. Intraoperatively, omental nodules were found, and biopsied. Histological examination showed malignant mesothelioma of the omental nodules and the appendix. A CT scan was done, and this revealed no discernible peritoneal nodules or ascites. This was followed with a positron emission tomography (PET)-CT scan that did not reveal any FDG-avid metastatic foci. Her tumour markers were normal. She was counselled for CRS. Intraoperatively, peritoneal nodules were found throughout the peritoneum, with some nodules in the small bowel serosa and mesentery, with significant bulk of the disease concentrated in the pelvis and omentum. She underwent CRS, which consisted of stripping of her entire peritoneum and an omentectomy, and HIPEC with cisplatin to target the smaller serosa and mesenteric nodules. She was commenced on EPIC the next day. On postoperative day 2, she complained of severe abdominal pain. On examination, her abdomen was tender and peritonitic. EPIC was stopped and she was taken into the emergency operating theatre for an exploratory laparotomy. This showed likely chemical peritonitis, with no evidence of intraabdominal sepsis. She recovered uneventfully, and was discharged healthy on postoperative day 12. She was also followed up in the outpatient clinic at 3 monthly intervals for the first 6 months, followed by 6 monthly intervals, with a CT scan of her abdomen and pelvis annually. Her recent review in the outpatient setting was 24 months after surgery, and she was reported to be well, with a normal CT scan and tumour markers.

The third patient was a 49-year-old female from Egypt. She presented with abdominal distension to a hospital in Egypt. A CT scan was performed and this showed ascites and peritoneal lesions. The largest of these lesions was biopsied percutaneously and the histology showed a malignant epithelial neoplasia suspicious for renal cell carcinoma; there were no renal masses seen on the scan. She came to Singapore for a second opinion, and a CT scan was repeated. The scan confirmed the findings of ascites and peritoneal nodules, with no evidence of renal cell carcinoma. In order to attain more tissue for histology, she underwent a diagnostic laparoscopy and biopsy of the peritoneal nodules. Intraoperatively, multiple peritoneal nodules were noted, with the tumour burden mostly over the right abdomen. The histology revealed a malignant peritoneal mesothelioma. She was referred to the surgical oncologists, who counselled her for CRS. Her preoperative tumour makers showed a raised CA 153 of 47.6 u/mL (<25.1 u/mL) and a normal CA 125 of 25.9 (<35.1 u/mL).

She underwent exploratory laparotomy, but CRS was abandoned as her disease was deemed too extensive, with multiple tumour nodules over her small bowel mesentery. She made an uneventful recovery and returned home for palliative chemotherapy.

The fourth patient, a 41-year-old Chinese female was found to have free fluid in the pouch of Douglas on a routine ultrasound by a gynaecologist. A CT scan was performed and this showed omental nodules and ascites. Her tumour makers were normal. She underwent a laparoscopic biopsy of the omental nodules that showed well differentiated mesothelioma. PET-CT confirmed that there were no distant metastases, and in January 2010, she underwent CRS and HIPEC. CRS consisted of stripping of bilateral paracolic and sub-diaphragmatic peritoneum, THBSO, appendicectomy, splenectomy and omentectomy. There was one chest tube placed intraoperatively, and HIPEC was with Cisplatin. She completed 5 days of EPIC, and recovered uneventfully to be discharged on postoperative day 14. She also continued follow-up at 3 monthly intervals for 6 months, and subsequently 6 monthly intervals, with an annual CT of her abdomen and pelvis. Her last follow-up was 15 months after surgery, with no nodules or ascites seen on CT scan.

The fifth patient was a 51-year-old female who had recurrent peritoneal mesothelioma. She was first diagnosed in August 2005, when she presented with abdominal distension. In 2005, she underwent a THBSO and omentectomy by a gynaeoncologist, and had adjuvant chemotherapy with carbo/paclitaxel. Her chemotherapy regime was changed after 2 cycles, to pemetrexed and cisplatin for 6 cycles, as she developed progressive disease on the carbo/paclitaxel. She continued to have annual follow-up with the medical oncologist, during which her CA 125 levels remained low. No CT scans were performed. In November 2009, she returned, complaining of abdominal distension. Her CA 125 level was normal, but had shown an increase from 5.3 u/mL to 21.8 u/mL in 3 months. A CT scan showed a new 6.2 cm by 7.4 cm soft tissue mass in the small bowel mesentery, abutting the anterior abdominal wall and displacing the small bowel loops, with some smaller mesenteric nodules in the mesentery. She underwent another 3 cycles of chemotherapy with pemetrexed and cisplatin with good response. Repeat CT scan post chemotherapy showed an interval decrease in the size of the mesenteric nodule from 7.4 cm to 5.3 cm, with stable small volume mesenteric nodes. She was referred for CRS, and underwent resection of the tumour, small bowel resection, segmental colectomy, cholecystectomy, omentectomy and stripping of bilateral paracolic, subdiaphragmatic, pelvic, and anterior parietal peritoneum, and HIPEC with cisplatin. She had one chest tube placed intraoperatively. She did not receive EPIC because of her history of chemotherapy resistance. Her postoperative course was uneventful, and she was discharged on postoperative day 10. She was followed up at 3 monthly intervals for 6 months, then at 6 monthly intervals. Her last follow-up was 15 months after surgery, during which a CT scan was performed, and showed no evidence of recurrent disease. Her CA 125 remains low at 10.3 u/mL.

The final patient was a 57-year-old male who was working as a manager in a commercial kitchen equipment company, and denied any asbestos exposure. He presented with abdominal pain for 2 months, associated with loss of weight and appetite. CT scans were done in another hospital, and this showed peritoneal disease, with minimal ascites. He underwent a laparoscopic biopsy, which revealed malignant mesothelioma. When he was referred to our centre, a CT-PET scan was done, and this showed hypermetabolic nodular omental and diffuse peritoneal thickening but no hypermetabolic extraperitoneal disease. His tumour makers revealed a raised CA 125 of 502 u/mL and CA 153 of 57.3 u/mL. He was planned for CRS and HIPEC. He underwent a laparotomy, which revealed that the main bulk of the disease was involving the omentum, with multiple small (<2 mm) nodules on the small bowel mesentery and serosa, and the peritoneum relatively spared by the disease. An omentectomy was performed and he was given HIPEC to address the small bowel nodules. He was subsequently discharged on postoperative day 8, but adjuvant chemotherapy was not instituted, because of his renal impairment. He remained asymptomatic, with improvement in weight and appetite. A CT scan performed 4 months after surgery showed no evidence of intra-abdominal disease, but a right pulmonary nodule suspicious for metastasis was noted. He was last seen 8 months after surgery, with a persistently high CA 125 level of 3436 u/mL.

In the work-up prior to surgery, contrast CT scans, PET-CT scans and tumour markers (CEA, CA 125, CA 19-9, CA 15-3, and AFP) were performed, but were not conclusive for the disease. Two of the 6 patients had elevated CA 153 levels, and 1 had elevated CA 125. One of the patients showed a normal, but rising CA 125 level. All the cases of peritoneal mesothelioma were diagnosed with intraoperative biopsies. The Egyptian patient returned to Egypt soon after surgery, and information regarding her case was limited. It is interesting to note, that half of these patients were diagnosed incidentally on scans or surgery for another pathology. Additionally, 5 of the 6 patients are female, with no history of exposure to asbestos.

The combination of CRS and HIPEC was performed in 4 patients, with abandonment of the procedure in 1 patient with extensive disease, who was treated with systemic chemotherapy instead. The last patient underwent limited

resection of his disease, with HIPEC.

The median duration of surgery, median length of hospital stay, and mean volume of estimated intraoperative blood loss were 7.04 hours, 11 days, and 600 mL respectively. One postoperative morbidity relating to chemical peritonitis required exploratory laparotomy with good outcome. There was no mortality. The median length of postoperative follow-up was 15 months, with overall survival ranging from 8 to 31 months. The 4 patients who underwent CRS and HIPEC remain disease free at this review. The details of all 6 patients are summarised in Table 1.

## Discussion

Peritoneal mesothelioma has been thought to carry a bleak prognosis with a median survival of 6 months to 1 year. Systemic chemotherapy alone has nominal effect on the natural history of the disease. Current reports have shown that with CRS and HIPEC, the median survival of patients with peritoneal mesothelioma can be increased to 92 months, with a 3-year overall survival of 59%.[1] In our case series, we have also demonstrated that CRS and HIPEC can offer prolonged disease free and overall survival in selected patients with peritoneal mesothelioma. We believe that as we continue to follow-up with these patients, survival will show to be significantly increased.

An important point which this case series highlights, is the diagnostic dilemma associated with peritoneal mesothelioma. A high index of suspicion is required, as patients usually present with non-specific symptoms of abdominal pain and distension. The majority of the patients in our case series were diagnosed incidentally on scans or surgery for another pathology. Tumour markers were also not elevated in the majority of our patients. However, there have been recent reports citing the usefulness of CA 125 and CA 153 in the diagnosis and monitoring of peritoneal mesothelioma.[2] In addition to the diagnostic difficulties encountered clinically, during pathological analysis, peritoneal mesothelioma is often hard to distinguish from adenocarcinoma, and requires additional immune-cytochemical stains. Mesothelioma typically stains positive for D2-40, cytokeratin 5/6 (CK 5/6), calretinin and wilms tumour-1 (WT-1), and negative for BerEP4 antibody and thyroid transcription factor 1 (TTF1).[3,4] Methods to increase the awareness and enable early detection of this neoplasm will serve to facilitate early implementation of the ideal treatment for patients with the disease, resulting in better outcomes.

CRS aims to remove all macroscopic tumour, which often includes stripping of the peritoneum in the case of peritoneal mesothelioma, as the peritoneal surface is often studded with tumour. As with CRS for other peritoneal-based malignancies, the main prognostic factor is completeness of resection.[5] The completeness of cytoreduction score (CC) proposed by Sugarbaker[6] is often used to document that completeness of resection, and is defined as follows: A CC-0 score indicates that no macroscopic tumour remains after cytoreduction. A CC-1 score indicates that tumour nodules persisting after cytoreduction are less than 2.5 mm. This is a nodule size thought to be penetrable by HIPEC. A CC-2 score indicates tumour nodules between 2.5 mm and 25 mm, and CC-3 score indicates tumour nodules

Table 1. Patient Details

| Patient | Age | Race | Sex | Presentation and Diagnosis | CT Scan Findings | CC Score | Chest Tube | Total Hospital Stay | Complications | Action |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 33 | Chinese | F | Incidental finding on laparoscopic myomectomy | Normal | 0 | 1 | 11 | Left pleural effusion | Left chest tube |
| 2 | 28 | Others | F | Open appendicectomy for presumptive appendicitis | Normal | 0 | 0 | 13 | Chemical peritonitis | Exploratory laparotomy |
| 3 | 49 | Others | F | Abdominal distension | Peritoneal nodules seen | \ | \ | 5 | \ | \ |
| 4 | 41 | Chinese | F | Free fluid in the pouch of Douglas on a routine ultrasound by the gynaecologist | Omental nodules seen | 0 | 1 | 15 | \ | \ |
| 5 | 51 | Chinese | F | Recurrent disease—abdominal distension | Small bowel mesenteric mass and nodules | 0 | 1 | 11 | \ | \ |
| 6 | 57 | Chinese | M | Abdominal pain, loss of weight and appetite | Peritoneal nodules | 7 | 1 | 0 | 9 | \ |

CC: cytoreduction score; CT: computed tomography; F: female; M: male

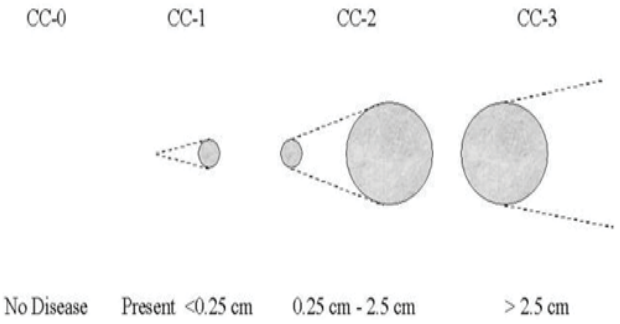


Fig.1. Figure showing the completeness of cytoreduction scores (CC-0 to CC-3). (Adapted from: Sugarbaker PH. Management of Peritoneal Surface Malignancy Using Intraperitoneal Chemotherapy and Cytoreductive Surgery: A Manual for Physicians and Nurses. 3rd ed. Grand Rapids, Michigan: The Ludann Company, 1998.

greater than 25 mm remain (Fig. 1). Optimal cytoreduction is often described as CC-0 and CC-1, as HIPEC has been shown to penetrate a depth of 2 mm to 3 mm.[7] In peritoneal mesothelioma, complete CRS ie. CC-0 or CC-1, confers a significantly better prognosis and longer survival, than suboptimal (CC- 2 or CC-3) resection.[8] In our case series, of the 5 who underwent CRS and HIPEC, CC-0 was achieved for 4 patients and CC-1 for the 6th patient in the series.

Currently, literature has shown the morbidity rates associated with CRS and HIPEC to be from 20% to 50% and the mortality rates to be 1% to 10%.[9-12] Sugarbaker et al[10] reported an overall morbidity rate of 23.5% and mortality rate of 7% in their series of CRC and HIPEC for peritoneal mesothelioma. In our case series, 1 patient had to be brought back into the operating theatre for HIPEC-related peritonitis, and 1 other patient had a chest tube inserted for postoperative pleural effusion. In their intial experience with peritonectomy and HIPEC, Teo et al,[13] advocated the insertion of chest tubes intraoperatively, for patients who underwent stripping of the subdiaphragmatic peritoneum. The patients who returned to the outpatient clinic for follow-up were reported to be well and back to their normal activities. This point stands to highlight the importance of further research into quality of life issues post CRC and HIPEC.

Patient selection is extremely important for this aggressive approach to the treatment of peritoneal mesothelioma. In addition to fitness for surgery, distant metastases must be excluded before considering CRS and HIPEC. The preoperative assessment of disease severity and resectability is also difficult as peritoneal disease is poorly assessed on current available imaging modalities. There have been attempts to improve image detection of unresectability by several authors,[2] but this still remains a problematic area in the treatment of the disease.

*Future Advances*

The treatment approach of aggressive CRS followed by HIPEC confers good survival for selected patients diagnosed with peritoneal mesothelioma. However, many questions remain unanswered, such as the aetiology, pathophysiology and the implications for the management of peritoneal mesothelioma. In particular, we feel that the following areas warrant more research:

*(i) Non-Asbestos Related Peritoneal Mesothelioma*

Traditionally, mesothelioma has always been linked to asbestos. However, the relationship between asbestos and peritoneal mesothelioma is much less significant when compared to pleural mesothelioma.[14] When looking at non-asbestos related mesothelioma, postulations with regards to radiation exposure, genetic factors, dietary factors, chemical exposure[15,16] and viruses have been mentioned.[17] Research into genetic factors show much promise, with the first exome sequencing of well differentiated papillary peritoneal mesothelioma.[18]

*(ii) Female Versus Male Peritoneal Mesothelioma*

Females have been shown to have a better prognosis[19] than males with peritoneal mesothelioma. This has been hypothesised to be due to the fact that women often have more favourable clinical features, and histological subtype of mesothelioma, but there needs to be research to have better understanding of this phenomenon.

*(iii) Ovarian Cancer and Peritoneal Mesothelioma*

The clinical presentation, radiological and operative findings of peritoneal mesothelioma in women are similar to those of ovarian adenocarcinomas. This has led surgeons, medical oncologists and scientists to approach peritoneal mesothelioma in women, in a similar fashion to advanced stage ovarian cancer. Additionally, these similarities have also raised the potential of using the tumour marker CA 125 in women with peritoneal mesothelioma.[20]

*(iv) Targeted Therapy*

Targeted agents have been extensively investigated in mesothelioma over the last decade. Many trials in pleural mesothelioma have tried to use agents that have shown promise in other diseases.[21] Similarly, the use of tyrosine

kinase inhibitors have been explored and proposed for mesothelioma treatment.[22] Other abnormalities in growth factor receptor pathways, angiogenesis, and apoptosis may be amenable to intervention.[21,23] Ongoing trials and investigations in these areas remain a challenging and an exciting part of the development of mesothelioma research. However this discussion is beyond the scope of this article.

## Conclusion

Due to the limited understanding of its biology and behaviour, peritoneal mesothelioma poses diagnostic and management challenges. However, in recent years, a better understanding of this disease has resulted in improved treatment policies. This improvement is largely contributed by the aggressive approach of CRS and HIPEC, achieving up to 63% 5-year survival. With additional research and targeted therapy regimes, we may be able to further improve the survival of this group of patients.

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