



# Evolution of management in peritoneal surface malignancies

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## ABSTRACT

Management of peritoneal surface malignancies has gradually evolved by the introduction of cytoreductive surgery in combination with intraperitoneal chemotherapy applications. Recently, peritoneal metastases of intraabdominal solid organ tumors and primary peritoneal malignancies such as peritoneal mesothelioma are being treated with this new approach. Selection criteria are important to reduce morbidity and mortality rates of patients who will experience minimal or no benefit from these combined treatment modalities. Management of peritoneal surface malignancies with this current trend is presented in this review.

**Keywords:** Heated chemotherapy, peritoneal metastases, colorectal cancer, gastric cancer, ovarian cancer, mesothelioma

## INTRODUCTION

Peritoneal surface malignancies (PSM) originating from the gastrointestinal tract organs, pseudomyxoma peritonei (PMP), ovaries and peritoneum have been considered as lethal diseases with dismal prognosis. The clinical course of tumors at this stage are characterized by a deterioration in quality of life and shortened life expectancy. Supportive care and systemic chemotherapy were the mainstay of treatment for these patients. However, continuous clinical research revealed that PSM treatment and even cure could be achieved with cytoreductive surgery (CRS) and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Appendiceal tumors or PMP (1, 2), and malignant peritoneal mesothelioma (3) have been treated successfully by CRS and HIPEC. Besides this, the role of CRS and HIPEC in the management of PSM that originates from ovary, stomach, colon and rectum is still under investigation. In this review, we summarized the results of CRS and HIPEC in the management of PSM as new treatment modalities.

## Colorectal Cancer

Isolated peritoneal metastases develop in 8.5-25% of patients with colorectal cancer (CRC) (4, 5). Median survival is expected to be 6 to 12 months when peritoneal metastasis (PM) of CRC is treated with palliative intent. Systemic chemotherapy does not seem to provide better survival rates for these patients (6-8). It has been reported that prolonged survival was obtained with CRS and HIPEC in CRC patients with PM (9-17). A randomized controlled study from the Netherlands Cancer Institute supported these results (18). According to 8-years follow up results of this trial, when a complete cytoreduction was achieved, a 5-year survival rate was observed in 45% of these patients.

Completeness of cytoreduction, biological characteristics of the tumors and the extent of disease were found to be significant prognostic factors (19, 20). Similarly, a recent consensus statement on PM of CRC highlighted the importance of complete cytoreductive surgery in these patients (21). Therefore, CRC cases with PM have to be referred to a Peritoneal Surface Malignancy Center and assessed properly to evaluate the extent of the disease prior to CRS and HIPEC.

Besides the improved outcome of these patients with these combined new treatment modalities, the question that remains to be solved is whether CRS and HIPEC are the best options for CRC patients with PM. After oxaliplatin- and irinotecan- based chemotherapy, and anti-VEGF biological therapy were introduced as new treatment strategies for metastatic CRC, the overall survival and progression free survival were improved in these patients with solid organ metastases such as lung and liver (22-25). However, abdominal diffusion of systemic chemotherapy may not be sufficient to the intraperitoneal cavity and peritoneal surfaces in the presence of metastatic nodules on peritoneal surface. Plasma peritoneal barrier (PPB) is usually 90 µm and diffusion of systemic chemotherapy from subperitoneal mesothelial tissue to the peritoneum is very limited or not possible especially if the tumor nodules penetrate to the peritoneal surface deeper than 5 mm. A clinical study comparing new systemic chemotherapy with CRS and HIPEC were required to evaluate the effectiveness of this combined approach versus systemic che-

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motherapy. This study showed that the median survival was 64 months in CRS and HIPEC arm while it was 23 months in modern systemic chemotherapy arm. The 5-year survival rate was 51% with CRS and HIPEC, and 13% with modern systemic chemotherapy. According to this study, CRS and HIPEC can prolong survival in patients with limited peritoneal metastasis of CRC. This combined approach, however, carries a high morbidity and mortality risk even though it has promising results with respect to disease free survival and overall survival. Therefore, patient selection is important to tailor therapeutic plan in patients with short life expectancy.

Colorectal cancer patients with peritoneal dissemination might also have liver metastases. A recent systematic review and meta-analysis investigated the outcomes of liver resections combined with CRS and HIPEC in CRC patients with hepatic and PM (26). This study showed that CRC patients with isolated PM have a much longer overall survival as compared to patients with liver and PM. Besides this, the patients in this study demonstrated an increased median overall survival after CRS and HIPEC with hepatic resection as compared to treatment with modern systemic chemotherapy. Ongoing prospective randomized clinical trial results will clarify the necessity of HIPEC after curative resection in these patients (27).

#### **Pseudomyxoma Peritonei**

Pseudomyxoma peritonei is a rare condition resulting from the rupture of mucinous appendiceal or ovarian tumors, or tumors of primary peritoneal origin. Pseudomyxoma peritonei is characterized by widespread mucinous deposits within the peritoneal cavity. Serial debulking and systemic chemotherapy were conventional treatment options of PMP with a high recurrence rate (28). The 10-year survival was 63% with CRS and HIPEC in patients with PMP (29). High-grade tumor histology, and induction chemotherapy were found to be poor prognostic factors in PMP patients (30).

Extent of the prior surgeries, high peritoneal cancer index (PCI) (31), elevated levels of CA19-9 (32) and CEA (33) were identified as poor prognostic factors by multivariate analysis. Peritoneal recurrence of PMP occurs as a result of the advanced stage of the disease at the time of initial diagnosis or as the consequence of relative chemoresistance to chemotherapy. Repeated CRS and HIPEC could be recommended to prolong survival in highly selected patients (34). Even though the treatment of PMP with CRS and HIPEC seems to provide promising results with low complication and mortality rates, the effects of this combined approach require further investigation to determine its potential benefits as a therapeutic procedure.

#### **Gastric Cancer**

Peritoneal metastases may be present in 5-20% of patients undergoing a potentially curative resection for gastric cancer (GC) at the time of initial diagnosis (35). Patients with PM that originated from GC have a poor prognosis and the estimated survival is 1-3 months without systemic treatment (36, 37). The median survival time does not exceed 9 months even with palliative systemic chemotherapy in these patients (38). Peritoneal involvement represents an independent risk factor for poor prognosis. Therefore, intraperitoneal chemotherapy has been proposed in GC patients with a high risk of peritoneal recurrence. Overall survival was prolonged in patients with in-

traperitoneal chemotherapy (39, 40). These results were also confirmed by a prospective randomized clinical trial (41). According to this study, even though the frequency of intraabdominal abscess and neutropenia were increased in surgery and HIPEC group, no statistically significant difference in morbidity was detected between radical surgery with HIPEC group and radical surgery group. Besides these improvements, the experience with CRS and HIPEC for PM of GC is still limited (42-45). Completeness of cytoreduction, PCI index less than 6, and response to systemic chemotherapy were found to be favorable prognostic factors in patients with PM of GC. Survival advantage with CRS and HIPEC can be obtained in patients with PM of GC (46). Recently, we reported that 152 of 194 (78.3%) PM of GC patients underwent CRS and HIPEC. In this group, the mortality was 3.9% and major complications occurred in 23.6% of patients. The median survival was 15.8 months and the 5-year survival rate was 10.7%. Multivariate analysis identified pathologic response to bidirectional intraperitoneal systemic chemotherapy, low tumor burden, and completeness of cytoreduction as prognostic factors (47). This study provides an important information in selection of cases who will benefit from this challenging combined approach.

Recent ongoing prospective randomized clinical studies will clarify the exact role of HIPEC and CRS in the management of PM of GC.

#### **Ovarian Cancer**

Standard management of patients with advanced stage ovarian cancer (OC) consists of optimal cytoreductive surgery followed by adjuvant systemic chemotherapy with taxane and platinum combination (48). However, despite the improved median overall survival with this regimen (up to 50 months), recurrence occurs in 75% of patients and 20-30% of these patients might have resistance to the platinum analogues (49). A survival benefit in patients treated with intraperitoneal chemotherapy and systemic chemotherapy as compared to systemic chemotherapy alone was also reported in a phase III trial (50). Intraperitoneal chemotherapy one dose prior to surgery yielded better survival rates than those who had only adjuvant systemic intravenous chemotherapy (51). Furthermore, the five-year survival rate can be increased from 17% to 58% with CRS and HIPEC in patients with recurrent ovarian cancer (52). Additionally, CRS with HIPEC might yield long-term survival in selected patients, especially in those with primary chemoresistance, and in recurrent advanced epithelial ovarian cancer patients (53). Complete cytoreduction was found to be a significant prognostic factor according to the results of this study. It has been reported that only 10% of patients with recurrent disease can undergo a complete resection, and the median overall survival can be only prolonged for 3 months according to the results of a recent meta-analysis (54). A clinical trial with a larger study group that addresses the role of CRS and HIPEC in recurrent ovarian carcinoma needs to be performed to determine the exact role of CRS and HIPEC in these patients.

Indeed, a phase III trial to examine the role of HIPEC in recurrent ovarian carcinoma was recently completed (55). In an 8-year period, the mean survival was 26.7 months in CRS with HIPEC and systemic adjuvant chemotherapy group, and was 13.4 months in patients treated with CRS and systemic adjuvant chemotherapy. The use of HIPEC, the extent of the dis-

ease, and the degree of cytoreduction have an important role in the survival of patients with recurrent ovarian cancer.

### Diffuse Malignant Peritoneal Mesothelioma

Diffuse malignant peritoneal mesothelioma (DMPM) was considered as a fatal condition. Systemic chemotherapy and surgery showed limited benefit in this entity (56). Cytoreductive surgery with HIPEC showed a clear improvement in the outcome of DMPM as compared to traditional systemic chemotherapy (57-62).

A significantly prolonged survival was achieved in 405 patients with diffuse malignant peritoneal mesothelioma using CRS and HIPEC in a multi-institutional study (61). According to this study, the overall median survival was 53 months, and 5-year survival rate was 47%. Epithelial subtype, absence of lymph node metastasis, completeness of cytoreduction, and HIPEC were found to be independently associated with improved survival. A TNM staging for diffuse malignant peritoneal mesothelioma was recently proposed, and this classification is significantly correlated with survival advantages of this technique (62). CRS with HIPEC can be considered as a standard of care for patients with DMPM if optimal cytoreduction can be achieved.

The effect of new systemic cytotoxic agents such as pemetrexed prior to surgery in the treatment of peritoneal mesothelioma is gaining attention (63). If the patients are not suitable for an immediate surgery and intraperitoneal chemotherapy, they may be potential candidates for systemic chemotherapy with these new agents prior to surgery.

### CONCLUSION

Peritoneal cavity needs to be considered as a specific organ consisting of two layers that cover the intraabdominal wall and serosal surface of intraabdominal organs. Peritoneal metastases can be treated with curative intent using CRS and HIPEC as a new evolving strategy. This approach achieves cure in many patients. The past three decades presented us sufficient information for patient selection and indications for the treatment of PM. HIPEC is the standard of care for PMP and PM of CRC, mesothelioma, and ovarian carcinoma while it is in the evaluation phase for GC. HIPEC is currently under investigation for treatment of PM of sarcoma, GIST, and small round cell desmoplastic tumors. Further studies will clarify the effectiveness of CRS in combination with HIPEC in PM of other intraabdominal solid organ tumors and primary peritoneal cancers.

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