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Current Indications, Techniques and Results of Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy for Intra-Abdominal Malignancies

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Abstract

Over the last decades, there has been a paradigm shift regarding the management of peritoneal dissemination of intra-abdominal malignancies. Previously believed to be an end-stage disease amenable only to palliative management, several studies have reported achieving significant survival advantage by applying cytoreduction of the tumour load with or without intraoperative hyperthermic intraperitoneal chemotherapy administration. It is hard to classify this procedure as curative despite the reported good results in achieving a reasonable 5-years survival. However, its ability to control the disease process is clearly recognized in different types of intra-abdominal malignancies and its role is better understood within the new concept of treating advanced cancer as a chronic disease. The aim of this review is to discuss the concept, techniques, results and complications of this approach. Current indications and future directions will also be emphasized.

Keywords: Peritoneal carcinomatosis; Mesothelioma; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy

Introduction

The peritoneum is the largest serosal membrane in the body, and consists, in the male, of a closed sac, while in female the free ends of the uterine tubes open directly into the peritoneal cavity. The peritoneum differs from the other serosal membranes of the body, as there is much more complex arrangement. It consists of two layers, one applied against the abdominal wall cavity while the second is reflected over the contained organs to form different structures such as ligaments, mesentery, omentum, and bursae.

Peritoneal Carcinomatosis (PC), the presence of cancer cells on the surface of the peritoneum, can originate from the peritoneum membrane itself or more frequently is a direct extension of cancer originating from abdominal organs to the peritoneum. Tumours that originate from the peritoneum are rare (1-2 million/year) [1,2]. This category includes mesothelioma and primary peritoneal serous carcinoma. Mesothelioma of the peritoneum resulting from asbestos exposure is less defined than that of pleural mesothelioma [3]. It is a difficult pathological diagnosis that can be mislabeled as an adenocarcinoma of unknown primary; therefore, extensive pathological workup with immunomarkers is essential for the diagnosis.

In the vast majority of PC, the primary origins of peritoneal implants are from malignancies of intra-abdominal organs including: appendix, colon, rectum, stomach, and ovaries. In 20-30% of abdominal malignancies, the only site of tumour recurrence remains intra-abdominal [4]. Ten percent of patients with colorectal cancer already have PC at the time of their diagnosis and 25% of remaining patients will develop PC later on in their disease process [5,6]. Other extra-abdominal organ malignancies such as the breast cancer can also extend to the peritoneum; however, few cases are reported [7-9].

Series reporting the natural history of peritoneal tumours showed poor prognosis despite the best systemic therapy [10-13]. For a long time PC was classified as a non-surgical advanced stage of the cancer disease process because of the wide territory of the peritoneum membrane and the frequent extension of the disease to multiple intra-abdominal organ. The possibility of complete surgical debulking through a long complex surgery, involving resection of multiple abdominal organs, was traditionally aborted as per the high risk of such approach with limited benefits. Similarly, systemic intravenous chemotherapy had a little peritoneal penetration and effect on the peritoneal tumours, as the peritoneum membrane anatomically constitutes a compartment separate from the vascular compartment.

Over the last decade, there has been a paradigm shift in the treatment of PC. With advancements in surgical techniques, equipment, and postoperative care, cytoreductive surgery has become a viable option for the treatment of PC. The peritoneum is considered an intra-abdominal organ that is amenable to resection called Cytoreductive Surgery (CRS). In parallel, a complex peritoneal and intrabdominal organ resection can be achieved with less subsequent mortality. The development of the intraperitoneal route of heated chemotherapy administration (HIPEC) allows for direct contact between the tumour cells and the chemotherapeutic agent to control all residual microscopic disease. The development of CRS-HIPEC revolutionized the natural history of peritoneal tumours. This review will outline the rationale, current applications, complications and future directions of CRS-HIPEC.

Principles and Techniques

Surgery for peritoneal carcinomatosis started in the 1980 in Japan, and then became popular in Europe in late eighties and in USA in 1995 [5,14]. Currently, there are about 20 centres in USA performing CRS-HIPEC. Generally, the procedure is performed through a median laparotomy, providing exposure for a complete meticulous

exploration for peritoneal deposits followed by peritoneal and organ resection. After surgical removal of malignant disease, intra-abdominal hyperthermic chemotherapy is administered. Different grading tools were suggested to report the extent of PC; however, the most popular one is the Peritoneal Cancer Index (PCI) [15,16] (Figure 1). Complete cytoreduction is achieved when the largest residual deposit is <2.5 mm. In order for CRS to be successful, a thorough lysis of adhesions from prior surgeries is necessary for full exploration. Frequently, complete liver mobilization is also needed to evaluate the disease extension behind the liver. The peritoneum with wide visible disease is surgically resected, while limited disease can be destroyed by electro fulguration. The apparently normal peritoneum is left and treated only with HIPEC. The omentum is systematically resected as per the frequency of the presence of cancer cells on its surface even if it grossly appears to be free from malignant disease. Segments of the visceral peritoneum with disease extension to underlying viscera need to be resected in totality with the involved viscera. Other segments with superficial disease can be treated with electro fulguration followed by immediate cooling of the underlying viscera to avoid its injury. The peritoneal route of chemotherapy is based on the peritoneal plasma partition concept that allows a high concentration of the chemotherapy to be in direct contact with cancerous cells with minimal systemic absorption and side effects. The most commonly used chemotherapeutic agents are mitomycin-c, oxaliplatin, irinotican and cisplatin. The addition of heat to the chemotherapy potentiates the activity of some chemotherapeutic agents and increase diffusion of the chemotherapeutic agents between the cells [17-19]. Immediate application of intraperitoneal chemotherapy after the CRS controls the sub-millimetric disease and diffuses through two or three layers of cells before the formation of early physiologic postoperative adhesions where these cells can be trapped away from the reach of the chemotherapy. The abdominal wall can be left open or closed during the HIPEC therapy period. In the open technique, the abdominal wall is elevated to create a funnel to accommodate the heated chemotherapy that circulates through inflow and outflow lines attached to a pump and heating unit (Figure 2). In the closed method, the skin is temporary closed after placing the inflow and outflow tubing through separated incisions (Figure 3). The abdominal cavity is then filled with the HIPEC solution that circulates using a pump with a heating unit. The HIPEC part of the procedure usually last about 90 minutes (60-120 minutes) with continuous cycling chemotherapeutic agent, which is kept around 42°C through a heated pump (Figure 4). In summary the surgical procedure is subdivided into three main parts:

Figure 1: The Peritoneal Cancer Index is a summation of scores given for tumour implant size present in the 13 abdominopelvic regions. The sum or the PCI is used to estimate the likelihood of complete cytoreduction in patients with carcinomatosis.

Figure 2: In the open abdominal technique for HIPEC or the "Coliseum technique", the skin edges are secured to abdominal wall retractors. A plastic sheet is often incorporated into the suture to provide a partial barrier. The theoretical benefit is of the open technique is that the heated chemotherapy is more adequately distributed throughout the abdominal cavity.
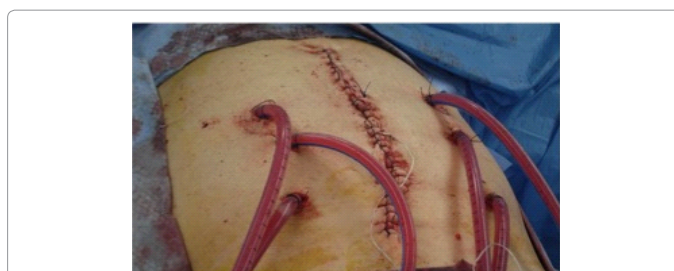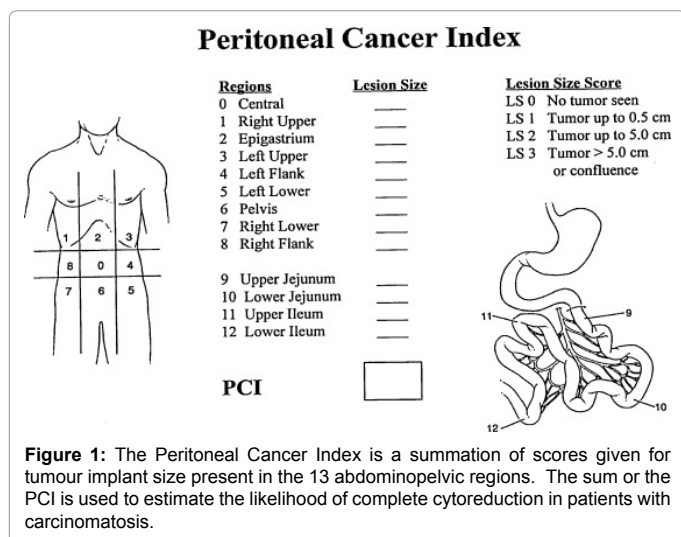

Figure 3: In the closed abdominal technique for HIPEC, catheter placments is the same, but the abdomen is sutured closed for creating a closed circuit for perfusion. The closed technique minimizes heat loss, maintaining hyperthermia during perfusion.

Figure 4: Laparoscopic approach to HIPEC.

1) Exploration, 2) Cytoreductive Surgery and 3) HIPEC. Only the HIPEC period has a fixed time limit from (60-120 minutes). The other two parts of the procedure are variable depending on the presence of adhesions and the extent of the disease, which may involve several abdominal organs requiring multiple resections. Generally speaking, the whole procedure time varies from 4-10 hours.

Current Applications and Results

The application of CRS-HIPEC therapy revolutionized the management of peritoneal carcinomatosis. For primary peritoneal tumours, malignant mesothelioma had a very poor prognosis in the past with median survival of 9-14 months. A multi-institutional registry study containing 405 patients (318 (79%) had epithelial tumours and 48 patients (12%) had biphasic or sarcomatoid tumours) demonstrated an overall median survival of 53 months and a 5-year survival of 47%. Variables associated with improved survival in the multivariate analysis included epithelial subtype (P<0.001), absence of lymph node metastasis (P<0.001), completeness of cytoreduction scores of CC-0 or

CC-1 (P<0.001), and HIPEC (P=0.002) [20]. In the case of peritoneal carcinomatosis from colorectal cancer, limited survival was obtained with the best systemic chemotherapy [21,22]. Several phase II studies of combined Cytoreductive surgery and Perioperative intraperitoneal chemotherapy have illustrated 3-year survival rates between 25-47% [23-25]. A randomized control trial conducted by the Netherland Cancer Institute comparing systemic fluorouracil and leucovorin and treatment with CRS-HIPEC demonstrated 2-year survival rates of 42% in the CRS-HIPEC group vs. 16% in the systemic chemotherapy group [12]. An international conference took place in 2006 to define the role and indications of HIPEC in colorectal cancer. According to these guidelines, CRS-HIPEC was recognized as the standard of care for PC dissemination from colorectal cancer provided the disease is limited to the abdomen and that a complete CRS can be achieved [26]. Pseudomyxoma Peritonei (PMP) originating from appendiceal mucinous neoplasms has an estimated incidence of approximately 1 person/million/year and is a biologically heterogenous disease [27]. The most widely accepted pathologic classification of PMP is the one proposed by Ronnett et al. [28], which proposed three subtypes of PMP with differing histology, biology and prognosis: (1) Disseminated Peritoneal Adenomucinosis (DPAM) (2) Peritoneal Mucinous Adenocarcinoma (PMCA) (3) Intermediate type PMP (PMCA-I). DPAM is a low-grade lesion, characterized by the presence of abundant mucinous ascites with scant cells with minimal atypical and rarely spread to lymph nodes or other organs. These typically have a good prognosis. On the other hand, PMCA is a high-grade adenocarcinoma that originates from appendix and colon and is characterized by abundant mucinous cells with histologic malignant characteristics and high metastatic potential. PMCA-I consists of peritoneal lesions that are predominantly composed of DPAM, but also contain focal areas of PMCA. In all the subtypes, the abundant mucinous ascites cause abdominal distention, pain and ultimately results in fibrosis that can cause bowel obstruction. Traditionally, treatment of this disease consisted of serial debulking and drainage of mucinous ascites. Gough et al. [29] reported a 10-year survival of 32% in a cohort of 56 patients with limited low-grade tumours who underwent surgical debulking. For mucinous adenocarcinoma, the 5-year survival after surgical resection was 6% [30]. A large multi-institutional trial demonstrated 10- and 15-year survival of 63% and 59%, respectively, after treatment with CRS-HIPEC for PMP [31]. Another study with 110 patients who underwent CRS-HIPEC had an overall 5-year survival of 53.4% across all histologic subtypes. DPAM and PMCA-I had higher 3-year survival rates (77% and 81%, respectively) when compared to PMCA (35%) [32]. It should be emphasized also that regardless of the survival benefit, a net improvement of the quality of life is obtained from the surgical management of these patients with dramatic improvement of abdominal distention, pain and bowel obstruction. For patients with diffuse peritoneal carcinomatosis from ovarian cancer, studies showed improved survival with five-year survival rate of 55% compared to the best non-surgical care with 0% survived at five years [33]. Similarly, Tentes et al. [34] demonstrated a 54% 5 year survival after CRS-HIPEC for advanced ovarian cancer. HIPEC for ovarian PC has proved to be a safe and effective therapy in conjunction with CRS or chemotherapy [35]. According to the current available data, it is evident that CRS-HIPEC has a beneficial role for patients with primary peritoneal cancer and peritoneal carcinomatosis of appendicular, colorectal and ovarian cancers. The results of these studies are dependent on the experience of the multidisciplinary team and the ability to achieve a complete surgical cytoreduction. Regarding peritoneal carcinomatosis from gastric cancer, the results of CRS-HIPEC are immature. Incomplete CRS does not provide any advantage for these patients and even complete CRS did not show the dramatic results obtained in the case

of mesothelioma or peritoneal carcinomatosis from colorectal cancer [14]. Earlier cohort studies have suggested that CRS plus HIPEC improved outcomes in patients with PC from gastric cancer [4,36,37]. A randomized prospective study demonstrated that CRS-HIPEC improved overall survival in gastric PC with acceptable morbidity and mortality (median overall survival in CRS only 6.5 months versus 11.0 months in CRS-HIPEC group, median follow-up 32 months) [38]. Yet, more prospective randomized clinical trials need to be performed to support this treatment strategy. For peritoneal carcinomatosis from the liver, bile duct and pancreas the role of CRS-HIPEC needs to be further elucidated and it is not currently indicated for these diseases.

Complications Related to CRS-HIPEC Therapy

As a major operation that may involve resection of multiple abdominal organs, CRS-HIPEC as expected, carries a considerable postoperative morbidity of 12-56% and a mortality of 0-12% [25,32,39-41] (Table 1). These complications can be grouped in three categories: A- Intra-abdominal leak abscess and fistula formation of about 15% (This is increased with the number of bowel resections and anastomoses). B- Abdominal wall morbidity related to wound infection, abscess and dehiscence/evisceration of about 15% (This is a consequence of impaired wound healing from the application of the HIPEC and potential CRS involving resection of abdominal wall deposits). C- Systemic complications (Including bone marrow suppression, sepsis and pulmonary complications related to the systemic effect of the absorbed peritoneal chemotherapy). From the surgical reductive point, two approaches aiming to decrease the rate of these complications need to be emphasized. First, the number of bowel segment resections should be minimized, favoring complete fulguration of minor deposits in bowel segments when applicable rather than resection. Secondly, in patients with a history of multiple prior abdominal surgeries, preoperative abdominal wall hernias or CRS involving the abdominal wall, the placement of a biomaterial mesh as adjuvant to abdominal wall closure to enhance the abdominal wall healing can minimize abdominal wall complications [42,43]. Finally, a multidisciplinary approach is crucial to discuss proper timing of the procedure and administration of neoadjuvant and adjuvant therapy, which is a critical component of this procedure. Few clinical trials have attempted to elucidate the role of neoadjuvent approaches. It is currently premature to report a universal agreement of when and what population will be benefited from neoadjuvant therapy. Generally, however, a patient who cannot be completely resected will receive neoadjuvent therapy. The recovery period is variable and is dependent on the extent of the resection, patient's age and comorbidities. Generally, the average length of stay for uncomplicated cases is 5-7 days. Most patients return to work one month postoperatively and return to baseline functional status within 3 to 6 months after CRS and HIPEC [44,45].

Future Directions

The diagnosis of small implants of PC by current radiological tools is limited. Rather patients present with radiological evidence of large deposits or more often with clinical complaints related to

Study (year)	N	Abdominal Wall Morbidity	Bowel and Intrabdominal Morbidity
Franko (2008)	65	10.7%	15.4%
Kianmanesh (2007)	43	11.6%	13.9%
Stewart (2006)	110	15.4%	6.3%
Sugarbaker (2006)	356	3%	5.47%
Witkamp (2001)	29	3%	3%

Table 1: Complications grouped in three categories.

the peritoneal carcinomatosis and abdominal organ involvement (abdominal distension, pain, bowel obstruction). No current data or guidelines exist today to answer this question. However, we know that the results of CRS-HIPEC are better when applied early in the disease process and it has been already described to offer a second look surgery for a selected group of patients identified as high risk for developing peritoneal carcinomatosis and to apply early/prophylactic HIPEC for these patients [46]. As per today, we do not have the results of such management in the long-term survival of these patients and currently randomized studies in Europe and USA are in process to demonstrate the role of prophylactic CRS HIPEC in colorectal cancer. CRS-HIPEC requires complete exploration of the abdominal cavity and potentially multiple resections of abdominal viscera rendering the laparoscopic approach of a limited value outside of the initial exploration. However, in selected group of patients with minimal CRS, or for the second look surgery and prophylactic HIPEC, laparoscopic HIPEC can be performed. The benefit of such approach includes the avoidance of a large abdominal incision with its related complications (about 15%). In addition laparoscopy is traditionally associated with less postoperative pain, shorter hospital stay and earlier returns to work activity.

Conclusion

CRS-HIPEC is a relatively new modality of management of patients with peritoneal carcinomatosis. A multidisciplinary approach plays a major role in patient selection, timing of the surgery, Perioperative therapy and is crucial to obtain favourable results. According to the current available data, the best results of CRS-HIPEC therapy are achieved in patients with primary peritoneal malignancy and/or only abdominal dissemination of colorectal, appendicular and ovarian cancer. Future directions include extending the indication to different types of cancers, the role of minimal invasive approach, and the use of prophylactic HIPEC for selected group of patients with the highest risk to develop peritoneal carcinomatosis.

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