Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy in the Management of Colorectal Peritoneal Metastasis

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KEYWORDS

- Peritoneal metastasis (PM) • Cytoreductive surgery (CRS)
- Hyperthermic intraperitoneal chemotherapy (HIPEC)
- Intraperitoneal chemotherapy (IP) • Peritoneal carcinoma index (PCI)
- CC score • R score

KEY POINTS

- Patients with peritoneal metastasis have poor prognosis and symptoms due to untreated peritoneal disease are common.
- Outcomes compared with patients with hematogenous metastasis receiving the same systemic chemotherapy continue to demonstrate a worse prognosis.
- Published data in patients treated with CRS + HIPEC reveal a survival benefit similar that observed in the surgical management of hepatic metastasis.
- Clinical trials will continue help optimize the management of patients with peritoneal metastasis.

INTRODUCTION

Since the 1990s, increasing evidence supporting the surgical management of peritoneal metastasis (PM) with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged, demonstrating improved survival and outcomes in highly-selected patients with several tumor histologies. The benefits of

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CRS and HIPEC (CRS + HIPEC) for colorectal cancer (CRC) have recently become a central focus in the literature. This article provides an overview of the mechanism of PM, the utility of CRS + HIPEC in, and outcomes of patients with CRC with using chemotherapy therapy alone compared with CRS + HIPEC in conjunction with chemotherapy.

BACKGROUND

Distant CRC metastasis develops from either hematogenous dissemination or direct seeding of the peritoneal space. Metastasis is a complex process that involves cellular proliferation, immune system evasion, epithelial-mesenchymal transition and invasion, endothelial adhesion at metastatic sites, endothelial translocation, and growth at metastatic sites.[1] Although the liver is the most common site of metastasis, 15% to 25% of patients with stage IV CRC present with isolated PM (CRC-PM).[2] Although the cellular and biological events necessary to establish PM are similar to hematogenous metastasis, PM occurs after serosal disruption or perforation of the primary tumor (T4) or capsular disruption of nodal disease. This results in microscopic tumor shedding that disperses throughout the abdominal cavity. The capacity for tumors to grow on the surface of different abdominal organs is linked to specific biological changes of the tumor and the extent of disease can range from adjacent disease near the T4 site to extensive dissemination to all peritoneal surfaces.

The management of PM with CRS was initially established for appendiceal malignancies, peritoneal mesotheliomas, and ovarian cancers. High peritoneal recurrence rates in these patient populations fostered an interest in the development of intraperitoneal (IP) therapies, including HIPEC. In all of these tumors, data have demonstrated that CRS + HIPEC can decrease peritoneal recurrence and prolong overall survival (OS).

Hyperthermia alone is cytotoxic to cancer cells and its effect is potentiated when combined with chemotherapy.[3] Administering chemotherapy into the peritoneal cavity permits higher concentrations of the drug to be delivered directly to tumor cells with less systemic toxicity due to the peritoneal-plasma partition. This same partition may also be a factor in the reduced systemic chemotherapy (SC) response observed in patients with PM.[4] Overall, HIPEC permits administration of concentrated doses of chemotherapy 20 to 50 times more concentrated than serum levels seen with SC.[5] Heat also decreases interstitial pressure, allowing for optimal diffusion of chemotherapy and increases cytotoxicity, preferentially killing susceptible tumor cells. Penetration depths of 2 mm are common but 5 mm is possible with therapies such as oxaliplatin.

It has also been identified that some characteristics of tumor cells, such as mucin production, may be a factor in the chemotherapy refractory nature of PM relative to hematogenous metastasis. Mucins are glycoproteins that may support tumor cells survival in the peritoneal cavity with minimal vascular support and is a common feature in patients with PM. Animal models have been a major tool in studying the efficacy and mechanism of IP and HIPEC therapy.[6–9]

VALUE OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN OTHER CANCERS

HIPEC has been used extensively in the management of appendiceal cancer with PM with a relatively large body of published data. Unfortunately, the low incidence of appendiceal tumors has been a barrier to conducting clinical trials. Evidence supporting the benefit of HIPEC in patients with low-grade pseudomyxoma peritonei was

reported by Smeenk and colleagues.[10] The investigators reviewed the literature and compared the outcomes of patients treated with CRS alone versus CRS + HIPEC. The 10-year survival for CRS alone was 21% to 32% with 3% to 12% of patients free of disease, whereas in the CRS + HIPEC group 10-year survival was 60% to 80%, with 55% to 74% of patients free of disease.

HIPEC has been used in patients with advanced or recurrent ovarian cancer for many years, and randomized clinical trials (RCTs) have demonstrated both a progression free survival (PFS) and OS benefit compared with subjects who received intravenous chemotherapy only following optimal cytoreduction.[11–17] One of these RCTs, published in 2001, showed that IP chemotherapy prolonged PFS from 22.2 to 27.9 months and OS increased from 52.2 to 63.2 months compared with intravenous chemotherapy alone. Regardless of intervention, most patients with ovarian cancer present with advanced disease and 5-year OS is less than 50%.[14] **Table 1** summarizes relevant studies on CRS + HIPEC for patients with advanced ovarian cancer.

PATIENTS WITH COLORECTAL CANCER WITH PERITONEAL METASTASIS TREATED WITH CHEMOTHERAPY ALONE

Natural History

The EVOCAPE-1 study explored and reported the outcomes of subjects with peritoneal disease from gastrointestinal primary tumors. In subjects with CRC-PM who received no treatment, the median and mean survival was less than 6 months.[18] The cause of death in these subjects was due to bowel obstruction, fistula, or malnutrition; indirect consequences of PM and not directly due to overwhelming cancer burden. Thus an opportunity to extend survival in CRC-PM starts by controlling the peritoneal disease burden and reducing or delaying these events.

Table 1
Benefits of cytoreductive surgery and heated intraperitoneal chemotherapy in patients with advanced ovarian cancer

Authors	Number of Subjects	Treatment or Group	Median OS (mo)	Median PFS (mo)
Markman et al,[12] 2001	227	IV Paclitaxel, then IV cisplatin	52.2	22.2
	235	IV paclitaxel, then IV carboplatin and IV paclitaxel and IP cisplatin	63.2	27.9
Armstrong et al,[13] 2006	210	Paclitaxel IV followed IV cisplatin	49.7	18.3
	205	Paclitaxel IV followed IP cisplatin	65.5	23.8
Deraco et al,[15] 2011	26	CRS + HIPEC w/cisplatin and doxorubicin then IV carboplatin and paclitaxel	NA 60.7% (5-y survival)	30 (15.2% 5-y survival)
Bakrin et al,[16] 2013	474	Recurrent OEC CRS + HIPEC	45.7	NR
Spiliotis et al,[17] 2015	60	CRS + HIPEC + SC	26.7	NR
	60	CRS + SC	13.4	NR

Abbreviations: IV, intravenous; NA, not applicable; NR, not reported; OEC, ovarian epithelial cancer.
Data from Refs.[12,13,15–17]

Outcomes with Chemotherapy

Outcomes for CRC-PM subjects treated with SC are summarized in **Table 2**. Chemotherapy based on 5- fluorouracil (FU) alone or in combination with other agents has been the primary treatment option for patients with CRC-PM.[19] Current regimens include 5-FU and leucovorin combined with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), as well as the possible addition of a biological agent such as bevacizumab or cetuximab. Clinical trials that established the benefit of these combinations have included both subjects with solid-organ metastases and with peritoneal disease. In general, survival has been shown to be worse for subjects with PM when compared with subjects who have solid-organ metastases and immeasurable peritoneal disease.[20–23] Both of these groups had improved survival when biological therapy was added.

CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY FOR COLORECTAL CANCER

Basic Principles

Patient selection for CRS + HIPEC is driven by the same principles in patient selection for the resection of metastatic disease to the liver. The 2 major factors include patient fitness for surgery and the ability to achieve a complete resection. To assess the overall burden of disease, scoring systems have been developed to help both select patients and help predict the relative benefit of CRS + HIPEC. The peritoneal carcinomatosis index (PCI) is a tool that measures disease burden. It can be determined radiographically before surgery with either computed tomography or MRI but is most accurately reported intraoperatively. The PCI divides the abdomen and pelvis into 13 domains, 4 of which are reserved for the small bowel. Disease severity in each domain is scored from 0 to 3, for a maximum score of 39, with higher scores associated with a worse prognosis. The PCI is predictive of long-term operative outcomes, and is used to select appropriate surgical candidates and evaluate response to chemotherapy.[24,25]

Once PCI is known, the next question is whether the tumor burden can be adequately cytoreduced. Two scoring systems commonly used are the completeness of cytoreduction score (CCS) and R score. The CCS was developed by Sugarbaker[25] as a scoring system for patients with PM. Scored CC-0 to 3, the CC score estimates the amount of residual disease at the completion of surgery. CC-0 denotes no visible residual disease, CC-1 if less than 2.5 mm in size, CC-2 for residual disease 2.5 mm to 2.5 cm in size, and CC-3 for anything larger than 2.5 cm.[25] R scoring is more widespread, with R0 indicating complete cytoreduction with negative margins, R1 indicating microscopically positive margins but no visible residual disease, and R2 indicating gross disease left behind. In the setting of residual disease, this is divided into R2a if less 5 mm, R2b if greater than 5 mm or less than 2 cm, and R2c if greater than 2 cm. Similar to the PCI, the CCS and R scores have been shown to be predictive of outcomes.[26]

Technical Details

CRS + HIPEC is typically performed for a highly selected group of patients. These patients typically have documented CRC and peritoneal carcinomatosis in the absence of solid-organ metastases. When these patients are identified, they will start with neoadjuvant SC, after which they are restaged to confirm there has not been any progression of disease. This prevents unnecessary operations for patients whose aggressive tumor biology negates the benefits of surgery.

Table 2
Outcomes with chemotherapy

Authors, Year	Subjects	Group	Treatment Regimen	PM (mo) Median OS	No PM (mo) Median OS
Klaver et al,[22] 2012 (CAIRO-1)	401	Sequential treatment	1st line: capecitabine 2nd line: irinotecan 3rd line: capecitabine + oxaliplatin	10.4	16.8
	402	Combination treatment	1st line: capecitabine + irinotecan 2nd line: capecitabine + oxaliplatin	7.8	17.9
Klaver et al,[22] 2012 (CAIRO-2)	192	Without cetuximab	Capecitabine + oxaliplatin + bevacizumab	15.2	21.4
	197	With cetuximab	Capecitabine + oxaliplatin + bevacizumab + cetuximab	13.9	20.4
Franko et al,[20] 2012 (N9741 and N9841)	2095	FU	Fluorouracil	12.7	17.6
		IFL or IRI	Irinotecan leucovorin, and fluorouracil or irinotecan		
		IROX	Irinotecan and oxaliplatin		
		FOLFOX	IV 5-FU, leucovorin, and oxaliplatin		

Data from Klaver YLB, Simkens LHJ, Lemmens VEPP, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. Eur J Surg Oncol 2012;38(7):617–23; and Franko J, Shi Q, Goldman, CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J Clin Oncol 2012;30(3):263–7.

HIPEC can be administered through either an open or a closed approach. Both techniques involve placement of inflow and outflow catheters connected to a perfusion device. The perfusion device heats the solution and circulates the solution through the inflow tubes with passive outflow drainage. Typically, a volume of 3 to 5 L is used and the level of hyperthermia achieved in the solution is typically 39.5° to 42.5°C. Perfusion is typically performed for 60 to 120 minutes.

The open approach, although less common, allows the surgeon to manipulate internal organs to disperse chemotherapy throughout the peritoneal cavity and perform concomitant debulking. Although the open technique is safe, most institutions perform HIPEC with the closed technique. One concern many HIPEC providers have to consider when establishing the procedure at a new facility is the perceived potential for chemotherapy exposure. Stuart and colleagues[27] demonstrated that there is no significant risk of exposure with the open technique. The closed method does circumvent the theoretic exposure risk and it involves temporarily closing the skin before HIPEC administration with gentle external agitation of the abdomen to distribute the chemotherapy.

Agents Used

In the United States, mitomycin C (MMC) is the most common drug used during HIPEC. It can be administered in 2 ways. The first is a standard 30 mg dose for the first 60 minutes with an additional 10 mg given for the next 30 to 60 minutes. The second is based on body surface area and is commonly dosed at 15 mg/m^2. Oxaliplatin has recently become more prominent as monotherapy. It is typically dosed around 460 mg/m^2.[28]

OUTCOMES OF CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN COLORECTAL CANCER

Reports demonstrating the value of CRS + HIPEC in CRC-PM began to emerge in the 1990s. Most of the literature has emerged from a small group of highly specialized CRS + HIPEC enthusiasts. Results from the first RCT were published in 2003,[19] comparing CRS + HIPEC to SC alone (5-FU monotherapy). Palliative surgery for subjects in the SC-only arm was performed if needed, including bowel resection or stoma creation. HIPEC was performed in an open fashion over 90 minutes, with perfusate heated to 41° to 42°C, consisting of 17.5 mg/m^2 of MMC followed by 8.8 mg/m^2 every 30 minutes up to 70 mg. A minimum of 3L of perfusate was used with flow rates varying from 1 to 2 L/min. In this study of 105 subjects, SC median OS was 12.6 months and CRS + HIPEC improved the median OS to 22.4 months ($P = .032$). Completeness of cytoreduction and extent of disease were predictive of outcomes after CRS + HIPEC. Specifically, subjects in whom an R0/R1 resection was achieved had a 3-year survival of 95%.

In 2008, the investigators published 6-year follow-up data from the original study to report the long-term outcomes of CRS + HIPEC. The initial survival advantage was maintained with a 12.6 month median OS in the SC-only group and 22.2 months in the HIPEC group, identical to the previous results. In addition, the 5-year survival was 45% for an R0/R1 resection, demonstrating that the long-term survival benefits of CRS + HIPEC are similar to the outcomes reported in hepatic resection for CRC liver metastasis (LM).[29]

A 2009 retrospective case-control study focused on 48 CRS + HIPEC in CRC-PM subjects treated with contemporary chemotherapy regimens, including FOLFOX or FOLFIRI, and compared the outcomes to 48 historical controls with SC only. Optimal

debulking was achieved in all 48 subjects. Although there were no significant differences in the chemotherapy regimens received, the CRS + HIPEC with SC group had a significantly longer survival with median OS of 62.7 months versus 23.9 months in subjects who received SC alone. Five-year survival rates were significantly higher in the CRS + HIPEC with SC group at 51% compared with 13% in the control arm ($P<.05$). No statistically significant differences in baseline subject characteristics were noted between the 2 arms other than there being older subjects in the control arm (51 years vs 46 years, $P = .01$). Tumors in the operative group were more frequently well-differentiated ($P = .02$).[28]

A 2010 multicenter French study analyzed 523 subjects who underwent CRS + HIPEC for CRC-PM, excluding appendiceal malignancies. For subjects undergoing CRS + HIPEC, median OS was 30.1 months with 5-year survival of 27%, comparable with previous studies. In this study, complete cytoreduction was obtained in 84% of subjects and predictors of a prolonged survival included complete cytoreduction, limited disease, no nodal involvement, and adjuvant SC.[30,31]

Outcomes for CRC-PM treated with CRS + HIPEC are outlined in **Table 3**. CRS + HIPEC has been shown to improve median OS by 12 to 40 months and it is associated with a 5-year OS of 27% to 45%, similar to survival rates reported for surgical resection of LM.[19,29,32–40]

The Role of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Patients with Both Peritoneal and Liver Metastasis

The liver is the most frequent site of metastasis in patients with CRC and patients with PM do present with synchronous LM. Few studies have investigated the utility of simultaneous resection of both LM and PM, and they have included a very small number of subjects because traditionally patients with solid-organ metastasis have been excluded from case series.

A 2013 systematic review demonstrated that survival for subjects treated with simultaneous resection for LM and PM (median OS 6–36 months) was shorter than subjects undergoing surgery for isolated PM (median OS 19–62.7 months). However,

Table 3
Outcomes for colorectal cancer present with isolated peritoneal metastasis treated with cytoreductive surgery and heated intraperitoneal chemotherapy

Author, Year	Number	Median OS (mo)	5-y Survival (%)
Verwaal et al,[19] 2003; Verwaal et al,[29] 2008	105	22	45
Glehen et al,[32] 2004	377	32	40
da Silva,[33] 2006	70	33	32
Shen et al,[34] 2008	121	34	26
Chua et al,[35] 2009	60	33	NA
Franko et al,[36] 2010	67	34	26
Elias et al,[30] 2010	523	30	27
Elias et al,[37] 2011	146	41	42
Ung et al,[38] 2013	211	47	42
Chua et al,[39] 2013	663	33	43
Esquivel et al,[40] 2014	705	41	58

Abbreviation: NA, not applicable.
Data from Refs.[19,29,30,32–40]

OS was superior to subjects who received SC only (median OS 5.2–23.9 months), demonstrating that simultaneous resection of LM and PM may be of benefit[41] for a highly selected group. Factors worthy of future investigation include the size, number, and location of lesions.[42]

Morbidity of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

In general, CRS + HIPEC is a very complex procedure with high rates of associated complications, including major morbidity rates as high as 62% and mortality rates up to 10%.[43] This has limited the enthusiasm for CRS + HIPEC among some members of multidisciplinary cancer teams because the rewards from the procedure must obviously outweigh the risks. One of the oncologist's biggest fears is that patients who experience complications will require a significant break from SC, allowing for significant disease progression.

An up-to-date, single-center study from Roswell Park demonstrated that CRS + HIPEC can be safe overall when performed by experienced surgeons.[44] These investigators reported a 60-day mortality rate of 2.7% (3 out of 112 subjects). Although they did not report an overall morbidity rate, surgical site infection was encountered in 26% of subjects, with 5.3% having cardiopulmonary complications, and a 6.3% rate of unplanned return to the operating room. For subjects with CRC-PM, the investigators reported a 5-year OS of 38%.

A 2013 retrospective, single-center study from Wake Forest reported an overall morbidity of 62% with a mortality rate of 7.7%.[45] This group found that functional status, including Eastern Cooperative Oncology Group (ECOG) scores and health-related quality-of-life scores, was predictive of outcome. The same group looked at quality of life after CRS + HIPEC, demonstrating that emotional wellbeing is improved after surgery, despite high rates of morbidity, and that subjects return to their baseline level of function after 3 to 6 months.[46]

CONTROVERSIES AND ONGOING STUDIES

CRS + HIPEC is slowly gaining momentum as a viable treatment option for select patients with CRC-PM. However, there is still a great deal of variation in the components of HIPEC, including the chosen chemotherapeutic agents, dosage, the temperature of the circuit, and the duration of perfusion. Although most US centers use mitomycin as first-line therapy, oxaliplatin is still used in many European centers in conjunction with systemic administration of 5-FU.

To try and answer the question of which chemotherapy agent is more effective, the American Society of Peritoneal Surface Malignancies conducted a retrospective review of 15 international databases comparing the OS in patients who underwent CRS + HIPEC with oxaliplatin versus MMC. Although the median OS of the 539 subjects with complete cytoreduction was not significantly different between the oxaliplatin cohort versus the MMC cohort, subjects with low PCI scores had significantly longer survival in the MMC cohort (54.3 months vs 28.3 months, $P = .012$).[47] Given the retrospective nature of this study, further prospective studies comparing chemotherapy agents and duration of therapy are warranted.

Another area of debate is the value of HIPEC following optimal CRS, and whether every patient requires HIPEC. Recently, a French multicenter randomized controlled trial, Prodige 7, was designed to evaluate this question, randomizing subjects with complete cytoreduction to CRS alone versus CRS + HIPEC with oxaliplatin. This trial has recently met accrual and the outcomes are pending.

Another area of interest is defining the role of adjuvant CRS + HIPEC in patients with colon cancer at high risk of PM. One theory is by exploring high-risk patients with second-look surgery, occult disease may be identified and early CRS + HIPEC can be performed based on the detection of disease. Elias and colleagues[37] conducted an interesting prospective trial that conducted systematic second-look surgeries plus HIPEC in 41 asymptomatic subjects previously treated for their primary colorectal tumors who were deemed to be high risk for development of carcinomatosis. Subjects were considered high-risk if they met 1 of the following criteria found at the index operation: (1) macroscopically visible and completely resected carcinomatosis, (2) ovarian metastasis, or (3) perforated tumor. After surgical resection of the primary tumor, these subjects received adjuvant FOLFOX or FOLFIRI chemotherapy regimens for 6 months. After systemic therapy was complete, if there were no symptoms, nor radiologic evidence of recurrence, nor tumor marker elevation, subjects were taken for a second-look laparotomy. Remarkably, macroscopic peritoneal carcinomatosis (median PCI 7.8) was discovered in 56% of the cohort and an R0 resection with HIPEC was performed in all subjects. Long-term results have not yet been published but at a median follow-up of 30 months, 5-year OS was 90% and 5-year disease-free survival was 44%.[37]

A second theory is to treat all high-risk patients early, with no disease burden in high-risk patients, in an effort to prevent the establishment of bulky peritoneal disease. The ProphyloCHIP randomized controlled trial is currently being undertaken in France to evaluate whether systematic second-look surgery plus HIPEC improves disease-free survival and OS in high-risk patients. A similar trial, COLOPEC is a randomized trial currently being conducted at 9 Dutch HIPEC centers to investigate the effectiveness of adjuvant HIPEC in preventing the development of peritoneal carcinomatosis in patients who underwent curative resection for T4 or intra-abdominally perforated colon cancers. Subjects will be randomized to adjuvant HIPEC followed by routine SC in the experimental group versus routine SC in the control group. Primary endpoint is disease-free survival and diagnostic laparoscopy will be performed in all subjects at 18 months if no evidence of disease recurrence on clinical or radiographic examination.

SUMMARY

Similar to the management of hepatic metastasis, a subset of patients with PM can achieve long-term survival when complete resection of all visible disease is possible. CRS + HIPEC can be performed safely and the number of centers offering CRS + HIPEC is increasing worldwide. With increased adoption of CRS + HIPEC, multi-institutional research efforts to improve patient selection and optimize timing of intervention will improve outcomes for patients with CRC-PM.

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