Treatment of Peritoneal Carcinomatosis of Colorectal Origin

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OVERVIEW

The management of peritoneal carcinomatosis from colon cancer remains a controversial issue. Peritoneal carcinomatosis is associated with worse survival and has led to an aggressive treatment that combines surgery and intraperitoneal chemotherapy (IPC). This review will describe the rationale behind this treatment and the current controversy surrounding it.

Metastatic colon cancer is generally considered incurable except for the setting of metastases that are isolated to the liver or lung and can be resected. During the last 20 years, there has been a marked improvement in the survival of patients with metastatic colon cancer because of the development of multiple anticancer drugs such as irinotecan, oxaliplatin, antivascular endothelial growth factor therapy, and anti-epidermal growth factor receptor therapy. When fluorouracil (5-FU) was the only available chemotherapy, the median survival and 5-year survival were 12 months and 1%, respectively.1 With the advent of combination chemotherapy and multiple lines of therapy, the median survival is now approximately 2 years and the 5-year survival is greater than 20%.2 Moreover, for those patients with disease isolated to the liver or lung that can be surgically resected, 20% to 40% of patients can be cured by complete resection of these metastases.

In response to these challenges, investigators have attempted to treat patients with isolated peritoneal carcinomatosis using cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Earlier studies estimated that peritoneal carcinomatosis occurs as the sole site of disease in as many as 25% of patients, but a recent study evaluating the subset of patients with peritoneal carcinomatosis in the North Central Cancer Treatment Group studies 9741 and 9841 demonstrated that 17% of patients (364 of 2,101) enrolled in these two studies had peritoneal carcinomatosis as a component of multisite disease, and only 2.1% of patients (44 of 2,101) had peritoneal carcinomatosis as the sole site of disease.3 Although the topic of CRS and HIPEC is often debated, the applicability to the management of metastatic colon cancer is uncommon.

METASTATIC COLORECTAL CANCER AND PERITONEAL CARCINOMATOSIS

Peritoneal carcinomatosis is regarded by the patient and physician as one of the most feared ways that colon cancer metastasizes. From a patient’s perspective, the presence of peritoneal metastases is not considered curable unlike resectable liver or lung metastases. Additionally, the presence of peritoneal carcinomatosis is associated with a worse overall survival compared with patients who lack any peritoneal carcinomatosis.3 Additionally, peritoneal carcinomatosis is associated with a high symptom burden including nausea, vomiting, abdominal pain, bloating, and intestinal obstruction. From the doctor’s perspective, these symptoms are often very difficult to control because of carcinomatosis and lead to frequent hospitalizations.4 The degree of symptom burden often precludes the use of standard chemotherapy regimens because of the poor performance status of the patient.5

CYTOREDUCTIVE SURGERY AND INTRAPERITONEAL CHEMOTHERAPY

CRS was introduced with the goal of removing all gross disease and, thus, prolonging survival.6 CRS involves surgical resection of visible disease in the abdomen and pelvis (including visceral organs if involved by tumor). The extent of disease is assessed at initial exploration by the surgeon using a peritoneal cancer index (PCI), as initially described by Sugarbaker et al.7 The abdominal cavity is divided into a grid of nine squares and the small bowel mesentery is separated into four quadrants; each grid or quadrant is scored, based on disease burden, on a scale of zero (no gross disease) to three (extensive disease). Therefore, the extent of disease can range from zero to 39; patients with a PCI of greater than 30 are generally thought to have a low likelihood of having a complete gross cytoreduction. After cytoreduction, a completeness of cytoreduction score (CCR) is then assigned. A CCR of zero signifies that no gross disease remains after CRS, whereas,
a score of one indicates that tumor nodules remain but are all 2.5 mm or less in diameter. Residual disease that is greater than 2.5 mm in diameter is assigned a CCR of two or three depending on the size and extent of the tumor left behind. Cytoreduction is considered to be therapeutic when a CCR of zero or one is obtained, and has been shown to be independently associated with improved survival.\(^9\) However, even with optimal cytoreduction, microscopic disease may be left behind. IPC was, therefore, developed to deliver regional chemotherapy into the peritoneal cavity, thereby attempting to eradicate the remaining microscopic disease.

The initial use of IPC was delivered in the postoperative setting and is known as EPIC (early postoperative IPC). In this approach, a catheter is placed intraoperatively and chemotherapy is administered into the peritoneum on several subsequent postoperative days. The drug most commonly used is floxuridine, which is a fluorinated pyrimidine analog of 5-FU. Although initial reports were promising, there were theoretical concerns of EPIC being unable to perfuse all peritoneal surfaces because of the onset of fibrosis and adhesions. Indeed, after a few cycles, many patients developed nausea, abdominal distension, and pain thought to be related to adhesions.

The advantage of IPC is that it enables the delivery of much higher doses of chemotherapy directly to the cancer cells than could be achieved systemically. First pass hepatic extraction of floxuridine is high, and, thus, high concentrations of floxuridine can be delivered into the peritoneum without substantial systemic absorption and toxicity.\(^8\) For these reasons, many centers have explored and utilized IPC with EPIC after CRS since the early 1990s. To date, however, there are no randomized clinical trials that support its benefit.\(^9\)

In an attempt to improve upon delivery of IPC, intraoperative delivery of heated chemotherapy was developed. HIPEC offers several theoretical advantages. First, it is given during the time of surgery, which minimizes the risk for adhesions. Second, the heated chemotherapy is thought to have increased cytotoxicity based on animal and preclinical data.\(^10-12\) Of note, a recent study using a rat model showed no benefit to HIPEC.\(^13\)

There were two randomized studies of HIPEC compared with systemic chemotherapy. In the first, Verwall and colleagues randomly assigned 105 patients younger than age 71 to CRS plus HIPEC (using mitomycin C) or systemic therapy (using 5-FU/leucovorin) alone. The patients treated with CRS plus HIPEC had an improved median survival of 22.4 months compared with 12.6 months (p = 0.032).\(^14\) Unfortunately, this study was conducted in the era of 5-FU therapy alone. The incremental survival benefit of 10 months is equivalent to what would be expected with modern systemic chemotherapy using oxaliplatin and irinotecan. Furthermore, the patients were not stratified based on prior 5-FU exposure, so it is not known whether they benefitted or progressed on 5-FU alone. Of the 105 patients, 18 (17%) had appendiceal tumors, which have variable histologies and can at times be more indolent than typical colorectal adenocarcinomas. Second- or third-line chemotherapy with oxaliplatin or irinotecan was not recorded, thus, we cannot learn if these subsequent regimens had an effect on outcome. Additionally, an important difference is noted between median survival of patients in the surgical arm between those who had limited peritoneal disease (29 months) and those with extensive disease (5 months). In the surgical group, 8% of patients died from postoperative complications. In a follow-up publication by Verwall et al with a median follow-up of 8 years, four out of 51 patients were alive in the systemic arm and five out of 54 in the CRS plus HIPEC arm.\(^15\)

The second randomized study was attempted by the French group, Elias and colleagues. Unfortunately, it was terminated early before reaching the target accrual of 90 patients because of poor accrual. Thirty-five patients were randomly selected to receive CRS plus EPIC or CRS alone. EPIC did not appear to improve outcomes, but patients with CCR0 had a 60% 2-year survival.\(^16\)

There are no randomized trials comparing HIPEC with EPIC. Elias et al reported a large retrospective cohort study of 523 patients from 23 centers who were treated with CRS and either HIPEC or EPIC.\(^17\) The median survival was 30.1 months. The overall 1-year, 3-year, and 5-year survival rates were 81%, 41%, and 27%, respectively with a median follow-up of 45 months. The rate of grade 3 to 4 complications was 31% and the death rate was 3.3%. Multivariate analyses revealed that the only factor that correlated significantly with overall survival was the PCI index (p < 0.0001). The use of adjuvant systemic chemotherapy and lymph node status (p = 0.02) were noted but did not reach statistical significance.

In a systematic review of CRS IPC studies and case reports before March 2006, Yan and colleagues reported that 5-year survival rates varied from 11% to 19%. Patients who received complete cytoreduction benefitted most with median survivals between 28 months to 60 months and 5-year survival ranging from 23% to 44%.\(^18\) Interestingly, Chua and col-

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**KEY POINTS**

- Isolated peritoneal carcinomatosis related to colorectal cancer occurs infrequently and is associated with a poor prognosis.
- Therapeutic cytoreduction may be achieved using systemic chemotherapy and/or cytoreductive surgery (CRS) and intraperitoneal heated chemotherapy (HIPEC).
- Optimal management of peritoneal carcinomatosis is determined by a multidisciplinary care team (medical oncologist and surgeon).
- Stringent selection criteria for patients undergoing CRS/HIPEC may reduce associated morbidity and mortality.
- The timing of CRS/HIPEC should be coordinated by the multidisciplinary care team.
leagues performed a meta-analysis of all CRS HIPEC cases performed between 1995 to 2009. In patients with complete cytoreduction (722 patients) the median overall survival was 33 months (range, 20 months to 63 months) and the median 5-year survival rate was 43% (range 20% to 51%). In contrast, the patients with incomplete cytoreduction had a much poorer outcome with a median overall survival of only 8 months and a 5-year survival of 0%. These findings strongly suggest that appropriate patient selection is key in the success of CRS and IPC.

It is evident that surgically rendering patients free of all disease is associated with an increased chance of cure for patients with isolated liver or lung metastases. Therefore, it is reasonable to conjecture that some patients with isolated and/or limited peritoneal metastases can be resected for cure. Although the surgical series suggest that this may be the case, it is difficult to tease out the independent effects of CRS from IPC since they are given concurrently. A well-designed multicenter randomized controlled trial by the Walter Reed Army Medical Center and the American College of Surgeons (ACOSOG-Z6091) attempted to answer this question, but unfortunately, closed to accrual 1 year after opening in 2011. The primary reason for failure to accrue was patients’ perception that randomization to an arm without IPC was unacceptable.

A second French multicenter randomized controlled trial (Prodige 7) recently completed accrual. In this trial, 280 patients with colorectal carcinoma underwent CRS and were randomly selected to receive HIPEC with oxaliplatin over 30 minutes at a minimum of 42°C and preceding intravenous 5-FU/leucovorin bolus or no HIPEC). Data analysis is ongoing. The primary endpoint is 3-year and 5-year overall survival. It is noteworthy that most investigators use mitomycin C as the HIPEC regimen and not oxaliplatin. Thus, the results of this trial might not change their clinical practice. Nevertheless, the results, which are expected to be reported this spring, are eagerly awaited.

MORBIDITY AND MORTALITY
The morbidity and mortality of CRS plus IPC are substantially higher than those of either systemic chemotherapy or CRS alone and should be addressed. In retrospective reviews, the range of postoperative mortality has been reported to range from 0% to 12%. In the two largest studies, including the Dutch randomized study, the range was 3% to 8%. Grades 3 and 4 toxicities have been reported in between 23% to 55.6% of patients, including respiratory complications, septic shock, and pulmonary embolism. Hematologic toxicity including hemorrhage, fistulae, peritonitis, cerebral stroke, and renal insufficiency were the most common complications. In addition, there is a steep learning curve associated with performing CRS/ HIPEC, requiring approximately 140 procedures to develop expertise. Similarly, a more recent study found that approximately 180 and 90 CRS/HIPEC procedures are required to improve operative and oncologic outcomes, respectively. These data exemplify the importance of developing well-organized, multidisciplinary teams that consists of surgeons, perfusionists, anesthesiologists, intensivists, nutritionists, oncologists, and nurse specialists to work together in lowering the associated morbidity and mortality of CRS/HIPEC procedures.

Stringent patient selection is also critical to optimizing operative and oncologic outcomes of patients undergoing CRS/ HIPEC. Patients older than 70 and those with significant comorbidities have higher rates of perioperative morbidity and mortality after CRS/HIPEC. To avoid treatment-related morbidity and mortality associated with CRS/ HIPEC, high-risk patients may be offered alternative treatments such as systemic therapy alone or CRS alone, particularly in the absence of prospective data that demonstrates the superiority of CRS/HIPEC. The timing of surgery also affects patient outcomes. To coordinate the timing of CRS/ HIPEC, patients with metastatic disease confined to the peritoneal cavity should be seen by both the experienced CRS/ HIPEC surgeon and the medical oncologist at the time of diagnosis of carcinomatosis or isolated peritoneal disease recurrence. Considerations that influence the timing of CRS/ HIPEC include response to systemic chemotherapy, availability of chemotherapy options, and the emergence of treatment-related toxicities. Treatment with effective systemic chemotherapy prior to CRS/HIPEC provides the advantage of reducing the bulk of disease identified at surgery, and, thereby, potentially lowering the initial PCI at the time of CRS/HIPEC.

CONCLUSIONS AND FUTURE DIRECTIONS
Although the data are difficult to interpret because of the lack of large randomized studies and the presence of numerous institutional series, CRS and IPC may provide a benefit to a certain subset of patients with peritoneal carcinomatosis of colorectal origin. The data available do demonstrate that the extent of peritoneal disease greatly affects outcomes. It is conceivable that patients with limited peritoneal disease that can be completely resected (CCR0) may experience a cure, but it is more likely that they will at least achieve better control of disease. The question remains whether the benefit is derived from CRS alone or the addition of IPC. Moreover, if IPC is helpful, it remains debatable whether HIPEC or EPIC is the best route. The French Prodigie study will hopefully provide insight into the benefit of adding IPC to CRS. An ongoing study at Memorial Sloan Kettering Cancer Center is evaluating CRS plus HIPEC compared with EPIC in patients with peritoneal carcinomatosis of colorectal or appendiceal origin. As is the case with most therapies, molecular and genetic profiling may identify patients who would benefit from regional therapies. Until these predictive profiles are identified, the optimal approach for patients with peritoneal carcinomatosis will remain controversial.
Disclosures of Potential Conflicts of Interest

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References


