Gastrointestinal Cancers With Peritoneal Carcinomatosis: Surgery and Hyperthermic Intraperitoneal Chemotherapy

This review focuses on the underlying rationale for the use of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CS + HIPEC) in the treatment of patients with primary gastrointestinal tumors with metastatic peritoneal disease.

Introduction and History

The senior author (BWL) began studying gastrointestinal (GI) cancers with peritoneal carcinomatosis and malignant ascites in 1992, and he published early findings on the use of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CS + HIPEC) for these cancers shortly afterward. Clinical studies of CS + HIPEC were driven by the extreme clinical frustration experienced as a result of the lack of good treatment options for these patients. Peritoneal dissemination was, and is, classified as M1 or stage IV disease (Figure 1A and 1B). At that time, the only active chemotherapy agent in broad use was fluorouracil (5-FU), with or without leucovorin. The poor overall clinical responses to systemic chemotherapy seen in these patients stood in stark contrast to the more favorable response rates with chemotherapy (albeit using different agents) in the treatment of stage III ovarian cancer. For chemotherapy-naive patients with metastatic colorectal cancer, clinical responses were around 25%, with less than 5% of patients exhibiting complete responses. It has been demonstrated that the responses to treatment with 5-FU seen in colorectal cancer with peritoneal carcinomatosis were worse than for other forms of metastatic spread, such as liver or lung, that received the same treatment, and survival was poorer as well. At that time, medical oncologists agreed that they had little to offer patients with peritoneal carcinomatosis, and nothing with a reasonable or consistent chance of prolonged survival. The observed natural history of the disease was grim. For patients with symptomatic obstruction or ascites, 6-month survival was unlikely. Even among patients who were asymptomatic and had low-volume disease, the vast majority were unlikely to survive 1 to 2 years. The results for attempted salvage surgery alone were equally bad, with high postoperative mortality and 50% disease-related mortality at 3 to 6 months postoperatively.

It could be argued that these earlier descriptive series represented outcomes based on generally more advanced disease, and also represented an earlier “surgical era” of patient care. However, a prospective multi-institutional study from France known as EVOCAPE I was published in 2000. The purpose of this study was to assemble a team from multiple institutions who could uniformly report staging in patients who underwent CS but no HIPEC. The investigators used a uniform postoperative staging system that had been proposed by François Gilly and colleagues from Centre Hospitalier Lyon-Sud (France), and they reported follow-up survival data. Patients underwent conventional surgical therapy and received systemic chemotherapy (including with oxaliplatin, available in France then[]), which was standard treatment for that time and place. Tumor debulking was performed, but patients received neither intraperitoneal (IP) chemotherapy nor HIPEC. The important and striking fact about this study was that in those patients with documented complete gross removal of disease, there were no long-term (5-year) survivors. Indeed, for this best-outcome group, 2-year survival was only 10%. That same year, Loggie et al published results of a prospective, National Institutes of Health–funded clinical treatment trial that showed an overall 5-year survival of 35% in patients with GI peritoneal carcinomatosis treated with CS + HIPEC.[7] Both studies showed that the presence of malignant ascites had a notable negative impact on survival.

Rationale for the Use of CS + HIPEC

Because the use of surgery or chemotherapy alone or as metachronous therapy had failed in the
past, CS + HIPEC was conceived as a form of combined-modality therapy to be simultaneously administered in a surgical setting. Surgery clearly would yield the most accurate staging, since all scanning modalities can often underestimate the extent of peritoneal carcinomatosis. Surgery was also the only method that could reduce the tumor and address issues of bowel obstruction or ascites. Thus, CS was conceived of as preliminary to and necessary for HIPEC.

The rationale for HIPEC stemmed from the potential benefits described for IP therapy—namely, very high drug concentrations in contact with floating tumor cells and at-risk lining surfaces, with limited drug absorption, thereby enhancing tumor drug exposure but limiting systemic toxicity. With mitomycin C, we demonstrated peak IP concentrations that were about 50-fold higher than peak serum levels.[8] Only HIPEC, or IP administration, is capable of achieving such high drug concentrations in vivo.

The plan called for HIPEC to be performed immediately following tumor debulking, in the operating room.[9] The tumors in question can sometimes recur rapidly in the postoperative period, mitigating benefit, as was suggested earlier by the ineffectiveness of surgery alone. Thus it seemed logical to introduce the IP chemotherapy element as soon as possible. The tumor nadir following CS is at the end of debulking, providing justification for immediate HIPEC.

Because of the time duration constraints of intraoperative administration of chemotherapy, hyperthermia was used in order to increase the intensity of therapy. The rationale for the use of hyperthermia grew out of strong basic research but had not been validated in practice, and has not been since. The decision to use hyperthermia resulted in the selection of agents for which heat was found to be synergistic in the laboratory, such as mitomycin C or cisplatin.

Another benefit of HIPEC is the limited systemic uptake of IP chemotherapy, which results in less systemic toxicity. Surgery adds a layer of complexity to patient care, and it was hoped that early chemotherapy that might have a negative impact on early postoperative outcomes might be limited. We wished to avoid major chemotherapy-related systemic toxicities, such as neutropenia or thrombocytopenia, in the early postoperative period. Variable degrees of bone marrow suppression have been demonstrated in a variety of series involving CS + HIPEC. Fortunately, however, only a small percentage of patients were seen to have grade IV marrow suppression in early clinical trials. Not surprisingly, systemic drug levels corresponded with systemic side effects. What was not entirely expected was a demonstration of improved long-term survival in patients with increased systemic drug exposure during HIPEC with mitomycin C.[10] Thus, the systemic uptake may be an important component of HIPEC treatment. This question is deserving of further study.

**Importance of Patient Selection**

Unfortunately, there are few formal guidelines for the selection of patients for CS + HIPEC. A consensus statement by surgical oncologists was published several years ago on the selection of patients with colorectal and appendiceal cancers.[11]

Ideal patients will have good performance status, no or minimal symptoms, and finite disease that can be removed completely (grossly) with a “reasonable” operation. The inability to demonstrate accurately the presence or absence of disease in critical areas by imaging mandates surgeon experience and clinical judgment. For patients deemed suitable for exploration, a final assessment and determination of whether to proceed to HIPEC is made in the operating room. For patients with high-grade cancers, such as signet ring cell carcinoma, symptomatic bulky disease is a contraindication for definitive surgical therapy. In patients with low-volume disease and good performance status, extensive involvement of small bowel serosal and mesenteric surfaces is a common cause for backing away from cytoreductive surgery; however, such involvement is often missed or underestimated by scans. When possible, we use a limited incision, typically with single-site incision laparoscopy, to allow for abdominopelvic assessment before proceeding.

For low-grade disease, such as low-grade pseudomucinous peritonei (PMP-1),[12] the inability to remove all gross disease does not necessarily preclude benefit from surgery but may affect surgical strategies. However, we and others have observed that the presence of PMP surrounding the portal vein predicts for the inability to remove upper and especially central disease. PMP surrounding the portal vein is typically seen in the presence of high-volume widespread disease with scalloping of the liver and spleen by adjacent diaphragm implants. The presence of a fixed tumor shelf in the pelvis on careful rectal examination must be regarded with alarm in all cases. The presence of hydrenephrosis calls for judgment. Retroperitoneal adenopathy needs to be assessed, with a determination made as to whether it represents reactive inflammatory disease or neoplastic disease, as the latter is a contraindication for CS in our view. MRI
with diffusion weighting allows for positron emission tomography (PET)-like assessment of some, but not all, anatomic areas. Biliary obstruction is not commonly seen but is also a contraindication. Distant metastatic disease, especially to the liver or lung, is a contraindication. However, it is worth noting that it is not uncommon to have small hepatic or pulmonary lesions that are too small to accurately categorize as benign or malignant. Such findings require clinical judgment, but if the clinical scenario is otherwise favorable, our inclination is most commonly to proceed to surgery. Some surgeons permit the presence of limited liver metastatic disease (three or fewer parenchymal lesions—not surface deposits), but this has not been our practice. PET scanning can be useful in high-grade cancers, especially to show retroperitoneal disease or disease at distant sites (or lack thereof). However, PET activity is dependent both on sugar uptake and tumor volume. Disease that is low in volume but that involves extensive small bowel surface can be obscured by the variable uptake in normal bowel. For low-grade PMP, even large masses may not be seen because of the low metabolic rates in this tumor. For this reason, we do not use PET for evaluation of low-grade PMP, whether low or high volume.

HIPEC with less than optimal CS can be effective palliation for patients suffering with symptomatic, rapidly recurrent malignant ascites. Many institutions have reported sustained clinical responses in the range of 80% to 90%. In our experience, patients with multifocal GI obstruction do not benefit from CS + HIPEC. One condition to watch for when conducting preoperative assessments is the presence of “pseudo-obstruction” from high-volume ascites, which can cause vomiting and early satiety related to abdominal pressure. If ability to eat is restored after paracentesis, demonstrating temporary reversal of obstructive symptoms, these patients can derive benefit from limited CS + HIPEC. Our view is that shunts are less effective and more morbid than limited CS + HIPEC for malignant ascites. We have not used CS + HIPEC for non-GI cancers, such as lung or breast primary cancers, metastatic to the peritoneum.

Technical Aspects of CS + HIPEC

Cytoreductive surgery

In general, the goal for CS is the gross removal of all visible disease. We would stress the importance of a reasonable operation: limited morbidity, no mortality, preserved physiology, and rapid return to good performance status. When feasible, visceral-sparing CS is preferred. By this we mean the avoidance of bowel resections. The surgeries that precede HIPEC can still be major operations. Omentectomy, splenectomy, cholecystectomy, appendectomy, and peritoneal stripping can all be a part of visceral-sparing CS, but gastrectomy or other major bowel resections cannot. The advantages of a visceral-sparing operation are no alteration of gut physiology, less likelihood of bowel leaks and other complications, more rapid return of bowel function, and shorter hospital stays. Good quality of life is desirable in and of itself and makes possible nonsurgical treatment options such as adjuvant or maintenance chemotherapy.

A variety of surgical techniques have been described for cytoreduction of GI cancers with peritoneal involvement. These range from standard procedures, such as small or large bowel resections, to more specialized techniques, such as peritoneal stripping techniques. The surgeries can range over the entire abdomen and pelvis. The extent of disease typically drives the extent of surgery. The learning curve for these surgeries has been documented to be fairly steep, such that it makes sense for more complex cases to be handled at specialized centers. Surgical experience is important. One pitfall is the temptation to do too extensive a surgery, with the result of permanently altered physiology, and with persistent or rapidly recurrent disease mitigating benefit. Complications after surgery have been associated with poor long-term outcomes.

Although complete cytoreduction is preferred, we have shown that leaving limited low-volume disease (nodules < 3–5 mm), similar to what has been described for “optimal debulking” in gynecologic oncology, can still result in long-term (5-year) survival, albeit not as long as in cases of complete cytoreduction. The reason long-term survival is sometimes seen in patients with limited low-volume residual disease may be the systemic effects of HIPEC. Typically, surgeries characterized by the leaving of tumor in excess of optimal debulking or by inability to resect the primary are of little to no value.

HIPEC

Two types of HIPEC have been described: open and closed. We have used only the closed technique (Figure 2). In discussions with operating room nurses at a number of centers, the principal author
has encountered antipathy toward an open technique because of fears of chemotherapy aerosolization. In the open technique, plastic sheeting is attached to the edges of the abdominal incision and the operator puts a hand in the belly to move contents around and uniformly disperse the chemotherapy solution. That fluid is perfused in and out with a heated pump perfusion circuit. This places the operator at risk for exposure if there are breaches in clothing. Because of this risk, we have not used the open method.

In the closed technique, tubing is placed for inflow and outflow into the abdomen and pelvis. The tubes can be placed through the incision or percutaneously. Temperature probes are placed to monitor inflow and outflow temperatures. Temperatures can also be monitored from internal locations if desired. Typically, we have the chemotherapy solution flow into the pelvis or the upper abdomen and use the opposite location for outflow. Other configurations are possible. The skin of the surgical incision is temporarily closed with a watertight suture. The size of the peritoneal surface can vary related to body surface area (about 60% of this area).

The perfusion volume after closing is variable and depends on the size of the individual, on how much ascites was present, and on how extensive a resection was performed. As a general rule, we have used perfusion volumes of around 3 liters for women and 4 liters for men. Once the heated perfusion has started, and it has been confirmed that there are no leaks and that the temperature is over 40°C, the drug is added to the circuit. The abdomen is gently shaken or kneaded during the perfusion in order to enhance uniform distribution. Variables from this point are the plateau or target inflow temperature, drug dosing (and in some cases re-dosing), and total time for perfusion. Perfusion times range from 30 minutes[13] to 2 hours, depending on the protocol.[9,14] Our current standard, using carboplatin, is 1 hour. These formulae vary by institution, and some experts have called for standardization. However, all protocols call for very high IP concentrations of the chemotherapeutic agent compared with serum levels. Differences in outcomes have been attributed to differences in drugs used.[15] The fact that outcomes vary when a difference in the drug used is the only major variable also suggests that the HIPEC is an active component of treatment; however, this has not been examined in clinical trials to date.

The addition of hyperthermia has been somewhat controversial. It was originally used to provide potential synergy with specific chemotherapy agents and because of the time constraints imposed by performing the perfusion in the operating room. In theory, the effect of adding hyperthermia is a variable that would be especially easy to study clinically. One could randomize and infuse chemotherapy at 37°C vs 42°C—a large, 5-degree difference. Clearly, using room temperature as the perfusion temperature is not desirable. Above 43°C, harm from the perfusion attributed to heat-related necrosis has been seen. However, the range of 37°C to 42°C has been safe in practice and in the normothermia-to-fever range. We have never seen a major problem that we could attribute to the use of hyperthermia. We do see temporary rises in core temperatures during perfusion, typically in the range of 38.5°C to 39.5°C, which rapidly revert to normal once the perfusion has terminated. These temperatures receive no specific treatment by anesthesia other than stopping applications of heat to fluids or skin surfaces (unpublished observations). However, to definitively prove the value of hyperthermia in a clinical trial, patients would have to be followed for many years, which would be prohibitively expensive. Thus, the advantage of adding hyperthermia, while theoretically quite plausible, remains unproven.

**Results**

Most data on the effectiveness of CS + HIPEC have come from the study of appendiceal cancers, including PMP and colorectal carcinomatosis. There are many studies that show that a subset of patients with colorectal carcinomatosis will have extended survival when treated with CS + HIPEC. However, there is still significant controversy surrounding this treatment. No one suggests that CS is not effective—in fact, it is the standard treatment—however, there are major discussions regarding the use of HIPEC.[16-19] The benefit of CS + HIPEC for colorectal carcinomatosis has been reported by many institutions. For example, Franko et al reported that CS + HIPEC is safe, and that with appropriate patient selection, a 50% rate of 5-year survival is possible.[13] In the EVOCAPE I trial, which studied CS plus systemic chemotherapy (no HIPEC), 5-year survival was 0%.[5] A case-controlled study looked at treatment with CS + HIPEC in 67 patients who had colorectal cancer with peritoneal carcinomatosis, compared with 38 registry control patients who received contemporary chemotherapy between 2001 and 2007. Careful multivariate analysis revealed a statistically significant improvement in median survival: 34.7 months vs 16.8 months, respectively.[11] A consensus from an international group of surgical
oncologists has been published recommending this treatment and giving guidelines for patient selection.[20] For peritoneal carcinomatosis resulting from colorectal cancers, Franko et al[13,21] looked at concurrent retrospective controls and concluded that compared with systemic chemotherapy alone, CS + HIPEC offered benefit. Others have also suggested benefit for HIPEC over no HIPEC.[11,22] In the only randomized controlled study completed to date, Verwaal et al[23] showed that patients treated with CS + HIPEC had a median survival double that of patients treated with best care alone. The study was considered flawed, however, as the control group had better than expected survival. A new French trial (PRODIGE 7) is comparing colorectal cancer patients with peritoneal metastasis treated with CS alone with a group treated with CS + HIPEC (using oxaliplatin).[18,20] The results of this trial are not available at this time but may eventually resolve the HIPEC controversy.

For other peritoneal cancers, such as those originating in the stomach[24-26] or neuroendocrine tumors,[20] the results are equivocal for a significant survival benefit for CS + HIPEC, although it has been suggested that HIPEC is useful for palliation in such cases.

In general, CS + HIPEC has become the standard of care for the treatment of peritoneal metastasis from PMP and malignant peritoneal mesothelioma.[20,27] It is approaching standard-of-care status for peritoneal metastasis from colorectal cancer and is still being evaluated for peritoneal metastasis from gastric tumors, neuroendocrine tumors, small bowel tumors, and other GI lesions. It is rarely used for the treatment of peritoneal metastasis from sarcomas, and benefit in this setting is uncertain.[20] For GI stromal tumors (GIST), new algorithms with targeted pathway drugs have radically altered approaches to care, and HIPEC is not used.

Cost of Therapy

Insurance companies will typically agree to cover proposed surgery. Some insurers may balk at coverage of HIPEC. Some view it as “standard of care,” while a minority argue that it is experimental. Most, however, will support it if appropriate documentation is provided. The cost of adding HIPEC to surgery is actually very modest compared with the cost of many cancer treatments. Cost is probably less than that of a month of conventional systemic therapy and certainly less than that of therapy with biologics. Expenses include the cost of operating room time for the perfusion set-up and perfusion time, the cost of supplies, and cost of the drug. We have used generic drugs with a history of IP use, and so drug cost has not been a major factor. (Some programs used oxaliplatin before this drug was available as a generic, but we did not, since for us this was cost-prohibitive.) It is possible that if newer drugs begin to be used for HIPEC, costs could escalate. Still, since CS + HIPEC is typically a one-time treatment, these are not recurring costs. Also, over the last 10 to 12 years, our institution’s program has not had instances of severe bone marrow suppression complicating care or other problems that could not otherwise be attributed to surgery (unpublished observations); thus, we have not incurred potential postoperative costs over and above those of CS alone.

Summary and Future Directions

CS + HIPEC is a surgically administered treatment modality for GI cancers with peritoneal carcinomatosis. This treatment can be used both with the intent of achieving long-term remission or for palliation, depending on the clinical scenario. Outcomes for CS + HIPEC have been shown to be primary site–dependent. The best outcomes have been seen in colorectal and appendiceal neoplasms with peritoneal spread, with a possibility for 5-year or greater survival that has been well documented (> 35% and > 50%, respectively). These numbers make it very unlikely that any randomized surgical trials will be conducted in this country to further study this.

The surgical management of peritoneal carcinomatosis has evolved. Levine et al in 2014 reviewed their institutional experience with 1,000 patients with peritoneal carcinomatosis associated with colorectal or appendiceal cancers treated with CS + HIPEC from 1991 to 2013.[15] They attributed improvements in outcomes over time to better patient selection, which was associated with a higher percentage of complete cytoreduction. The 5-year and 10-year overall survival rates were 32% and 18%, respectively. Overall mortality was 3.8%.[15]

In terms of palliation, CS with nonoptimal debulking plus HIPEC can treat or prevent malignant ascites in 80% to 90% of cases. In our opinion, CS + HIPEC should be considered standard of care for peritoneal carcinomatosis associated with colorectal cancers and cancers of the appendix, including PMP.

For other GI sites, recommendations are less clear. The low incidences and clinical heterogeneity make any trials very difficult to implement and surgical trials even more so. Good front-line
chemotherapy with high response rates, such as is the case in ovarian cancer, is not available for small bowel, gastric, gallbladder, and pancreatobiliary cancers at this time. If the primary cannot be effectively managed, then the role of CS + HIPEC will be limited to palliation. Where the primary is amenable to definitive surgical management and peritoneal disease can be eradicated with a “reasonable” operation, the addition of HIPEC seems rational. Because of the small numbers and variable case selection, it is not possible to show definitely that the addition of HIPEC improves long-term outcomes in peritoneal carcinomatosis from other primary sites. However, the costs—both in dollars and in increased morbidity—of adding HIPEC to “standard” surgery are low. We know that surgery alone does not eradicate peritoneal disease, but the addition of HIPEC may consolidate R1 surgery. For gastric cancer, for example, low-volume peritoneal dissemination can be found at surgery in up to half of cases without obvious distant dissemination on scanning. Future death from peritoneal carcinomatosis is highly likely in such settings. Again, CS + HIPEC appears rational, certainly given the lack of other good options. The same is true for small bowel adenocarcinomas with peritoneal carcinomatosis. A case can also be made for using CS + HIPEC for those cancers if a response to systemic therapy has been documented, suggesting sensitivity to some chemotherapy agents. Finally, little or no harm can be specifically attributed to HIPEC (over and above problems after CS), and potential benefit for a proportion of patients cannot be ruled out. With low cost and potential benefit, the cost-benefit ratio seems favorable for HIPEC in the absence of other data.

What is the future of CS + HIPEC? As more surgical oncology fellows are trained in these techniques and more centers offer this approach, it is unlikely that this specialized technique will go away. The rationale of offering a second look, potentially including HIPEC therapy, in known or high-risk cancer seems logical. New HIPEC drugs or drug combinations, including the combination of HIPEC with perioperative systemic therapy, may be explored. As new and more effective systemic therapies are introduced, the selective use of CS may increase: it can be used to relieve GI obstruction, to remove bulky disease, or to restore performance status and quality of life so that low-volume residual disease can be treated systemically.

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**References:**


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