

Hypothermic Intraperitoneal Chemotherapy for Gastrointestinal Malignancies—A Relic of the Past or Useful Tool for Today?

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Effective treatment options for peritoneal carcinomatosis from gastrointestinal malignancies are limited. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) have played an increasing role in patients with gastrointestinal malignancies and isolated peritoneal metastases, particularly in appendiceal and colorectal cancer, where it may offer benefit in highly selected patients. In this review, we discuss the rationale of cytoreductive surgery and HIPEC, its potential role in the management of peritoneal carcinomatosis related to gastrointestinal malignancies, and the current data supporting its use.

Keywords

Peritoneal carcinomatosis, isolated peritoneal metastases, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, gastrointestinal malignancies, colorectal cancer, gastric cancer

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Peritoneal carcinomatosis, defined as tumor dissemination in the peritoneal cavity, is a common manifestation of gastrointestinal malignancies. However, isolated peritoneal metastases (IPM) are relatively rare, though appendiceal tumors and peritoneal mesothelioma have a propensity to involve only the peritoneum. Cytoreductive surgery including hyperthermic intraperitoneal chemotherapy (HIPEC), are now considered standard treatment for appendiceal tumors with peritoneal dissemination.^{1–3} However, there is a paucity of robust high-quality data informing the role of cytoreductive surgery and IPC in patients with other gastrointestinal malignancies who have IPM. This is in contrast to ovarian cancer, for which a recent prospective trial suggested a survival benefit with HIPEC in patients with stage III disease.⁴ This may be because patients with ovarian cancer are generally highly chemosensitive, with higher, more durable response rates to first-line therapy than those observed in gastrointestinal malignancies.^{5–7} Despite this, HIPEC has not been widely adopted in the treatment of ovarian cancer in the United States due to continued uncertainty regarding the benefit of hyperthermia over IPC alone and potential morbidity and prolonged post-operative recovery that could result in a treatment delay or decreased dose intensity.

Treatment of peritoneal carcinomatosis

Effective treatment options for peritoneal carcinomatosis from gastrointestinal malignancies have historically represented an unmet need. Management of peritoneal carcinomatosis is challenging due its associated high symptom burden and resultant impact on performance status and ability to tolerate systemic therapies. Furthermore, disease extent is often underrepresented on imaging. Peritoneal carcinomatosis has also been associated with a poorer prognosis compared with metastatic disease at other sites.^{8,9} In this context, there has been considerable interest in evaluating the role of cytoreductive surgery with IPC for IPM, and it has been postulated that IPM may represent a regional, rather than a systemic, disease. Original studies by Sugarbaker reported that cytoreductive surgery could be utilized to remove gross disease, resulting in prolongation of survival.^{10–12} It was also hypothesized that delivering IPC to residual small volume gross or microscopic disease may improve outcomes.¹²

Hyperthermic intraperitoneal chemotherapy

Recognition of the peritoneum as a hypoxic environment through which chemotherapy penetrates poorly, prompted evaluation of HIPEC with the hypothesis that heat (41–43° Celsius) might promote drug penetration.^{13,14} In addition, hyperthermia is cytotoxic to tumor cells through denaturation of proteins and inhibition of nuclear matrix-mediated functions essential to DNA replication, transcription, and repair.^{15–17} It has also been shown to inhibit angiogenesis.^{18,19} Furthermore, early studies observed that significantly higher chemotherapy concentrations in peritoneal fluid versus systemic blood could be achieved.^{20,21} For example, peak intraperitoneal concentrations of mitomycin have been demonstrated to be approximately 100-fold higher than peak serum levels.²¹ While

mitomycin is no longer a standard therapy in gastrointestinal malignancies, it is considered an ideal agent for HIPEC for several reasons. Firstly, a high intraperitoneal concentration can be achieved—it is a large-sized molecule that is not rapidly absorbed systemically and it is stable at high temperatures.¹⁴ Hyperthermia has also been shown to potentiate the cytotoxic effect of both mitomycin C and oxaliplatin, an active systemic agent in gastrointestinal malignancies that has also been used as an intraperitoneal agent in gastrointestinal malignancies.^{14,15} The synergistic effect of heat and cytotoxic drugs is thought to arise from increased membrane permeability and transport, resulting in increased drug uptake as well as alteration of cellular metabolism and changes in pharmacokinetics and secretion. The limited drug absorption seen with IPC is also attractive, as systemic toxicity is reduced.

Many questions remain regarding appropriate patient selection for cytoreductive surgery and IPC, the additional benefit of IPC over cytoreductive surgery alone, whether hyperthermia is necessary, and if so, for what duration. The optimal drug of choice also remains unclear. Although mitomycin is no longer utilized as systemic therapy in gastrointestinal malignancies it continues to be administered intraperitoneally. Therefore, techniques remain heterogenous between high volume institutions.

Because cytoreductive surgery and HIPEC may be associated with considerable morbidity, a multidisciplinary approach for appropriate patient selection is important and the use of the peritoneal carcinomatosis index (PCI) can play an important role in predicting the possibility of obtaining a complete cytoreduction. Retrospective series⁷ have reported 5-year overall survival (OS) in >50% for patients achieving complete cytoreduction compared to a 20% 5-year OS in patients who undergo suboptimal surgery.^{22–24}

Colorectal cancer

IPM from colorectal cancer (CRC) occur in 2–8% of patients and appear to be associated with shorter median survival (13–16 months) than patients with isolated disease at other sites.^{8,25,26} Until recently, only one prospective study had evaluated cytoreductive surgery and HIPEC for IPM in CRC. In this study, 105 patients were randomized to 5-fluorouracil/leucovorin alone or cytoreductive surgery and HIPEC with mitomycin C for 90 minutes, followed by 5-fluorouracil/leucovorin.²⁷ Median OS was significantly improved with cytoreductive surgery and HIPEC (22.3 versus 12.6 months; $p=0.032$). The post-operative mortality rate was 8%. With advances in systemic therapy, it is unknown if the outcomes reported here are better than the outcomes that could potentially be achieved with use of contemporary chemotherapy regimens. Furthermore, small numbers of patients were accrued, including patients with peritoneal carcinomatosis of appendiceal origin (17%), who may obtain more benefit from surgical intervention. Long-term follow-up showed that the 5-year disease-free survival rate was 45% in patients who had surgery and HIPEC with complete cytoreduction followed by systemic therapy versus <10% in patients who underwent incomplete cytoreduction at time of surgery and HIPEC or those treated with chemotherapy alone.²⁸

Results from the phase III PRODIGE-7 study were recently reported and addressed the specific role of HIPEC in addition to cytoreductive surgery.²⁹ Patients with a PCI <25 received chemotherapy before and/or after cytoreductive surgery and were randomized to receive HIPEC with oxaliplatin. There was no difference in median relapse-free survival or OS between the groups. Morbidity was significantly higher in the HIPEC arm. In an unplanned subgroup analysis, patients with a PCI of 11–15 who

underwent HIPEC showed an OS benefit. Criticisms of this study include the accrual of patients with PCI of 15–25 and only a 30-minute administration time for oxaliplatin.

Retrospective studies have shown benefit for cytoreductive surgery and HIPEC. Elias et al. compared patients with CRC and IPM treated with contemporary chemotherapy ($n=48$) to patients who underwent cytoreductive surgery and HIPEC using oxaliplatin ($n=48$); median survival was 24 versus 63 months ($p<0.05$), respectively.³⁰ Franko et al. reported improved OS in patients who had cytoreductive surgery and HIPEC versus chemotherapy alone, with a median OS of 35 and 17 months ($p<0.001$), respectively.³¹ Both studies included selected patients with asymptomatic peritoneal carcinomatosis and the use of contemporary chemotherapy is reflected in the favorable survival rates in the chemotherapy only arms. Finally, a multicenter study examined outcomes of patients ($n=506$) treated with cytoreductive surgery plus HIPEC (54%), early post-operative IPC (EPIC; 24%) or both (22%). Median OS was 19.2 months. Patients who had complete cytoreduction had improved median OS compared to those who did not (32.4 months versus 8.4 months, $p<0.001$).³²

Preliminary results from two randomized studies (PROPHLOCHIP and COLOPEC) evaluating the role of adjuvant HIPEC, in patients considered at high risk of peritoneal recurrence, have recently been presented.^{33,34} There was no improvement in outcomes with the addition of HIPEC in either study. The ICARuS study (ClinicalTrials.gov identifier: NCT01815359) is an ongoing randomized phase II study evaluating EPIC (with floxuridine) versus HIPEC (with mitomycin C) following optimal cytoreductive surgery for colorectal and appendiceal cancers with IPM. EPIC and HIPEC have not previously been compared prospectively. When delivered intraperitoneally, hepatic extraction of floxuridine (a fluorinated pyrimidine) is high, allowing high doses to be administered with minimal systemic toxicity. However, EPIC can only penetrate 3 mm of peritoneal tissue, and may not reach all tumor cells. Potential advantages of HIPEC are that it is given before post-operative adhesions develop (which may prevent uniform perfusion of peritoneal surfaces with EPIC) and hyperthermia is recognized to be cytotoxic in itself.¹⁵ No cytoreductive surgery only arm was included in this study. The ACOSOG-Z6091 trial attempted to evaluate this question but failed to accrue due to patient perception that randomization to an arm without IPC was unacceptable.

Overall, the role of cytoreductive surgery and especially HIPEC remains controversial in CRC as benefit in the contemporary era has not been definitively shown. National Comprehensive Cancer Network (NCCN) guidelines suggest it can be considered in experienced centers for selected patients with limited peritoneal metastases for whom complete cytoreduction can be achieved. The independent contribution of HIPEC over cytoreductive surgery alone remains difficult to assess since they are undertaken synchronously, and recent data, using oxaliplatin, is unconvincing. Improvements in systemic therapies may negate the potential benefit of HIPEC. However, the median OS of approximately 40 months in the PRODIGE-7 study is favorable when compared to historical controls, suggesting that cytoreductive surgery may have a role in selected patients. PCI has been validated as a prognostic indicator and can be used as a guide for intraoperative decision making.³⁵ Upfront chemotherapy may facilitate identification of patients most likely to benefit. Importantly, the mortality risk of cytoreductive surgery and HIPEC has fallen in contemporary studies with rates of 1.1–4.0% reported.^{32,36,37} With improved understanding regarding

patient selection, cytoreductive surgery remains reasonable in high volume centers. However, the additional benefit of HIPEC is questionable.

Gastric cancer

The role of cytoreductive surgery and HIPEC in patients with gastric cancer and IPM remains very unclear. Studies from East Asia, mostly retrospective, suggest a benefit for HIPEC.³⁸⁻⁴⁰ In 2011, Yang et al. reported the results of a randomized phase III trial of almost 70 patients, comparing cytoreductive surgery alone to cytoreductive surgery plus HIPEC. An OS benefit was observed in the patients who underwent HIPEC compared to those who underwent cytoreductive surgery alone (11 versus 6.5 months; $p < 0.05$).⁴¹ The GYMSSA trial also showed an improvement in median OS in patients who underwent cytoreductive surgery plus HIPEC versus patients who received chemotherapy (11.3 versus 4.3 months).⁴² Patients in the surgery arm who survived > 1 year all had complete cytoreduction. However, this study enrolled only 17 patients and is considered hypothesis-generating at best. Results of a retrospective French study, CYTO-CHIP, reported outcomes of 180 patients who underwent cytoreductive surgery and HIPEC compared to 97 patients who underwent cytoreductive surgery alone.⁴³ PCI was higher in the HIPEC arm (6 versus 2, $p = 0.003$) and there was no difference in completeness of cytoreductive surgery between groups. HIPEC was associated with improved OS (median, 18.8 versus 12.1 months; 5-year OS, 20% versus 6%). Morbidity and mortality were similar between groups.

The use of HIPEC in gastric cancer remains experimental in light of conflicting results from underpowered studies and absence of high-level data. NCCN guidelines suggest that gastric cancers should be considered unresectable with any evidence of peritoneal involvement including positive peritoneal cytology. Of note, one retrospective study suggested that patients with positive peritoneal cytology who have cleared cytology after a period of chemotherapy have improved disease-specific survival compared to patients who do not.⁴⁴ Furthermore, several studies have shown that patients who undergo complete/near complete resection have improved survival over patients who undergo incomplete resection.^{41,45,46} Therefore, there may be a role for HIPEC in highly selected patients with positive peritoneal cytology or minimal gross disease that is diagnosed using laparoscopy but is not visible on imaging. Patients who manifest chemosensitive disease through resolution of gross disease and/or positive peritoneal cytology may be candidates for gastrectomy and HIPEC, hypothesizing that patients with disease sensitive to chemotherapy

may be more sensitive to HIPEC. While survival may be extended over chemotherapy alone, it is unlikely that patients can be cured with this approach. A standardized multimodal approach to this group of patients remains an unmet need. If considered, surgery and HIPEC should only be undertaken in specialized centers.

Other gastrointestinal malignancies

There is limited data regarding the role of cytoreductive surgery and HIPEC in other gastrointestinal malignancies. Peritoneal mesothelioma is a rare malignancy characterized by progression restricted to the peritoneum. Several studies have reported a median survival of 3–5 years with cytoreductive surgery and HIPEC which compares favorably to historical studies reporting survival without surgery of approximately 1 year.⁴⁷ Patient selection is key and surgical intervention should be undertaken only in experienced centers. Data regarding the merits of an aggressive surgical approach in patients with hepatobiliary and pancreas cancers is extremely limited. Two small retrospective studies suggested improved survival outcomes in small cohorts of patients with biliary and hepatocellular cancers respectively.^{48,49} No conclusions can be drawn due to study size and lack of prospective data.

Conclusion

The benefit of cytoreductive surgery with or without HIPEC in gastrointestinal malignancies may never be clearly defined. The shortcomings of retrospective studies combined with limited prospective randomized data means there is little to guide management of this patient subgroup, especially in non-CRC/appendiceal malignancies. Large informative trials are not feasible in a Western population in gastric cancer and in CRC it is difficult to accrue patients to studies in which they forego treatment with surgery or HIPEC.

It is likely that there is a small subset of patients whose disease does not have a propensity to metastasize to other sites, on a spectrum ranging from appendiceal neoplasms and peritoneal mesothelioma to gastric, colorectal and hepatobiliary-pancreatic cancers. Future directions may involve determining, through molecular genetic profiling, which patients are likely to have disease confined to the peritoneal cavity and those destined to progress at other sites. Improved detection techniques would also help improve our knowledge of disease extent and biology. In the right patients, it is likely that cytoreductive surgery with or without HIPEC can improve outcomes and sometimes result in long-term remission. □

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