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REVIEW ARTICLE

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Current role for cytoreduction and HIPEC for gastric cancer with peritoneal disease

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Abstract

Gastric cancer (GC) is an aggressive malignancy with a high burden of peritoneal disease. Evidence regarding the use of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) to improve outcomes has been growing. However, given multiple limitations, there remains a lack of international consensus regarding the optimal treatment paradigm. This review article discusses the burden of peritoneal disease in GC patients and the role of CRS + HIPEC in all treatment intents—curative, prophylactic, and palliative.

KEYWORDS

cytoreductive surgery, gastric cancer, HIPEC, peritoneal carcinomatosis

1 | BURDEN OF DISEASE

Gastric cancer (GC) is the fifth most common cause of malignancy and the fourth leading cause of cancer-related mortality worldwide. It alone accounted for over a million new cancer diagnoses in 2020.[1] Unfortunately, up to 40% of GC patients have synchronous peritoneal carcinomatosis (PC) at the time of diagnosis. Furthermore, recurrence after curative surgery is common, with 46% of the patients having a recurrence in the peritoneum and 60% having peritoneal disease at death.[2–4] Peritoneal disease has a poor prognosis with a median survival of 3–6 months and a 5-year survival rate of 0%.[2,5] Despite multiple advancements in therapeutics, the National Comprehensive Cancer Network (NCCN) guidelines recommend systemic chemotherapy or best supportive care for GC with peritoneal dissemination.[6]

GC has the highest burden of peritoneal disease of any gastrointestinal malignancy.[7] Tumor cells are hypothesized to spread to the peritoneal cavity by direct contact, once full-thickness invasion of the gastric wall occurs. Roviello et al.[5] showed that GC with serosal infiltration had higher odds of peritoneal recurrence. At other times, surgical trauma may allow for the dissemination of cells. Tumor at the margin of resection along with lympho-vascular transection leads to spillage of malignant cells into the peritoneal cavity.[2,8–10] Tumor dissemination in the peritoneum leads to a number of changes: (1) inflammation at the site of implantation alters tissue morphology allowing subsequent invasion by surviving tumor cells and (2) during the process of wound healing, fibrin deposition not only protects tumor cells but also entraps growth factors that aid in their proliferation.[8] Furthermore, alteration of peritoneal function slowly renders it incapable to carry out the effective exchange of fluid, resulting in ascites, bowel obstruction, and pain that eventually leads to mortality.[8,9]

Historically, GC with PC has not been considered for surgical resection. Chemotherapy has been the mainstay of treatment despite inadequate data on its efficacy given limited trial opportunities for patients with PC.[11–13] It is hypothesized that intravenous chemotherapy does not adequately transfer across the blood-peritoneal barrier, limiting its ability to penetrate and kill peritoneal cancer cells.[14] This scenario raises the need for alternative strategies to improve outcomes for GC patients with PC. The Peritoneal Surface Oncology Group International (PSOGI) has proposed the use of cytoreductive surgery (CRS) combined with intraperitoneal

chemotherapy as a new paradigm of care when PC is present.[15] In the following review, we will outline the role of CRS in combination with intraperitoneal (IP) chemotherapy, most notably hyperthermic intraperitoneal chemotherapy (HIPEC). In most sections, surgical management will focus on synchronous dissemination unless otherwise specified.

2 | WHAT IS HIPEC?

In 1980, Spratt et al.[16] described the first case of HIPEC delivery in a human subject. The authors reported extensive abdominal resection for a patient with pseudomyxoma peritonei followed by warming the intraperitoneal cavity to 42°C and circulating chemotherapy. Following this, Sugarbaker in 1998 described the principles of CRS + HIPEC management with (1) selecting a patient cohort that has disease limited to the surface of the abdomen or pelvis only, (2) maximally reducing disease burden by CRS—resection of involved viscera plus peritonectomy and (3) using maximum intraperitoneal and systemic chemotherapy to achieve the best outcomes.[10]

The goal of CRS is to remove all visible peritoneal lesions so that HIPEC is used only for free-floating cancer cells and micrometastases on the peritoneum.[17] Since the penetration of drugs in HIPEC is limited to 1–2 mm, it is imperative that any nodule larger than this size is surgically removed during CRS.[10] Following surgery, heated chemotherapy is delivered intraoperatively to the peritoneum to eradicate free tumor cells. The goal is to use agents that have increased efficacy with heat (i.e., Mitomycin C, cisplatin, or doxorubicin).[10] Furthermore, heat allows increased uptake of drugs by impairing DNA repair mechanisms in tumor cells and inducing apoptosis via denaturation of proteins.[18–20] The blood-peritoneal barrier permits large doses of cytotoxic drugs to be administered without significant systemic side effects.[17] In general, HIPEC is done after CRS based on the notion that surgical trauma can shed tumor cells and the injured peritoneal surface can be vulnerable to seeding by free cancer cells. The use of HIPEC has gradually gained recognition as a novel treatment modality for a select group of GC patients for prophylaxis, cure, and palliation.

For patients with PC, staging the extent of disease is a crucial component of decision making and identifying those who may qualify for surgical intervention. As described by Jacquet and Sugarbaker,[21] the peritoneal carcinomatosis index (PCI) is the near-universal means by which assessment is made. PCI scores are calculated by dividing the abdomen into nine quadrants plus four regions encompassing the small bowel.[21] Each region is given a score based on the largest implant size (LS 0–3), where LS-0 is no lesion seen, LS-1 is lesion up to 0.5 cm, LS-2 up to 5 cm and LS-3 is for implants greater than 5 cm. The PCI quantitatively assesses each region of the abdominopelvic cavity for a maximum score of 39.

We are currently limited in accurately identifying the peritoneal burden in GC patients. Up to 40% of patients with no signs of peritoneal metastasis on preoperative imaging can have disease on diagnostic laparoscopy.[22,23] Even at the time of laparoscopy that shows no visible disease, up to 13% of the patients can have positive peritoneal cytology.[24] When patients with negative cytology are followed, they tend to recur most commonly in the peritoneum by 1 year.[25] Allen et al.[6] found that peritoneal cytology had a sensitivity of 64% for detecting disease and that improvement in cytological techniques was necessary. Even with a negative staging laparoscopy and receipt of preoperative therapy, up to 12% of the patients can have disease progression to peritoneal or unresectable disease on repeat diagnostic laparoscopy at the time of surgical resection.[23] This highlights the fact that diagnostic modalities are currently imperfect, and that it is important to accurately identify disease burden so that unnecessary postoperative morbidity can be avoided by futile surgery.

3 | CRS WITH HIPEC IN GC WITH PC—CURATIVE INTENT

The notion that peritoneal spread in GC is a fatal discovery is gradually being challenged. Multiple retrospective studies have reported improved outcomes in GC patients with PC with the addition of CRS and HIPEC. Glehen et al. conducted a large, multicentric, retrospective study in France that evaluated 159 patients with PC who underwent CRS along with intraoperative and/or postoperative intraperitoneal chemotherapy. Patients with limited disease and complete cytoreduction (CC-0) had an improved survival of 15 months, with 61% —1 year and 23%—5-year survival rates.[26] The CYTO-CHIP study compared CRS with CRS + HIPEC in GC patients with PC and revealed higher 1-year (67.9% vs. 48.5%), 3-year (27.1% vs. 13.1%), and 5-year (20.2% vs. 7.4%) survival with CRS + HIPEC compared to CRS alone.[27] Multiple other observational studies and clinical trials have also reported that carefully selected patients with limited PC can achieve improved outcomes with CRS + HIPEC.[28–30] Yang et al.[31] randomized patients to CRS + HIPEC versus CRS alone and noticed that the combination arm had a longer median survival (11.0 vs. 6.5 months, $p = 0.046$), whereas the rate of serious adverse events was similar in both arms. The GYMSSA trial, performed in an American cohort, randomized 17 gastric carcinomatosis patients—9 into the CRS + HIPEC + chemotherapy arm (GYMS) and 8 into chemotherapy only (FOLFIXIRI) arm (SA).[32] A median survival advantage of 11.3 months was seen in the experimental GYMS arm compared to 4.3 months in the SA arm.

Rau et al.[33] in 2021 published results from a multicenter, randomized controlled trial (RCT) (GASTRIPEC-I-trial) exploring the impact of HIPEC after CRS on survival. The CRS + HIPEC arm (52 patients) had similar median survival (14.9 vs. 14.9 months, $p = 0.16$) when compared to CRS-only arm (53 patients); however, both the progression-free survival (7.1 vs. 3.5 months) and metastasis-free survival (10.2 vs. 9.2 months) were significantly improved in the combination arm.[33] Other studies have also reported minimal survival benefits of CRS + HIPEC. In a single-institution study, Kim et al.[34] reported no improved outcomes with CRS + HIPEC over CRS alone in GC with PM (peritoneal metastasis) patients. Similar results were

reported by Hirose et al.[35] as well, although both studies were limited by their small sample size ($n = 17–28$).

To evaluate the true benefits of HIPEC in GC with peritoneal disease patients, Desiderio et al. performed a meta-analysis on 32 studies from 1985 to 2016. Among a group of 620 patients with PC, 289 underwent CRS + HIPEC and 331 were controls (CRS or systemic chemotherapy). A median overall survival (OS) of 11 vs. 7 months ($p < 0.001$) was noted in the CRS + HIPEC group along with a survival advantage at 1-year follow-up, although no statistical difference was found at 2 or 3 years.[3] The review, however, was limited by the highly heterogenous patient population—ranging from stage II to IV, tumor differentiated to undifferentiated, and cytology positive versus negative.[3] Granieri et al.[36] updated the literature with a meta-analysis of RCTs ($n = 12$) that were conducted up to 2020 and evaluated CRS + HIPEC in GC patients with and without peritoneal disease.[36] The authors noted survival benefits at 1, 2-, 3-, and 5-year follow-ups for patients undergoing treatment with prophylactic intent; however, no difference was found in patients with peritoneal disease undergoing curative intent with CRS + HIPEC. Additionally, a higher postoperative morbidity (RR: 1.08) and morality (RR: 2.25) were noted with CRS + HIPEC (statistically insignificant). Although the review selected randomized trials only, it was limited by the fact that patients involved in the analysis were enrolled from 1980 to 2016. During this period, diagnostic and treatment modalities have evolved. Furthermore, of the 1376 total patients, only 43 underwent curative-intent treatment for analysis. The authors also combined GC patients with and without peritoneal disease—two very different cohorts.[36]

Ultimately to receive benefit, patient selection is key to achieving maximum survival benefit from CRS + HIPEC. Factors most identified with superior outcomes are completeness of cytoreduction (CC) and low burden of disease similar to other histologies undergoing CRS + HIPEC. Coccolini et al.[37] reported a meta-analysis of nine trials conducted on 748 GC with PC patients to evaluate the role of complete cytoreduction. The authors found that at all time points (1-, 2-, 3-, and 5-year follow-ups) CC-0 or -1 had improved survival compared to CC-2 or -3 and in fact, at 1 and 3 years, CC-0 had even better outcomes than CC-1. However, for complete cytoreduction in GC, it is important to acknowledge the disease burden in which feasibility for CRS is framed. The PCI for GC is much lower than all other histologies considered for CRS + HIPEC.[38] Yonemura et al.[39] reported that successful complete cytoreduction decreased from 86% to 7% as the PCI increased from <6 to >13. Although most studies report a lower PCI to be associated with higher survival, the exact PCI cut-off is yet to be determined. Yang et al. used a PCI < 20[31] whereas others have suggested <12 as an indication for better outcomes with CRS + HIPEC.[26,37] Chia et al.[40] reported that of the 81 GC patients who underwent CRS + HIPEC, 11% patients were disease-free at 5 years and had a PCI < 7. These findings of improved prognosis with a PCI < 7 are supported by multiple other studies.[39,41] While no PCI cut-off has been determined, consensus surrounds the use of a PCI < 7 to consider CRS + HIPEC in this patient population.[42]

Other factors associated with improved outcomes with CRS + HIPEC are optimal preoperative performance status, response to neoadjuvant chemotherapy, synchronous PC and more than six cycles of chemotherapy.[26,31] Factors that have been identified with poor survival are the presence of ascites, incomplete cytoreduction, unresectable primary tumor, signet ring cell histology, diffuse or mixed type, poor tumor differentiation, a high T-stage and nodal involvement, and resection of more than five organs.[27,29,43]

While diagnostic laparoscopy can help identify appropriate patients by staging their disease and assessing carcinomatosis burden, it also offers the advantage of laparoscopic (LS) HIPEC at the same time. Badgwell et al.[44] reported results on a phase-II trial after performing LS-HIPEC in 19 GC patients in the western population. Seven patients had the absence of peritoneal disease after therapy. The authors concluded that the treatment was safe and allowed patients to undergo gastrectomy.[44] This was further corroborated by Newhook et al.,[45] who evaluated 71 LS-HIPEC procedures performed in 44 GC patients with the peritoneal disease and reported low rates of morbidity (1.4%), with up to 25% of the patients undergoing gastrectomy.[45]

Other studies have also noted that laparoscopic HIPEC is a safe procedure that can improve eligibility for surgery by decreasing the burden of peritoneal disease. Yonemura et al.[46] combined LS-HIPEC with three cycles of neoadjuvant intraperitoneal/systemic chemotherapy (NIPS) followed by CRS in 52 GC patients. A significant reduction in PCI at the time of CRS was noted compared to the PCI at LS-HIPEC (PCI 14.8 > 9.9). In the majority of the patients (22/31) peritoneal cytology also converted to negative.[46] Long-term follow-up revealed that most of the patients (63%) who underwent NIPS had a complete cytoreduction and a median survival of 20.5 months.[47] The safety and efficacy of this technique have also been reported by other authors.[41,48,49] Another modality that has recently gained interest is using high pressures in the peritoneum to deliver heated chemotherapy—pressurized intraperitoneal aerosol chemotherapy (PIPAC). It is hypothesized that the elevated pressures generated will enhance chemotherapeutic drug uptake, whereas aerosolization will improve the area of coverage, resulting in improved antitumor efficacy.[50] Nadiradze et al. evaluated PIPAC in 24 PC patients—most of whom had signet-ring histology with a high mean PCI of 16—and found median survival to be 15.4 months. Despite the presence of high-risk features, objective tumor response was seen in 50% of the patients.[51] A review of all studies conducted till 2018 evaluated 10 articles with 129 GC patients for PIPAC.[52] Other than one study evaluating its use as neoadjuvant therapy to downgrade PCI, all were for palliation. Most studies found that PIPAC stabilizes quality of life (QOL) and the authors concluded it to be a safe & feasible tool.[52]

More recently, Di Giorgio et al.[53] combined PIPAC with systemic chemotherapy in 28 GC patients with PM. The median survival was 12 months and increased to 15 months in patients undergoing more than one PIPAC therapy. Multiple perioperative options exist to deliver intraperitoneal chemotherapy (NIPS, HIPEC, EPIC) depending upon the timing of delivery. Future studies are needed to determine which regimen has superior outcomes for this aggressive disease. A multicenter, phase-III, randomized trial will enroll 326 advanced GC patients into gastrectomy + chemotherapy arm versus

LS-HIPEC + chemotherapy followed by gastrectomy + HIPEC + chemotherapy arm. The study is aimed to evaluate the impact of intraperitoneal chemotherapy and is expected to complete in December 2021.[54]

4 | CRS WITH HIPEC IN ADVANCED GC (AGC)—PROPHYLACTIC INTENT

The peritoneum accounts for up to 45% of all recurrences in GC, with a worse prognosis compared to other metastatic sites.[2] To evaluate therapeutic options for addressing the peritoneum prophylactically for metastasis, Koga et al. in 1988 compared the addition of HIPEC to curative gastrectomy alone in GC patients with serosal invasion and no macroscopic peritoneal metastasis. The authors reported an improvement in the survival rate (83% vs. 67%) as well as a decreased peritoneal recurrence (36.4% vs. 50%) in the HIPEC group.[55]

Over the years, a number of trials have provided evidence of a decrease in peritoneal recurrence and improved survival by using HIPEC as a prophylactic therapy in AGC patients.[2] Beehary et al. randomized 80 patients with locally AGC—40 in the curative surgery + HIPEC arm and 40 in the control arm (curative resection-only). Up to 7.5% in the HIPEC and 15% in the control group experienced postoperative morbidities. At 3 years follow-up, the HIPEC group had a lower peritoneal recurrence rate (3% vs. 23%, $p < 0.05$) and a higher disease-free survival (93% vs. 65%, $p = 0.0054$).[56] The authors concluded that HIPEC was a safe multimodal treatment offering improved clinical outcomes. Similarly, Reutovich et al.'s randomized trial evaluated HIPEC's ability to reduce metachronous peritoneal lesions in serosal-invasive GC patients.[57] The authors compared HIPEC plus surgery with surgery-only and reported a decreased rate of peritoneal metastasis (12.8% vs. 27.6%) and a higher 3-year progression-free survival (47% vs. 27%) in the HIPEC group.[57] Such improved outcomes are possibly attributed to HIPEC reducing free intraperitoneal cancer cells[58]—both from large volume fluid washout and chemotherapeutic action of the drugs.[2]

Desiderio et al.[3] in their meta-analysis also analyzed the role of CRS + HIPEC as prophylactic therapy in AGC. The authors included 1810 patients in the analysis of AGC without carcinomatosis, of which 731 underwent combination therapy (gastrectomy + HIPEC) and 1079 gastrectomy alone. Most studies included patients based on cT4 staging. No survival benefit was noticed between the two groups at 1-year follow-up; however, modest differences were noted at 3-year (RR = 0.71, $p = 0.03$) and 5-year (RR = 0.82, $p = 0.01$) endpoints for the HIPEC group. A significant advantage in overall disease recurrence was also noticed in the HIPEC group (RR = 0.73, $p = 0.002$).[3] When recurrence by site was analyzed, a reduction in peritoneal metastasis was observed (RR = 0.63, $p < 0.01$), but no differences were noted for local, lymph nodal, liver, or distant sites.

Sun et al.[59] and Mi et al.[60] published a meta-analysis of 10 and 16 randomized controlled trials respectively, comparing the benefit of HIPEC in AGC patients who underwent resection. Both authors reported improved survival and reduced recurrence rate in the CRS + HIPEC versus CRS-only groups.[59,60] Other meta-analyses have similar conclusions—adjuvant intraperitoneal chemotherapy confers a survival advantage.[61–64] However, these reviews are limited by the highly heterogenous studies they pool together. Another limitation is the quality of studies included. Sun et al.[59] reported only half of the studies evaluated were of high quality. In fact, Xu et al.[64] in their review noted, only 1 out of 11 RCTs were of high quality. Other concerns are the dissimilarities in study designs. The type of drug(s) used intraperitoneally, their duration and dosage, the length and technical aspects of the procedure, the temperature of the perfusate, and the timing/receipt of neoadjuvant therapy are a few of those concerns. Even when data such as that on recurrence or morbidity were recorded, lack of standardization made pooled analysis imprecise.[60,64] Lastly, in most of the meta-analyses, a majority of the trials reported were from Asian countries which may make their applicability to the Western populations challenging. Despite the available data suggesting that HIPEC as a prophylactic therapy after curative surgery can improve survival in AGC patients, there remains a need for higher quality, well-designed, multi-institutional studies for definitive answers given these aforementioned limitations. Therefore, currently, the use of prophylactic HIPEC is not utilized in the practice of most peritoneal surface malignancy surgeons.

5 | CRS WITH HIPEC—PALLIATIVE INTENT

Extensive peritoneal disease along with gross metastasis precludes curative-intent surgery. PC alters the physiology of the peritoneum by causing an obstruction to fluid drainage, and along with fluid buildup induced by tumor-produced proteins, results in malignant ascites.[65] Subsequent pain worsens quality of life. Other than repeated paracentesis, one treatment option is HIPEC for palliative purposes. Randle et al.[66] reviewed 299 patients with various primary tumors who had ascites and underwent CRS + HIPEC. The authors reported a 93% resolution rate of ascites at 3 months follow-up regardless of CC score. Importantly, however, major morbidity was noticed in 25% of the patients. While treatment was able to resolve ascites in patients with a median OS of 5.6 months, offering CRS + HIPEC for palliation may not be appropriate given the high morbidity rate and the fact that most of those 5 months would be spent recovering from the procedure.[66] Yarema et al.[67] treated 117 GC patients with PM in a European population using HIPEC. In 10 patients who had severe ascites, a mean PCI of 30.6 was noted and a palliative approach was undertaken that resolved ascites in all patients. The median OS of this group was only 3.5 months. Furthermore, a 29.1% postoperative morbidity and 5.1% 30-day mortality was noted for the entire cohort of 117 patients.[67] Other studies evaluating GC patients have reported similar outcomes of a complete resolution of ascites in the majority of the patients after HIPEC administration, although morbidity has not been negligible.[68,69]

A better option for palliation might be laparoscopic HIPEC (LS-HIPEC) without CRS. Facchiano et al.[70] performed LS-HIPEC in five patients with unresectable peritoneal GC who had debilitating

malignant ascites and reported complete clinical regression along with minimum morbidity and no mortality. Similarly, Garofalo et al.[71] performed LS-HIPEC in 14 patients with malignant ascites from various primary tumors and reported comparable results. In a systematic review evaluating eight studies on laparoscopic HIPEC, four were aimed for palliation. Of the 76 patients treated for debilitating malignant ascites, 95% had success with nine minor complications and no mortality.[65] The authors concluded that when other methods (chemotherapy, diuretics, or repeated paracentesis) have failed, laparoscopic HIPEC is a safe and effective procedure for palliation of malignant ascites. Such minimally invasive approaches lower surgical stress since they do not involve major incisions, intestinal anastomoses, or lengthy operative times, and offer faster recovery—factors that are critical when recommending palliative procedures.

6 | FUTURE DIRECTION AND NEXT STEPS

The National Institute for Health and Care Excellence (NICE) in the United Kingdom released updated guidelines in 2021 after performing a comprehensive review of the literature. It recommends that CRS + HIPEC for gastric PC should be used in the context of a clinical trial only, whether it is for treatment or preventative intent, given insufficient evidence.[72] Earlier in 2008 however, there was consensus between an international group of experts that peritonectomy + HIPEC for GC patients might be beneficial if there is an absence of distant metastasis or ascites and complete cytoreduction is possible.[73] There are multiple reasons why there is such a discordance between various organizations. Trials are often heterogenous in their techniques, underpowered, and of suboptimal quality. Additionally, expertise and resources limit centers that can offer such procedures. Also, a majority of the literature analyzing the role of HIPEC in GC patients originates from Eastern Pacific countries which is why they have not gained widespread acceptance in the West.

With the advancement in chemotherapeutic drugs, a trial comparing HIPEC with modern polychemotherapy is warranted. Furthermore, a combination of HIPEC with EPIC (early postoperative intraperitoneal chemotherapy), open versus closed techniques, dosage of selected chemotherapeutics, and timing of therapy and number of cycles of HIPEC are all questions that need validation. Clinicaltrials.gov mentions multiple studies evaluating some of these questions. PIPAC-GA01 is a phase II study in Germany assessing the safety and efficacy of aerosolized intraperitoneal chemotherapy in GC with PC patients.[74] The GASTRICHIP and GOETH studies are randomized phase III trials that will compare HIPEC + gastrectomy with gastrectomy-only for AGC patients.[75,76] A phase-II RCT from China will evaluate HIPEC followed by CRS and extensive intraperitoneal lavage versus all therapies at the same time for GC patients with positive cytology to determine appropriate initial treatment.[77] The PERICLES study will evaluate the role of ctDNA in predicting clinical stage or treatment response in GI PC patients.[78] Furthermore, molecular profiling data on GC are being used for prognosis and recurrence prediction.[79] How these data further clinical research by tailoring patient-specific treatments is yet to be determined. This review highlights the need for large, multi-institutional, randomized controlled trials which are rigorous in their methodology and use internationally accepted. Nevertheless, with the current evidence available, CRS + HIPEC appears to be a promising modality for GC patients with peritoneal disease and should be considered especially on protocol for patients with PC.

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DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

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