The Role of Cytoreductive Surgery and Intraperitoneal Chemotherapy in Gastric Cancer

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Abstract: Gastric cancer (GC) with peritoneal carcinomatosis (PC) progresses rapidly and has historically dismal survival rates. Given the aggressive tumor biology and poor survival outcomes of patients with GC/PC, additional treatments beyond systemic chemotherapy are needed. Cytoreductive surgery and intraperitoneal chemotherapy have been effective management options for peritoneal surface malignancies, with increasing data to support their use in GC/PC. This review highlights the evolution of the surgical treatment of GC/PC, and discusses critical studies supporting the role of cytoreductive surgery, appropriate patient selection, and various methods in the delivery of intraperitoneal chemotherapy for patients with GC/PC.

Keywords
Cytoreductive surgery, gastric adenocarcinoma, hyperthermic intraperitoneal chemotherapy, normothermic intraperitoneal chemotherapy, peritoneal carcinomatosis

Introduction

There are approximately 1.1 million new cases of gastric cancer (GC) globally each year, contributing to nearly 800,000 deaths annually.[1] The incidence of peritoneal carcinomatosis (PC) in gastric adenocarcinoma can be as high as 30% to 40% with the utilization of diagnostic laparoscopy.[2] Prognosis is generally poor in GC/PC, with expected survival in the range of 6 to 15 months with systemic chemotherapy (SC) alone.[3] The aggressive nature of GC and its historically dismal survival outcomes pose therapeutic challenges for patients with GC/PC.

Given the poor response of GC/PC to SC, an increasing number of published studies have investigated the role of cytoreductive surgery (CRS) and regional therapy options such as intraperitoneal (IP) chemotherapy. In patients undergoing CRS for GC/PC, complete cytoreduction (CC0) and lower peritoneal carcinomatosis index (PCI) have been shown to be independent predictors for overall survival (OS).[4,5] Hyperthermic intraperitoneal chemotherapy (HIPEC),

Table 1. Completed Clinical Trials in Cytoreductive Surgery and Intraperitoneal Chemotherapy

Study, Authors (y)	Design	Location (Size)	Arms	Outcomes
SC vs NIPEC/SC				
PHOENIX-GC, Ishigami et al (2018)[8]	Phase 3	Japan, multicenter (N=164)	S-1 + IV cisplatin vs S-1 + IP/IV paclitaxel	Median OS 17.7 mo (IP/IV) vs 15.2 mo (IV only), *P*=.08; 3-y OS 21.9% (IP/IV) vs 6% (IV), *P*<.05
FNF-004, Lin et al (2019)[9]	Phase 2	China, multicenter (N=89)	FOLFOX vs IV paclitaxel + FOLFOX vs IP paclitaxel + FOLFOX	Median PFS 6.4 mo (IV) and 6.2 mo (IP), both significantly improved over FOLFOX alone (4.1 mo)
Kang et al (2022)[11]	Phase 1	South Korea, single-center (N=13)	IV FOLFOX + IP paclitaxel (≤60 mg/m^2)	Median OS 16.6 mo; median PFS 9.6 mo; all tolerable and manageable adverse events
SC vs CRS/HIPEC/SC				
GYMSSA, Rudloff et al (2014)[12]	Phase 3	US, single-center (N=17)	IV FOLFOXIRI vs CRS/HIPEC (IP oxaliplatin) with IV FOLFOXIRI	Median OS 11.3 mo (CRS/HIPEC/IV) vs 4.3 mo (IV only); N too small to make statistical comparison
CRS vs CRS/HIPEC				
Yang et al (2011)[13]	Phase 3	China, single-center (N=68)	CRS vs CRS/HIPEC (IP cisplatin/MMC)	Median OS 11.0 mo (CRS/HIPEC) vs 6.5 mo (CRS), *P*=.046
GASTRIPEC, Rau et al (2021)[14]	Phase 3	Germany, multicenter (N=105)	CRS vs CRS/HIPEC (IP MMC/cisplatin)	Study closed early owing to poor accrual; median OS 14.9 mo in both groups, *P*=.16; PFS 3.5 mo (CRS) vs 7.1 mo (CRS/HIPEC; *P*=.047), distant metastasis-free survival 9.2 mo (CRS) vs 10.2 mo (CRS/HIPEC; *P*=.029)
Nonrandomized CRS/HIPEC				
PERISCOPE I, van der Kaaij (2020)[16]	Phase 1/2	Netherlands, multicenter (N=25)	CRS/IP (HIPEC oxaliplatin, NIPEC docetaxel)	Safety and feasibility study; treatment-related mortality 8%
Badgwell et al (2017)[17]	Phase 2	US, single-center (N=19)	Iterative HIPEC (IP MMC and cisplatin)	N=5 downstaged to resectability; median OS from first laparoscopic HIPEC 20.3 mo
Badgwell et al (2021)[18]	Phase 2	US, single-center (N=20)	Iterative HIPEC, gastrectomy, CRS/HIPEC (IP MMC and cisplatin)	Median OS from CRS/HIPEC 16.1 mo; 1-, 2-, 3-y OS 90%, 50%, 28%, respectively
PIPAC				
Struller et al (2019)[24]	Phase 2	Germany, single-center (N=25)	PIPAC (IP cisplatin and doxorubicin) repeated every 6 wk for 3 procedures	Median OS 6.7 mo; 40% radiologically complete response, partial response, or stable disease; complete or major histologic regression in 36%; grade 3 toxicities 12%, grade 4 toxicities 0%

CRS, cytoreductive surgery; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; FOLFOXIRI, leucovorin, 5-fluorouracil, oxaliplatin, and irinotecan; HIPEC, hyperthermic intraperitoneal chemotherapy; IP, intraperitoneal; IV, intravenous; MMC, mitomycin C; mo, months; NIPEC, normothermic intraperitoneal chemotherapy; OS, overall survival; PFS, progression-free survival; PIPAC, pressurized intraperitoneal aerosolized chemotherapy; SC, systemic chemotherapy; US, United States; wk, weeks; y, year.

which utilizes heat to augment the cytotoxicity of specific chemotherapy agents, is commonly used along with CRS for treatment of peritoneal surface malignancies. Normothermic intraperitoneal chemotherapy (NIPEC) involves the delivery via IP port systems of agents that lack heat augmentation properties, such as paclitaxel.[6] Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is the most recent technique of IP drug delivery to show initial promise in this arena. However, IP treatment protocols vary worldwide and lack standardization.

This review highlights the evolution of the surgical treatment of GC/PC and discusses critical trials supporting the role of CRS with variations in the delivery of IP chemotherapy. Although there is increasing evidence supporting improved survival outcomes with CRS and regional therapy for patients with GC/PC, current guidelines from the National Comprehensive Cancer Network remain sparse.[7] Table 1 (completed clinical trials) and Table 2 (completed retrospective studies) summarize the findings from many of the landmark publications that are contributing to the growing literature addressing the role of CRS/IP chemotherapy in patients with GC/PC.

Systemic Chemotherapy With or Without NIPEC

The PHOENIX-GC trial from Japan was a multicenter, phase 3 study with 2:1 randomization that compared combined NIPEC and SC with SC alone in patients with GC/PC.[8] Patients in the combination arm received IP/intravenous (IV) paclitaxel plus oral S-1 vs IV cisplatin and oral S-1 in the control arm. There was no significant difference in median OS between the groups (17.7 months in the IP/SC arm vs 15.2 months in the SC-only arm); however, 3-year OS was significantly higher in the IP/SC group (21.9% vs 6%). In addition, the IP/SC group experienced significantly more ascites, and after adjusting for baseline ascites in the sensitivity analysis, there was improved survival within the IP/SC arm (hazard ratio, 0.59; P=.008). Although it was a negative study, this trial suggested possible clinical benefits of NIPEC with IP paclitaxel for GC/PC.

Two additional trials that examined the feasibility of a more modern chemotherapy regimen (leucovorin, 5-fluorouracil [5-FU], and oxaliplatin [FOLFOX]) with IP paclitaxel in GC/PC are important to highlight. The FNF-004 trial was a multicenter, phase 2 study from China of patients with advanced GC who were randomly assigned to one of 3 groups: FOLFOX alone (n=30), IV paclitaxel and FOLFOX (n=30), and IP paclitaxel and FOLFOX (n=29).[9] Both the IV paclitaxel and IP paclitaxel groups demonstrated significantly improved progression-free survival (PFS) compared with the FOLFOX arm (median PFS, 6.4 months for IV paclitaxel vs 6.2 months for IP paclitaxel vs 4.1 months for FOLFOX alone). With a median follow-up of 41 months, the median OS was improved for patients who received IV or IP paclitaxel vs FOLFOX alone, at 10.2 months vs 6.9 months, respectively.[10] The authors concluded that both infusional and IP administration of paclitaxel with FOLFOX improved PFS and OS more than with FOLFOX alone, with similarly manageable adverse effects.

Recently, Kang and colleagues designed a single-center, phase 1 dose-escalation study in South Korea examining the safety and efficacy of IP paclitaxel with IV FOLFOX in GC/PC.[11] The maximum tolerated dose was found to be 60 mg/m^2, with a median OS of 16.6 months and a median PFS of 9.6 months for the total cohort. These 2 trials showed promising results in the administration of IP paclitaxel combined with modern SC/FOLFOX for GC/PC, with tolerable adverse events and improved survival outcomes.

Systemic Chemotherapy vs Cytoreductive Surgery/HIPEC/Systemic Chemotherapy

The GYMSSA trial was a single-center, randomized, phase 3 study from the United States that compared gastrectomy/metastasectomy plus SC with SC alone in patients with GC metastasis.[12] Although the study closed owing to poor accrual after enrolling only 17 of a desired 136 patients, the authors reported the outcomes of patients with GC/PC. Patients in the experimental arm received CRS, HIPEC with IP oxaliplatin, and IV leucovorin, 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI), whereas patients in the control arm received IV FOLFOXIRI only. OS was 11.3 months in the CRS/HIPEC/SC group vs 4.3 months in the SC group, with no patient in the FOLFOXIRI-only arm surviving past 11 months. The CRS/HIPEC/SC group also had a considerably high reoperation rate of 44%, although 4 patients lived longer than 1 year and 1 patient lived longer than 4 years. All patients who survived beyond 12 months achieved CC0 and a PCI of no more than 15, illustrating the potential impact of complete cytoreduction and lower PCI score on OS in GC/PC. Although no statistical comparison was possible because of the study's small number of participants, the preliminary results highlighted the need for further studies to investigate the multimodality treatment approach consisting of CRS and regional therapy in addition to SC in the treatment of patients with GC/PC.

Cytoreductive Surgery vs Cytoreductive Surgery/HIPEC

The only randomized controlled trial comparing CRS

with CRS/HIPEC in GC/PC was published by Yang and colleagues in 2011.[13] This was a single-center, phase 3 study in China with 68 patients (34 patients per arm). HIPEC was performed with IP cisplatin and mitomycin C. Median OS was higher in the CRS/HIPEC arm than in the CRS-only arm (11.0 months vs 6.5 months; *P*=.046); however, this difference was not seen in the low PCI (<20) group (10.2 months vs 10.5 months, respectively). On multivariate analysis, CRS/HIPEC, synchronous PC, CC0-1, SC of more than 6 cycles, and the absence of serious adverse events were independent predictors for improved survival. The authors of this trial concluded that CRS and HIPEC provided survival benefit for select patients with GC/PC. Although published in 2011, this study was not widely adapted at the time owing to the lack of granular details reported, as well as the low OS in both groups.

The GASTRIPEC trial was a multicenter, phase 3 study from Germany that compared the addition of HIPEC to CRS with CRS alone in patients with GC/PC.[14] Patients in both arms received preoperative and postoperative SC in addition to cytoreduction, and patients in the CRS/HIPEC arm also received IP chemoperfusion with mitomycin C and cisplatin during CRS. A total of 105 patients were randomized in the first 4 years of the study, which closed early owing to poor accrual. Fifty-five patients stopped treatment before CRS owing to disease progression or death. The median OS for both groups was 14.9 months (*P*=.16), but the CRS/HIPEC group demonstrated significantly improved PFS and distant metastasis-free survival. Although the study ended early owing to slow recruitment and the final sampling was not adequately powered, the authors stated that further investigation seemed worthwhile, given the positive results from this trial.

CYTO-CHIP was a retrospective multicenter study from France, supplemented by propensity score analysis, that also compared CRS with CRS/HIPEC and demonstrated improved survival with the addition of HIPEC.[15] The HIPEC regimens consisted of mitomycin C, oxaliplatin, or cisplatin with or without irinotecan and doxorubicin. Median OS was higher in the CRS/HIPEC arm than in the CRS-only arm (18.8 months vs 12.1 months; *P*<.001). Furthermore, 3- and 5-year recurrence-free survival was significantly greater with CRS/HIPEC, and the addition of HIPEC resulted in a remarkable 5-year OS of 20%. Patients were selected from 19 centers over 25 years, averaging to less than 1 enrolled patient per center per year. Coupled with a low median PCI of 3 for the total cohort, this suggested a highly selective nature of patients with GC/PC undergoing surgical treatment within the study.

Nonrandomized Cytoreductive Surgery/ HIPEC Studies

The PERISCOPE I trial from the Netherlands was a multicenter, phase 1 and 2 safety and feasibility study of CRS/HIPEC in GC patients with limited peritoneal dissemination following SC.[16] Patients received HIPEC (hyperthermic oxaliplatin) followed by NIPEC (normothermic docetaxel). The study found that the maximum tolerated dose of IP docetaxel was 50 mg/m^2, the rate of serious adverse events was 68%, the reoperation rate was 16%, and the rate of treatment-related mortality was 8%. The authors concluded that CRS with IP chemotherapy (HIPEC followed by NIPEC) was both safe and feasible.

Badgwell and colleagues conducted a single-center, phase 2 trial in the United States that investigated laparoscopic iterative HIPEC after completion of SC for gastric or gastroesophageal adenocarcinoma, with gastrectomy offered if the peritoneal disease resolved.[17] Using IP chemotherapy with mitomycin C and cisplatin, up to 5 iterative HIPEC procedures were performed; most of the patients had a single session. In this small study of 19 patients, 5 patients were downstaged to resectability, with a median OS of 20.3 months from the first laparoscopic HIPEC. These findings suggested that this minimally invasive approach to iterative HIPEC was safe, with encouraging outcomes in an identified subset of patients.

A follow-up phase 2 trial published later by the same group further examined patients with GC/PC who had completed SC and laparoscopic iterative HIPEC, were amenable to complete cytoreduction, and proceeded with gastrectomy and CRS/HIPEC using mitomycin C and cisplatin.[18] The median OS for the 20 patients in this study who underwent CRS/HIPEC was 16.1 months, and the 1-, 2-, and 3-year OS rates were 90%, 50%, and 28%, respectively, for a median follow-up of 34 months. The authors concluded that this aggressive approach to treat GC/PC with CRS/HIPEC was encouraging, and that further randomized trials were needed to confirm safety and survival outcomes.

In Europe, 3 retrospective studies investigating the role of CRS/HIPEC have also contributed to the growing literature on regional therapy in gastric adenocarcinoma with peritoneal metastases:

(1) Glehen and colleagues reported findings from a multicenter study in France in which 159 patients with GC/PC underwent CRS and either HIPEC and/or early postoperative intraperitoneal chemotherapy (EPIC; a form of NIPEC).[19] HIPEC regimens included mitomycin C or oxaliplatin with or without IV 5-FU and leucovorin. The EPIC regimen consisted of mitomycin C followed by 5-FU. The median OS for the total cohort was 9.2 months, and

Table 2. Completed Retrospective Studies in Cytoreductive Surgery and Intraperitoneal Chemotherapy

Study, Authors (y)	Location (Size)	Arms	Outcomes
CRS vs CRS/HIPEC			
CYTO-CHIP, Bonnot et al (2019)[15]	France, multicenter (N=277)	CRS vs CRS/HIPEC (IP MMC, oxaliplatin, or cisplatin +/- irinotecan and doxorubicin)	Median OS 18.8 mo (CRS/HIPEC) vs 12.1 mo (CRS), *P*<.001; 3- and 5-y RFS 20.4% and 17.1% (CRS/HIPEC) vs 5.9% and 3.8% (CRS), *P*=.001
CRS/HIPEC			
Glehen et al (2010)[19]	France, multicenter (N=159)	CRS/HIPEC (IP MMC or oxaliplatin +/- IV 5-FU and leucovorin) and/or EPIC (IP MMC and 5-FU)	Median OS 9.2 mo; 1-, 3-, 5-y OS 43%, 18%, 13%, respectively
Rihuete Caro et al (2018)[20]	Spain, single-center (N=35)	CRS/HIPEC (IP cisplatin and doxorubicin)	Median OS 16 mo; 1-, 3-, 5-y OS 70.8%, 21.3%, 21.3%, respectively
DGAV-HIPEC, Rau et al (2020)[21]	Germany, multicenter (N=235)	CRS/HIPEC (IP cisplatin, MMC, doxorubicin, oxaliplatin)	Median OS 13 mo; 5-y OS 6%
PIPAC			
Alyami et al (2021)[23]	France, single-center (N=163)	PIPAC (IP cisplatin and doxorubicin) repeated every 6-8 wk for at least 3 procedures	Median OS 19.1 mo; complete disappearance of ascites after third PIPAC in 50% of patients; major complication rate 3.1%; 14.3% became resectable after a median of 3 cycles of PIPAC and CRS/HIPEC

5-FU, 5-fluorouracil; CRS, cytoreductive surgery; EPIC, early postoperative intraperitoneal chemotherapy, HIPEC, hyperthermic intraperitoneal chemotherapy; IP, intraperitoneal; MMC, mitomycin C; mo, months; OS, overall survival; PIPAC, pressurized intraperitoneal aerosolized chemotherapy; RFS, recurrence-free survival; wk, weeks; y, year.

1-, 3-, and 5-year survival rates were 43%, 18%, and 13%, respectively. Completeness of CRS was the only independent prognostic indicator for survival, and the median OS was 15 months for patients treated by complete cytoreduction, with 1-, 3-, and 5-year survival rates of 61%, 30%, and 23%, respectively. Unfortunately, subgroup analyses between the HIPEC and EPIC groups were not performed owing to limited proportions in the EPIC group.

(2) Rihuete Caro and colleagues performed a single-center study in Spain in which a small cohort of 35 patients with GC/PC underwent CRS/HIPEC using cisplatin and doxorubicin.[20] Grade 3 or higher complications occurred in 25.7% of patients. The median follow-up for the entire cohort was 54 months. OS rates at 1, 3, and 5 years were 70.8%, 21.3%, and 21.3%, respectively. Median OS for the total cohort was 16 months, but 19 months for patients with PCI no greater than 6. The authors concluded that survival improved in selected patients with GC/PC undergoing CRS/HIPEC and perioperative SC.

(3) DGAV-HIPEC was a multicenter study from Germany that examined patients with GC/PC undergoing CRS/HIPEC.[21] The most frequently used chemotherapeutic agents were cisplatin, mitomycin C, doxorubicin, and oxaliplatin. Median OS was 13 months, and 5-year OS was 6%. Similar to prior studies, median OS was found to be inversely proportional to PCI, with lower scores correlating with improved survival (median OS of 18 months with PCI 0-6, 12 months with PCI 7-15, and 5 months with PCI 16-39; *P*=.002). Limitations to this registry study included short mean follow-up (10.8 months for the total cohort), and a 5-year study period across 52 hospitals equating to less than 1 patient per center per year.

Pressurized Intraperitoneal Aerosolized Chemotherapy

PIPAC has been proposed as an alternative method of IP delivery, claiming improved drug distribution, enhanced tissue uptake, better tolerance, and repeatability using minimally invasive access.[22] Moreover, PIPAC techniques are homogeneous throughout expert centers and have less variability of administration compared with other forms of IP delivery. Alyami and colleagues conducted a single-institution retrospective review in France of patients who received pressurized aerosol containing the chemotherapy agents cisplatin and doxorubicin, repeating PIPAC every 6 to 8 weeks with SC alternating between procedures.[23] The study involved 163 PIPAC procedures

Table 3. Ongoing Prospective Clinical Trials in Cytoreductive Surgery and Intraperitoneal Chemotherapy

Study, Authors or PI	Start Date	Design	Location (Size)	Arms	Endpoints
GASTRICHIP, Glehen et al[25]	2013	Phase 3	France, multicenter (N=367)	Gastrectomy + D1-2 vs gastrectomy + D1-2 + HIPEC (IP oxaliplatin)	Primary: 5-y OS; secondary: RFS, locoregional survival, treatment-related morbidity and mortality, QOL
PERISCOPE II, Koemans et al[27]	2017	Phase 3	Netherlands, multicenter (N=182)	Palliative systemic chemotherapy vs CRS/IP (HIPEC oxaliplatin, NIPEC docetaxel)	Primary: 5-y OS; secondary: PFS, treatment-related toxicity, costs and health benefits
National Cancer Institute, Davis[30]	2020	Phase 2	US, single-center (N=74)	IP/IV paclitaxel + oral capecitabine	Primary: PFS; secondary: OS, morbidity, intraperitoneal PFS, histopathologic response, extraperitoneal DFS
STOPGAP, Senthil[29]	2021	Phase 2	US, single-center (N=35)	Systemic chemotherapy followed by IP paclitaxel + IV paclitaxel, 5-FU, leucovorin + CRS (PCI ≤10)	Primary: 1-y PFS, treatment related adverse events; secondary: OS, QOL, expression of plasma and ascites exosomal gene signature (EXOSIG), and correlation of EXOSIG to treatment response

5-FU, 5-fluorouracil; CRS, cytoreductive surgery; D1, limited lymph node dissection; D2, extended lymph node dissection; DFS, disease-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; IP, intraperitoneal; IV, intravenous; NIPEC, normothermic intraperitoneal chemotherapy; OS, overall survival; PCI, peritoneal carcinomatosis index; PFS, progression-free survival; PI, principal investigator; QOL, quality of life; RFS, recurrence-free survival; y, year.

in 42 consecutive patients, with a median of 3 PIPAC sessions per patient. A total of 6 patients proceeded to CRS/HIPEC for curative intent once the disease status was considered resectable, with a clear decrease in PCI at the time of cytoreduction. The authors concluded that PIPAC with low-dose cisplatin and doxorubicin was safe and feasible, with encouraging survival data.

Struller and colleagues performed the first single-center, phase 2 trial from Germany investigating the safety and feasibility of PIPAC in recurrent GC/PC.[24] The study enrolled 25 patients, each scheduled for 3 courses of PIPAC with cisplatin and doxorubicin every 6 weeks. Ten patients (40%) had a complete radiological response, partial response, or stable disease, and 36% demonstrated complete or major regression on histology, with no unexpected serious adverse reactions, treatment-related deaths, or severe toxicities. Based on the positive results of this phase 2 trial, the authors recommended proceeding with randomized controlled trials in PIPAC, highlighting that the good tolerability of PIPAC is a novelty compared with other IP chemotherapy regimens, which can be limited by high local toxicity.

Ongoing Clinical Trials

Given the overall improvement in survival seen with cytoreduction and IP chemotherapy in the surgical management of GC/PC, several additional clinical trials are currently underway to explore additional treatment options and modalities. Table 3 summarizes findings from active clinical trials in GC/PC and IP chemotherapy that are ongoing worldwide. Chief among these ongoing studies are the GASTRICHIP, PERISCOPE II, and STOPGAP trials.

(1) The GASTRICHIP trial is a multicenter, randomized, controlled, phase 3 study from France exploring the effects of HIPEC with oxaliplatin on patients with GC with serosal invasion and/or lymph node involvement and/or positive peritoneal cytology, treated with perioperative SC and D1 (limited lymph node dissection) or D2 (extended lymph node dissection) curative gastrectomy.[25] The 2 study arms are gastrectomy alone and gastrectomy plus HIPEC (with oxaliplatin). Enrollment began in 2013 with an estimated study completion date through 2026 and an actual enrollment of 367 participants.[26] This trial will provide metrics on survival, toxicity, and quality of life, with the key goal of determining whether the addition of HIPEC to gastrectomy confers a survival benefit in patients with locally advanced GC with positive peritoneal cytology.

(2) The PERISCOPE II trial is a multicenter, randomized, controlled, phase 3 study from the Netherlands

examining patients GC/PC with limited peritoneal dissemination (PCI <7) and/or tumor-positive peritoneal cytology.[27] It is a continuation of the PERISCOPE I trial that studied the safety and efficacy of HIPEC with hyperthermic oxaliplatin followed by NIPEC with normothermic docetaxel. The study is designed to compare outcomes of patients treated with palliative SC alone (standard treatment) with those of patients who undergo gastrectomy and CRS/IP chemotherapy with oxaliplatin and docetaxel (experimental treatment) after 3 to 4 cycles of SC. Enrollment began in 2017 with an estimated study completion date through 2029 and an estimated enrollment of 182 participants.[28] This important trial will determine whether CRS/IP chemotherapy confers a survival benefit in patients with GC/PC compared with SC alone. The study will provide data on survival, toxicity, cost effectiveness, and quality of life in patients with GC/PC undergoing CRS/IP chemotherapy, with the goal of defining whether cytoreduction and IP chemotherapy administration can be used as a standard treatment option for GC with limited peritoneal disease.

(3) The STOPGAP trial is a single-center, phase 2 study from the United States assessing the safety and efficacy of sequential SC and paclitaxel NIPEC in patients with primary gastric and/or gastroesophageal junction cancer and PC.[29] Patients with post-NIPEC PCI of 10 or less are eligible to undergo CRS/HIPEC. Enrollment began in 2021 with an estimated study completion date through 2025 and an estimated enrollment of 35 participants. All patients will complete preoperative SC followed by diagnostic laparoscopy with port placement and IP paclitaxel. Patients will undergo restaging imaging and laparoscopy after approximately 3 to 4 cycles of NIPEC to assess treatment response. Based on the response and extent of disease on restaging scans, patients will be triaged to one of the following treatment plans: stable disease or response and PCI greater than 10 (continue IP chemotherapy regimen), progression (switch to second-line regimen), response with PCI of 10 or less and complete cytoreduction is feasible (consider CRS/IP chemotherapy). This study will assess the safety of iterative NIPEC as an intermediary treatment prior to cytoreductive surgery in patients with GC/PC.

(4) Another ongoing, single-center, phase 2 study from the United States is from the National Cancer Institute and is similarly assessing the efficacy of IP and IV paclitaxel with concomitant oral capecitabine in patients with primary gastric and/or gastroesophageal junction cancer and PC.[30] Enrollment began in 2020 with an estimated study completion date through 2027 and an estimated enrollment of 74 participants. All patients complete diagnostic laparoscopy with port placement, followed by NIPEC with paclitaxel, IV paclitaxel, and oral capecitabine for a 21-day cycle. Treatment response is assessed with imaging and laparoscopy after completion of 3 cycles, and additional courses of therapy may be offered. This trial will study the efficacy of IP chemotherapy as a route of administration of chemotherapy in patients with GC/PC.

Prophylactic Intraperitoneal Chemotherapy

The concept of utilizing IP chemotherapy to reduce the incidence of metachronous PC in patients with locally advanced GC continues to be an important area of investigation. Several retrospective studies have been published in recent years comparing patients with advanced GC undergoing radical surgery (including D2 lymphadenectomy) and HIPEC with radical surgery alone, with improvement in disease-free survival, OS, and peritoneal recurrence rate in the prophylactic HIPEC group. The clinical rationale for prophylactic IP chemotherapy to patients at risk of peritoneal dissemination as an adjunct to gastrectomy and D2 lymphadenectomy is strong, as preventing PC is likely to be associated with better outcomes than treatment of GC/PC; however, this has yet to be validated in clinical trials.

(1) As such, there are several ongoing clinical trials evaluating the use of prophylactic IP therapy (HIPEC and PIPAC) in the treatment of locally advanced GC. Some of the key ongoing randomized studies are summarized in Table 4. A single-center, phase 2 randomized study from Wuhan University in China by Xiong and colleagues is currently examining the efficacy of HIPEC in locally advanced GC.[31] All patients complete neoadjuvant SC followed by radical gastrectomy with D2 lymphadenectomy. The HIPEC arm also receives IP paclitaxel and 5-FU intraoperatively. Patients in both groups receive postoperative chemotherapy (6 total cycles including neoadjuvant chemotherapy). Enrollment began in 2020 with an estimated study completion date through 2025 and an estimated enrollment of 100 participants. The primary endpoint is 5-year OS, and secondary endpoints include PFS, distant metastasis rate, peritoneal metastasis rate, local recurrence rate, and complication rate. This study will assess the efficacy of HIPEC in patients undergoing perioperative chemotherapy and gastrectomy with lymphadenectomy for locally advanced GC.

(2) The CHIMERA trial is a multicenter, phase 3 study from Poland that aims to evaluate the efficacy of preoperative 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy with prophylactic HIPEC plus gastrectomy in patients with locally advanced GC who are at high risk of developing PC.[32] Enrollment began in 2021 with an estimated study completion date through 2026 and a targeted accrual of 600 participants. All

Table 4. Ongoing Randomized Clinical Trials in Prophylactic Intraperitoneal Chemotherapy

Study, PI (y)	Start Date	Design	Location (Size)	Arms	Endpoints
Prophylactic HIPEC					
Wuhan University, Xiong[31]	2020	Phase 2	China, single-center (N=100)	Neoadjuvant chemotherapy + radical gastrectomy and D2 + adjuvant chemotherapy +/- HIPEC (IP paclitaxel + IV 5-FU)	Primary: 5-y OS; secondary: PFS, distant metastasis rate, peritoneal metastasis rate, local recurrent rate, complication rate
CHIMERA, Pach[32]	2021	Phase 3	Poland, multicenter (N=600)	FLOT + gastrectomy vs FLOT + HIPEC + gastrectomy	Primary: 6-mo peritoneal recurrence rate; secondary: OS, local recurrence rate, systemic recurrence rate, complication rate, QOL
Prophylactic PIPAC					
GASPACCO, Zakharenko[33]	2020	Phase 3	Russia, single-center (N=304)	Neoadjuvant chemotherapy + gastrectomy/ D2 +/- PIPAC (IP cisplatin and doxorubicin)	Primary: 5-y OS; secondary: OS, PFS/DFS, peritoneal relapse, adverse events, QOL, pain scores, postoperative morbidity and mortality

5-FU, 5-fluorouracil; CRS, cytoreductive surgery; D1, limited lymph node dissection; D2, extended lymph node dissection; DFS, disease-free survival; FLOT, 5-FU, leucovorin, oxaliplatin, and docetaxel; HIPEC, hyperthermic intraperitoneal chemotherapy; IP, intraperitoneal; IV, intravenous; NIPEC, normothermic intraperitoneal chemotherapy; OS, overall survival; PCI, peritoneal carcinomatosis index; PFS, progression-free survival; PI, principal investigator; QOL, quality of life; RFS, recurrence-free survival; y, year.

patients receive neoadjuvant FLOT followed by diagnostic laparoscopy. If no metastatic disease is visible, patients are randomized to either gastrectomy plus HIPEC with irinotecan vs gastrectomy alone. All patients complete adjuvant FLOT chemotherapy. The primary outcome is the peritoneal recurrence rate at 6 months, and secondary endpoints include OS, local recurrence rate, systemic recurrence rate, complication rates, and quality of life assessment. This ongoing clinical trial will help address whether prophylactic HIPEC can reduce short-term peritoneal recurrence rates and OS in patients at high risk for GC/PC.

(3) The GASPACCO trial is a single-center, randomized, phase 3 trial from Russia evaluating the efficacy of PIPAC in preventing PC in patients with locally advanced GC.[33] Enrollment began in February 2020 with an expected completion date through 2029 and an estimated enrollment of 304 participants. All patients are receiving neoadjuvant FLOT followed by diagnostic laparoscopy and peritoneal lavage, with randomization to gastrectomy and D2 lymphadenectomy with PIPAC using cisplatin and doxorubicin, or surgery alone. Both study groups are receiving adjuvant chemotherapy. The primary endpoint is 5-year OS, and secondary endpoints include PFS, disease-free survival, peritoneal relapse, serious adverse events, quality of life assessment, pain assessment, and postoperative morbidity and mortality. This novel, ongoing clinical trial in patients with advanced GC is one of the first studies to examine the impact of prophylactic PIPAC on survival outcomes.

Conclusion

Owing to the poor prognosis of patients with metastatic GC to the peritoneum, treatment options beyond SC are needed, as are more randomized trials validating their survival benefits. Because of the aggressiveness of PC in gastric adenocarcinoma, there is a biological need for regional IP treatment. Over the past 3 decades, regional therapy for GC/PC has evolved to include the addition of various forms of IP chemotherapy with cytoreduction. These studies warrant further investigation into optimizing the delivery of IP chemotherapy in this disease state.

The challenge of conducting clinical trials in this highly specific population of GC is highlighted by the premature closure of several trials owing to poor accrual. Furthermore, the biological differences between GC from Eastern and Western countries add to the complexity of identifying standard-of-care therapy based on international trials. GC from Eastern countries (eg, Japan and Korea) have lower proportions of adverse factors such as signet ring histology and proximal stomach involvement. As a result, most large randomized trials from Eastern countries demonstrate survival rates that are 30% to

40% higher than trials from Western countries.[34] Additional immunohistochemical studies show distinct tumor immunity signatures related to T-cell function in patients with GC from Asian and non-Asian countries.[35] These differences in tumor biology across geographic regions challenge the global application of study results to standard clinical practice.

Nevertheless, the observations from many of these studies provide valuable guidance for patient selection. The importance of SC prior to CRS cannot be overemphasized, as more than 50% of these patients will experience disease progression during SC and therefore may not derive a meaningful survival benefit with CRS. Hence, optimizing systemic control, then using multimodality diagnostic evaluations including cross-sectional imaging and diagnostic laparoscopy to assess response of systemic therapy, PCI, and feasibility of complete cytoreduction prior to proceeding with CRS is strongly recommended. Repeatedly, low peritoneal tumor burden and complete cytoreduction have been associated with improved survival.

The other important treatment option to consider is IP chemotherapy with NIPEC or HIPEC prior to CRS both to achieve maximal peritoneal disease control prior to CRS and to possibly convert patients to CRS candidates. The optimal sequence of systemic and IP chemotherapy, the conditions of IP chemotherapy (normothermic vs hyperthermic), and the best IP drug and drug combinations are areas that need further investigation. Additionally, the adjuvant management of patients post-CRS/HIPEC is an area that needs further investigation to extend the durability of survival benefit. The evolving landscape of systemic therapy options including immunotherapy and targeted therapies supply significant promising research opportunities but are beyond the scope of this review. The rapid improvement in systemic treatment options and novel drug discoveries combined with development of in vitro tumor models to assess treatment response may provide a path forward to effectively test and synergize systemic and IP drug combinations to ultimately improve survival outcomes in this devastating disease.

The results of ongoing trials are eagerly awaited to provide evidence and create new treatment paradigms in the management of GC/PC. Concomitantly, these findings will provide new questions and avenues for further research regarding the optimal treatment approach to improve survival outcomes in GC/PC.

Disclosures

Drs Young, Ostowari, Yu, Eng, and Senthil have no relevant disclosures to report. Dr Dayyani has received research grants to his institution from AstraZeneca, Bristol Myers Squibb, Merck, Genentech/Roche, Taiho, Exelixis, Trishula Therapeutics, and Leap Therapeutics; speaker honoraria from Amgen, Eisai, Ipsen, Exelixis, Sirtex, Deciphera, Ipsen, and Natera; and consultancy honoraria from Natera, QED Therapeutics, Eisai, Exelixis, and Genentech/Roche.

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