Review Article

Hyperthermic intraperitoneal chemotherapy for gastric cancer: a narrative review

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Background and Objective: Gastric cancer (GC) is the 5th most common malignancy globally, and although there have been modest gains in improving survival rates, it remains a leading cause of death. A component contributing to the poor survival rates includes advanced disease stage at presentation. Approximately 30–40% of GC patients present with metastases at diagnosis, with poorer outcomes when peritoneal metastases are present. However, recent studies have demonstrated potential utility of hyperthermic intraperitoneal chemotherapy (HIPEC) for GC with peritoneal carcinomatosis (GCPC) and for prevention of peritoneal carcinomatosis in high-risk patients. HIPEC for GC is highly debated. It is currently not recommended as part of standard of care for GC. The objective of this study is to discuss the various factors influencing the success of HIPEC, current intraperitoneal (IP) chemotherapy treatment regimens, timing of HIPEC administration, major randomized controlled trials (RCTs) and non-RCTs (NRCTs), and meta-analyses in GC patients.

Methods: A review of the Library of Congress, the Cochrane Review, Google Scholar, PubMed, and ClinicalTrials.gov was performed. All articles and trials with available data in English with full text were considered. Necessary keywords used to search included "gastric cancer" and/or "HIPEC". Included articles were independently reviewed by authors.

Key Content and Findings: Optimal HIPEC administration timing is unclear, but many utilize it in a neoadjuvant or prophylactic setting. Signet ring pathology and epithelial mesenchymal transition (EMT) cell histologic subtypes may have more aggressive pathology, limiting HIPEC success rates. Patients who receive complete cytoreduction and have low peritoneal carcinomatosis index (PCI) burden have been shown to have improved median overall survival (OS) after HIPEC. The data suggests in GCPC, HIPEC can modestly improve recurrence-free and OS. The data regarding benefits of prophylactic HIPEC in advanced GC (AGC) remains mixed.

Conclusions: HIPEC for GC is controversial. Much of the literature is exploratory in nature or difficult to compare, as many outcomes are novel/not cross validated against substantial preceding data, with highly variable patient populations and study designs. However, in certain clinical scenarios in high volume centers, some patients with non-metastatic or low burden disease who undergo prophylactic or intraoperative HIPEC may benefit with improved overall and recurrence free survival (RFS).

Keywords: Hyperthermic intraperitoneal chemotherapy (HIPEC); gastric cancer (GC); cytoreductive surgery (CRS); peritoneal carcinomatosis index (PCI); stage

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Introduction

Gastric cancer (GC) is the 5th most common cancer and 3rd leading cause of cancer-related deaths globally. GC with peritoneal carcinomatosis (GCPC) has a particularly poor prognosis, with 5-year overall survival (OS) at several months, with many patients presenting with advanced disease (1). However, recent studies have demonstrated potential utility of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in GCPC patients both for treatment of and prophylaxis against peritoneal disease.

GCPC is resistant to standard intravenous chemotherapy due to diffuse tumor burden, the "plasma-peritoneal barrier", and poor vascular delivery to the peritoneal space itself. Consequently, direct regional therapy via intraperitoneal (IP) chemotherapy has been pursued to reduce or prevent disseminated peritoneal disease. IP chemotherapy regimens utilized in HIPEC often are heated, hydrophilic, ionized, and have high molecular weight. These properties allow increased passage of agents while limiting systemic toxicity through passive diffusion (2). Tissue penetration of most commonly used drugs ranges from 3 to 5 mm at maximum (3).

HIPEC is not currently recommended by the National Comprehensive Cancer Network (NCCN) guidelines. Moreover, current standard of care for advanced GC (AGC) is chemotherapy alone, supported by the REGATTA trial findings, which was a large phase 3 East Asia randomized control trial which found gastrectomy followed by chemotherapy did not demonstrate significant OS improvement when compared to chemotherapy alone (14.3 *vs.* 16.6 months respectively) (4). Thus, utilization of HIPEC for GC remains debated. This review discusses factors that may influence HIPEC outcomes, chemotherapy regimens, timing, and major studies that have evaluated HIPEC for GCPC patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-90/rc).

Methods

A targeted literature search to identify preclinical and clinical studies discussing outcomes of HIPEC for GC published prior to July 1, 2023 (*Table 1*). ClinicalTrials.gov, PubMed, Google Scholar, Library of Congress, and the Cochrane Review were searched for relevant studies. A strategy employing two vital keywords to search the databases included "gastric cancer" and/or "HIPEC" as necessary phrases, with additional phrases of "peritoneal carcinomatosis", "advanced gastric cancer", "early gastric cancer", "randomized trials", "non-randomized trials", "meta-analysis", "clinical trials", and "hyperthermic intraperitoneal chemotherapy".

As part of this narrative review, relevant and significant randomized controlled trials (RCTs), non-RCTs (NRCTs), and meta-analyses drawn from ClinicalTrials.gov, PubMed, Google Scholar, Library of Congress, and Cochrane Review limited to both AGC without PC and GCPC patient populations for curative and prophylactic intent will be discussed. The aforementioned databases were searched from inception until June 2023 to identify pertinent literature for this review. During the search, key phrases such as "gastric cancer" and/or "HIPEC" were necessary as criteria, but otherwise no restrictions were applied to the rest of the search in terms of publication status, journal, year of publication, etc. The compiled literature used for this review were independently searched for by the two junior authors, and the senior author reviewed chosen publications for relevance and significance and resolved any disputes.

Factors impacting GC HIPEC outcomes/selection

Genetic/histologic subtypes

Diagnostic laparoscopy with cytologic washings is recommended as part of staging workup for GC with clinical staging T1bN0 or greater per NCCN Practice Guidelines in Oncology, Gastric Cancer, Version 2.2022 guidelines as the incidence of peritoneal disease in T2 and/or N1 GC patients is high. Consequently, more GC patients are diagnosed earlier with peritoneal metastasis. Recent studies have shown promising results that analyses of GCPC cells from cytologic washings/malignant ascites have demonstrated various features that can influence CRS/HIPEC efficacy; however, these findings have yet to be translated to the clinical sphere. In multiomic malignant ascites studies, researchers identified two GCPC molecular subtypes—non-epithelial mesenchymal transition (non-EMT) and EMT. EMT is linked to drug resistance and cancer stem cell-ness acquisition in GC and is a process both found in diffuse and intestinal GC, although the precise gene pathways related to EMT for diffuse and intestinal-type GC appear to have multiple gene differences (5). EMT subtype patients developed PC more frequently and had worse prognoses compared to non-EMTs (6). Another study investigating GC cells of

Table 1 Search strategy for relevant HIPEC for gastric cancer articles

Items	Specification
Date of search	Oct 1, 2022 to Jul 1, 2023
Databases and other sources searched	ClinicalTrials.gov, PubMed, Google Scholar, Library of Congress, and Cochrane Review
Search terms used	Gastric cancer, peritoneal carcinomatosis, advanced gastric cancer, early gastric cancer, randomized trials, non-randomized trials, meta-analysis, clinical trials, hyperthermic intraperitoneal chemotherapy, HIPEC
Timeframe	Up to July 1, 2023
Inclusion and exclusion criteria	All pre-clinical and clinical trials, both randomized and non-randomized, and meta-analyses were included based on the above search criteria. For clinical trials, studies were excluded if outcomes were not reported in forms of data, an abstract, or a manuscript
Selection process	An independent search was individually conducted by all authors for relevance and quality of included studies

HIPEC, hyperthermic intraperitoneal chemotherapy.

patients with peritoneal dissemination found that ADP-ribosylation factor-like 4C was a peritoneal dissemination-linked gene which was positively correlated with EMT genes, supporting EMT phenotypes were more likely to have peritoneal disease (7). Wang *et al.* revealed increased MYC activation, genome doubling, impaired immunity, chromosomal instability, and higher numbers of *TP53*, *CDH1*, and *KMT2C* mutations were found in aggressive, minimally responsive PC phenotypes (8).

Cell expression response variants also influence HIPEC response. Zhang *et al.* demonstrated increased *miR-218* presence in GC taken from human patients was associated with increased chemosensitivity to cisplatin following HIPEC (9). Additional studies investigating other miRNA following HIPEC revealed *miR-218* upregulation decreased GC invasion via *E-cadherin* interference (10). These studies suggest amongst GCPC patients, there are subsets with inherently more unfavorable phenotypes.

Signet ring cell pathology

GC patients with signet ring cell pathology have worse overall outcomes. A retrospective analysis by Solomon *et al.* demonstrated on subgroup analysis that CRS with HIPEC had no difference on OS when signet ring cell pathology was present, reinforcing the negative prognosis (11). However, more studies are needed to support these findings as to determine if aggressive pathology may limit patient surgical candidacy, as few other studies have studied this particular subset following CRS/HIPEC.

Completeness of cytoreduction

One of the most influential predictors of improved survival for GCPC after CRS/HIPEC is completeness of cytoreduction. Patients with complete CRS have notably better oncologic and OS outcomes compared to those with residual disease (12). The degree of CRS for benefit was demonstrated in a study by Ji *et al.* where patients with CC-0 *vs.* CC-1–3 had a significantly longer median OS (30.0 *vs.* 7.3 months, P<0.01), with no OS differences among CC-1, 2, and 3 CRS (13). Conclusions taken from both the aforementioned studies draw from the studies specifically reported the proportion of patients in their studies that were grouped into CC-0 to CC-3, with both studies containing over 100 patients. Thus, though there are no RCTs on the level of CRS for GCPC patients, current evidence suggests obtaining as complete a cytoreduction as possible.

PCI burden

Another potential predictor for survival in GCPC is peritoneal carcinomatosis index (PCI). While multiple studies have posited that PCI score thresholds may influence survival, there is no consensus on the limit. For example, in a meta-analysis of 748 patients by Coccolini *et al.*, they found the threshold for significant changes in prognosis was at a PCI ≤12 *vs.* Brandl *et al.*, where a majority of the patients who underwent CRS + HIPEC had PCI <6 and demonstrated improved OS (14,15).

GC patients who appear to benefit most from HIPEC are those with no macroscopic metastases but have positive cytology. This is particularly intriguing, as the currently the literature suggests that the median survival of GC patients who undergo curative resection but have positive cytology is similar to that of GCPC patients (16). Some studies have shown increases in OS in subgroups of cytology-positive, macroscopic PC-negative patients who underwent HIPEC, suggesting HIPEC may be able to significantly impact treatment outcomes in a common GC subgroup that had equivalent outcomes to GC patients with widely metastatic macroscopic peritoneal disease (17,18). Importantly, evidence suggests patients who convert from positive to negative cytology have improved survival, highlighting some patients may benefit from HIPEC as a measure to improve outcomes and to prevent macroscopic spread or recurrence (19).

Systemic chemotherapy response

An additional prognostic factor identified is response to systemic chemotherapy. In one study, patients eligible for CRS and HIPEC who received extended pre-operative systemic chemotherapy had decreased survival rates despite receiving HIPEC even with PCI <12 (20). In contrast, tumor regression with systemic therapy with CRS and HIPEC positively influences survival. For example, a single center study in Italy comparing stage IV GC patients with complete regression of cancer following chemotherapy to those with partial regression found improved OS of 60.4 *vs.* 31.2 months respectively after HIPEC, supporting HIPEC may be beneficial in chemo-responsive patients (21). The findings of such studies however may be potentially reflective of tumor biology, delayed referral to a HIPEC center, and chemoresistance.

IP Chemotherapy regimens

IP chemotherapy regimens for GCPC vary. The most common regimens involve mitomycin C and cisplatin, which are both alkylating agents (22). A meta-analysis by Desidero *et al.* found most utilized mitomycin C (MMC) alone, cisplatin alone, or combinations (cisplatin and etoposide, MMC and cisplatin or etoposide) (23). A different review of 32 GC HIPEC regimens reported instillment times from 60 to 90 minutes but as short as 30 minutes (24). A meta-analysis in 2017 by Feingold *et al.* suggested a potential benefit of mitomycin C over cisplatin, although the model incorporated more trials utilizing mitomycin C and had more non-Western patients (25). As such, ideal drug selection and timing has yet to be delineated.

Complications

HIPEC is often reported to have complications post-operatively. Common complications include respiratory failure/distress and pleural effusions, ileus, anastomotic leaks, hepatic dysfunction, renal dysfunction, bone marrow suppression, and intra-abdominal infection. However, conflicting data exists over whether there truly is an increased risk of complications. Some meta-analyses posit increased complication likelihood such as from Desiderio *et al.*, who found higher post-operative overall complication risk in both AGC [risk ratio (RR) 2.17, P<0.01] and GCPC patients (RR 2.15, P<0.01) (23). Yet, other studies suggest HIPEC and curative intent resection with/without cytoreduction *vs.* curative intent resection with/without cytoreduction alone has no increased risk of aforementioned complications (26). However, mortality rates for HIPEC *vs.* surgery alone are agreed to be comparable (27).

HIPEC timing/intent

Neoadjuvant

Timing of HIPEC utilization in GC for optimal benefit is debated. Some suggest effect with bidirectional chemotherapy, with administration of both systemic and IP chemotherapy in a neoadjuvant setting. This neoadjuvant IP and systemic chemotherapy (NIPS) approach was shown by Yonemura *et al.* in 2006 and Canbay *et al.* in 2014 to have more patients with negative peritoneal cytology prior to resection (56% and 78% of patients, respectively); those who underwent complete resection had improved median survival (20.4 *vs.* 14.4 months) (28,29).

Separately, in a phase II trial by Badgwell *et al.*, 19 patients underwent neoadjuvant laparoscopic HIPEC, of which 7 had no macroscopic PC with negative peritoneal cytology after final HIPEC. Five of the 7 patients with no peritoneal disease underwent definitive surgical resection (30). A follow-up study demonstrated that 25% of patients had resolution of peritoneal cytology after laparoscopic HIPEC and were able to proceed to gastrectomy for curative intent (31). Ultimately, these studies demonstrate neoadjuvant HIPEC can reduce

peritoneal disease and allow for curative-intent gastrectomy.

Adjuvant/EPIC

Early post-operative intraperitoneal chemotherapy (EPIC) has also been reported for GC patients. This approach seeks to avoid potential morbidity associated with intra-operative HIPEC. A phase III randomized control trial study by Yu *et al.* investigated use of EPIC in AGC patients without distant metastases. EPIC plus surgery patients had improved 5-year OS compared to surgery alone (54% *vs.* 38%, P=0.002) (32). In another study for GC patients without PC, Feingold *et al.* demonstrated intraoperative IPC had improved OS compared to EPIC (OR 0.54, P=0.004) (25). Yet, a phase II Swedish study of GCPC patients who underwent neoadjuvant chemotherapy, CRS and HIPEC followed by EPIC demonstrated a median survival of 10.2 months (33).

Prophylactic

Some have suggested the use of prophylactic HIPEC for high-PC risk (diffuse subtype, lymphovascular invasion, and >T2) GC patients. Desiderio *et al.* found that patients with cT3–4 disease with and without peritoneal deposits had decreased disease recurrence (RR 0.73) in addition to improved 3- and 5-year OS (RR 0.71, P=0.03 and RR 0.82, respectively) after HIPEC (23). Reutovich *et al.* performed a randomized trial investigating the ability of HIPEC to reduce serosal-invasive GC patient development of metachronous PC and found a lower peritoneal metastasis (12.8% *vs.* 27.6%) rate in addition to improved 3-year PFS with those who underwent HIPEC (34). Sun *et al.* had similar findings for T4a AGC patients, with reduction in peritoneal metastases development (RR 0.45), peritoneal recurrence (RR 0.45), and improved OS in HIPEC patients (RR 0.69, all P<0.001) (35). While these studies are limited to meta-analysis results, finding concordances despite different study composition over the years is suggestive that prophylactic HIPEC may be effective at preventing peritoneal metastasis in GC (27).

HIPEC outcomes

RCTs

AGC

Several studies have examined the impact of HIPEC for the treatment of resectable AGC without PC. A RCT by Cui *et al.* in 2014 investigated HIPEC for patients with AGC who had already undergone surgery. Of treatment groups, the recurrence free survival (RFS) of the joint (received neoadjuvant plus surgery plus HIPEC) group was significantly better than the control (surgery only), and the HIPEC and joint groups had significantly improved 3-year survival rates (58.3% and 75.0% respectively) *vs.* the control (35.4%) (36). A Chinese RCT of 60 patients divided between surgery alone *vs.* surgery and HIPEC also found improved 3-year OS and recurrence, with a 3-year OS of 63.3% *vs.* 40% and recurrence rate of 20% *vs.* 40% in the HIPEC group *vs.* the control (P<0.05) (37). These findings were not replicated in a phase II trial of prophylactic HIPEC by Fan *et al.* in 2021, where HIPEC administration following radical gastrectomy in AGC patients without peritoneal spread did not result in significant 3-year RFS (38). While currently most published RCTs for HIPEC with AGC demonstrate modest improved OS, RFS, and disease-free survival (DFS), conflicting data exists partly due to varying study design/populations making direct comparison difficult.

GCPC

Most RCTs regarding the use of HIPEC in GC have evaluated HIPEC in GC without PC or in mixed patient cohorts. There are, however, a several notable RCTs evaluating HIPEC in GCPC populations.

In the 2014 GYMSSA study, a single-center American prospective RCT evaluating gastrectomy, metastasectomy, HIPEC, and systemic FOLFOXIRI (GYMS arm) *vs.* FOLFOXIRI alone (SA arm) randomized 17 resectable GCPC patients per trial arm. Of the 9 patients who underwent multimodality GYMS treatment, 7 had complete cytoreduction and had a median OS of 11.3 *vs.* 4.3 months to the SA arm. Additionally, 4 GYMS patients survived over a year compared to 0 SA arm patients. However, findings were limited in statistical comparisons due to low power (39).

While the GYMSSA trial gave evidence that multimodality treatment with HIPEC and CRS was superior to chemotherapy alone in GCPC patients, a preceding trial by Yang *et al.* in 2011 assessed whether HIPEC with CRS was better than CRS alone. In their phase 3 RCT involving 68 GCPC patients, they found that median survival was 6.5 *vs.* 11.0 months in the CRS *vs.* CRS and HIPEC group (P=0.05) overall (40).

Most recently, a multicenter RCT phase III trial named the GASTRIPEC-I trial published preliminary results in

2021 for GCPC patients receiving pre- and post-operative chemotherapy who were randomized to curative-intent CRS *vs.* CRS and HIPEC. While 55 of 105 enrolled patients stopped treatment prior to CRS due to death or progression prohibiting resection, both groups had a median OS of 14.9 months (P=0.1647). Yet PFS significantly improved from 3.5 to 7.1 months in the CRS *vs.* CRS plus HIPEC group (P=0.05) as did metastasis-free survival (9.2 *vs.* 10.2 months respectively, P=0.03) (41).

There are additional ongoing RCTs for CRS and HIPEC for AGC and GCPC patients. One is the PERISCOPE II trial, which is a two-armed phase III multicenter RCT with 106 patients randomized between systemic chemotherapy alone *vs.* gastrectomy with CRS and HIPEC after several cycles of chemotherapy for patients with PCI <7 and/or positive peritoneal cytology (42). Another major RCT is the GASTRICHIP trial, which aims to assess oxaliplatin-based HIPEC for AGC and/or with positive cytology patients following perioperative systemic chemotherapy and D1–D2 gastrectomy (43).

NRCTs

AGC

Several larger retrospective studies have utilized high patient number and propensity-score matching to minimize error and assess individual variables of interest. A single-center propensity-scored matched retrospective study by Diniz *et al.* investigated the impact of HIPEC following perioperative chemotherapy and surgery in gastroesophageal junction (GEJ) and GC patients. They found no difference between groups for OS or DFS but noted T- and N-stages were independent DFS predictors. Their findings are unsurprising, given the wide clinical stage range of their study, as outcomes of stage I–IIB GC are vastly different from stage III. Additionally, there were few HIPEC group patients (n=28) *vs.* no HIPEC patients (2:1 propensity matched n=56) and more AGC patients in the HIPEC group *vs.* no HIPEC group (67.9% *vs.* 46.4% clinical stage III) (44).

Other NRCTs studies have found improvements in OS, DFS, and recurrence for AGC in contrast. As early as 1988, Koga *et al.* demonstrated the addition of prophylactic HIPEC in GC patients with serosal invasion but without macroscopic PC resulted in a reduction of peritoneal recurrence from 50% to 36.4% (45). A smaller study by Zhu *et al.* found similar results. In their study, they found a median OS of 33.1 months in the chemotherapy only group *vs.* not reaching median OS in the HIPEC group, with a hazard ratio for OS of 0.443 *vs.* 0.518 for chemotherapy and HIPEC *vs.* chemotherapy alone (46). Additionally, a retrospective study in 2014 similarly found increased median survival from 12 to 22.5 months for a cohort of 49 GC patients with AGC and/or GCPC who received HIPEC compared to patients who underwent chemotherapy only (47). Thus, in many AGC retrospective studies, there appears to be some benefit to DFS or peritoneal-DFS following HIPEC, although median OS improvements are unclear, likely due to lack of statistical power.

GCPC

There are several large NRCTs that provide additional evidence that GCPC patients can benefit from HIPEC. Hall *et al.* showed at a high volume HIPEC center, GCPC patients with complete CRS with HIPEC had similar 1- and 2-year outcomes compared to post-gastrectomy patients without peritoneal surface involvement (48). The findings of survival benefit of HIPEC for GCPC patients at high volume centers was corroborated by a French multicenter retrospective study of 159 patients, where they found on multi-variate analysis a strong influence on survival, morbidity, and mortality based on center performance (12).

Other multicenter NRCTs continue to show benefit of HIPEC for GCPC patients. The CYTO-CHIP study took a propensity-matched multi-decade approach to study GCPC CRS/HIPEC patients across 19 centers. Not only did they demonstrate improved OS and RFS despite varying institution volume and long-term data, they also found CRS/HIPEC patients had higher 1-, 3-, and 5-year OS compared to CRS alone (49). An analysis of an Italian GCPC patient database from 2006–2015 demonstrated prophylactic HIPEC *vs.* surgery alone and curative HIPEC *vs.* surgery alone both had significantly improved patient 5-year OS and 5-year DFS (50). These large retrospective multicenter database analyses demonstrate OS and DFS benefits of HIPEC for GCPC patients consistently in comparison to RCT findings, which have shown more modest outcome benefits.

Meta-analyses

Given the heterogeneity, generally small number of patients per study, and varying comparisons for studies evaluating HIPEC for GC patient populations, several meta-analyses sought to evaluate the effectiveness of HIPEC in GC and assess prognostic factors based on pooled data.

One of the earliest GC HIPEC meta-analyses was performed by Desiderio *et al.*, combining both RCTs and NRCTs, totaling 2,520 patients (23). While several endpoints, such as PC prevention and neoadjuvant use did not reach statistical significance, the study analysis of patients without PC demonstrated improved OS rates when undergoing HIPEC at 3 and 5 years. Additionally, there was a modest median survival improvement of 4 months for GCPC patients, although there was no difference at 3-year OS. They reported limited efficacy of HIPEC on patients with large lymph node burden or for prevention of lymph node recurrence. Their study was limited by analysis of cytology positivity and due to their widely heterogenous population of patients incorporated into the analysis despite the subgroup analyses, as the authors acknowledged themselves. These limitations are important to consider when assessing outcomes, as both limitations have been shown to have an impact on survival and recurrence for GC.

A separate meta-analysis by Granieri *et al.* later in 2021 evaluated the impact of CRS with HIPEC on only RCTs. In their study, they included both AGC patients and GCPC patients. In comparison to Desiderio *et al.*, Granieri *et al.* noted only OS improvements with HIPEC for patients treated for prophylaxis of PC but not for curative intent. Their study was much more limited in scope, with a small intent to treat population of 43 out of 1,376 patients. Moreover, although their meta-analysis was composed only of randomized patients, they included GCPC and no PC patients, which have significantly different clinical prognoses (51).

In contrast, Martins *et al.* performed a meta-analysis only of GCPC patients from NRCTs. Based upon their analysis, there was a significant OS improvement with a meta-analysis random-effects RR of 3.65 for CRS and HIPEC compared to CRS alone at 1 year and of 3.25 at 5 years without significant complication differences. Furthermore, peritoneal recurrence risk was significantly smaller with the addition of HIPEC to CRS, with an RR of 0.23. However, the authors found significant heterogeneity and cautioned that their findings, though statistically significant, could potentially contain indication bias causing confounding due to lack of randomization and potential compound effect of small sample sizes in the original studies. Generalizability was also limited as there was a predominant Asian institution-lean in proportion of their studies used for analysis (52).

Limitations

This study suffers from several notable limitations. First and foremost, this is a narrative review. Because a narrative review does not follow a systematic, exhaustive literature search, the presented literature is dependent on subjective author opinion in terms of salience. Consequently, it is possible relevant literature may have been overlooked despite best efforts. Additionally, part of the topics reviewed here have a paucity of data; while this may thereby bias interpretation of possible data on factors influencing HIPEC in GC, we feel that given the general rarity of the HIPEC in GC and translational/basic science research related, the presented studies are reflective of what is currently known in the field at this time. Lastly, this review suffers from lack of cohesive, summarized clinical data outcomes. A compilation of all relevant clinical data may certainly provide insights into the overall data behind HIPEC in GC at this time. However, many of the reported clinical outcomes vary widely in study design (randomized, non-randomized), patient demographic/region, GC stage and type, surgical approach, HIPEC regimen and methodology, study design, clinical course, and even data chosen to be reported. Because of the heterogeneous nature of these studies, we felt presenting a synthesized form would potentially be misleading regarding generalizable outcomes. Additionally, in this manner of narrative review, we may also critique meta-analyses over time that have similarly tried to approach understanding the overall body of literature for HIPEC and GC, which have demonstrated differing conclusions from each other despite significant overlap in their references.

Conclusions

GC carries an abysmal prognosis when found in advanced stages, particularly when PC is present. Given several other malignancies that are prone to peritoneal metastases like peritoneal mesothelioma, colorectal cancer, and appendiceal malignancies have shown improvement in outcomes with use of HIPEC (50), there has been interest in whether GC patients may likewise benefit. Here in this review, we discuss how HIPEC is associated with some degree of improvements in OS and even DFS and RFS in certain GC patient subsets, such as in the subset with cytology positivity only without macroscopic peritoneal metastases. However, some patients may inherently be poor responders due to a variety of clinical/genetic factors. The degree of cytoreduction is also associated with improved HIPEC outcomes, although a few studies have demonstrated CRS alone compared to HIPEC with CRS is inferior in

OS, therefore validating the benefit of HIPEC itself as a component of care. Findings of the ongoing PERISCOPE II, GASTRIPEC, and GASTRICHIP trials may provide much needed additional level I evidence regarding the benefits of the HIPEC for AGC with and without PC. Thus, while the NCCN guidelines do not definitively suggest the role of HIPEC for stage IV GC patients, other groups include consideration of HIPEC in their guidelines, such as in the Chicago Consensus Guidelines for synchronous metastases in GC with stable or improved GCPC or those with AGC without PC (51). Ultimately, though there are significant limitations in the research regarding treatment of AGC without PC or GCPC, consideration of incorporating CRS and HIPEC should be strongly considered in appropriately selected patients during multidisciplinary treatment based on the overall findings of the literature thus far, particularly in patients with good functional status or good response to treatment.

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References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Isaza-Restrepo A, Martin-Saavedra JS, Velez-Leal JL, et al. The Peritoneum: Beyond the Tissue - A Review. Front Physiol 2018;9:738.
3. Brücher BL, Piso P, Verwaal V, et al. Peritoneal carcinomatosis: cytoreductive surgery and HIPEC--overview and basics. Cancer Invest 2012;30:209-24.
4. Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 2016;17:309-18.
5. Tanabe S, Quader S, Ono R, et al. Molecular Network Profiling in Intestinal- and Diffuse-Type Gastric Cancer. Cancers (Basel) 2020;12:3833.
6. Tanaka Y, Chiwaki F, Kojima S, et al. Multi-omic profiling of peritoneal metastases in gastric cancer identifies molecular subtypes and therapeutic vulnerabilities. Nat Cancer 2021;2:962-77.
7. Hu Q, Masuda T, Sato K, et al. Identification of ARL4C as a Peritoneal Dissemination-Associated Gene and Its Clinical Significance in Gastric Cancer. Ann Surg Oncol 2018;25:745-53.
8. Wang R, Song S, Harada K, et al. Multiplex profiling of peritoneal metastases from gastric adenocarcinoma identified novel targets and molecular subtypes that predict treatment response. Gut 2020;69:18-31.

9. Zhang XL, Shi HJ, Wang JP, et al. MicroRNA-218 is upregulated in gastric cancer after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy and increases chemosensitivity to cisplatin. World J Gastroenterol 2014;20:11347-55.
10. Ruan Q, Fang ZY, Cui SZ, et al. Thermo-chemotherapy Induced miR-218 upregulation inhibits the invasion of gastric cancer via targeting Gli2 and E-cadherin. Tumour Biol 2015;36:5807-14.
11. Solomon D, DeNicola N, Feingold D, et al. Signet ring cell features with peritoneal carcinomatosis in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are associated with poor overall survival. J Surg Oncol 2019;119:758-65.
12. Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol 2010;17:2370-7.
13. Ji ZH, Yu Y, Liu G, et al. Peritoneal cancer index (PCI) based patient selecting strategy for complete cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy in gastric cancer with peritoneal metastasis: A single-center retrospective analysis of 125 patients. Eur J Surg Oncol 2021;47:1411-9.
14. Brandl A, Yonemura Y, Glehen O, et al. Long term survival in patients with peritoneal metastasised gastric cancer treated with cytoreductive surgery and HIPEC: A multi-institutional cohort from PSOGI. Eur J Surg Oncol 2021;47:172-80.
15. Coccolini F, Catena F, Glehen O, et al. Complete versus incomplete cytoreduction in peritoneal carcinosis from gastric cancer, with consideration to PCI cut-off. Systematic review and meta-analysis. Eur J Surg Oncol 2015;41:911-9.
16. Suzuki O, Fukuchi M, Mochiki E, et al. Prognostic role of gastrectomy in patients with gastric cancer with positive peritoneal cytology. Int Surg 2014;99:830-4.
17. Yonemura Y, Prabhu A, Sako S, et al. Long Term Survival after Cytoreductive Surgery Combined with Perioperative Chemotherapy in Gastric Cancer Patients with Peritoneal Metastasis. Cancers (Basel) 2020;12:116.
18. Ishigami H, Yamaguchi H, Yamashita H, et al. Surgery after intraperitoneal and systemic chemotherapy for gastric cancer with peritoneal metastasis or positive peritoneal cytology findings. Gastric Cancer 2017;20:128-34.
19. Valletti M, Eshmuminov D, Gnecco N, et al. Gastric cancer with positive peritoneal cytology: survival benefit after induction chemotherapy and conversion to negative peritoneal cytology. World J Surg Oncol 2021;19:245.
20. Rau B, Brandl A, Thuss-Patience P, et al. The efficacy of treatment options for patients with gastric cancer and peritoneal metastasis. Gastric Cancer 2019;22:1226-37.
21. Morgagni P, Solaini L, Saragoni L, et al. Conversion Surgery in Gastric Cancer Carcinomatosis. Front Oncol 2022;12:852559.
22. Gill RS, Al-Adra DP, Nagendran J, et al. Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. J Surg Oncol 2011;104:692-8.
23. Desiderio J, Chao J, Melstrom L, et al. The 30-year experience-A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. Eur J Cancer 2017;79:1-14.
24. Mazurek M, Szlendak M, Forma A, et al. Hyperthermic Intraperitoneal Chemotherapy in the Management of Gastric Cancer: A Narrative Review. Int J Environ Res Public Health 2022;19:681.
25. Feingold PL, Kwong ML, Davis JL, et al. Adjuvant intraperitoneal chemotherapy for the treatment of gastric cancer at risk for peritoneal carcinomatosis: A systematic review. J Surg Oncol 2017;115:192-201.
26. Zhang JF, Lv L, Zhao S, et al. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Combined with Surgery: A 12-Year Meta-Analysis of this Promising Treatment Strategy for Advanced Gastric Cancer at Different Stages. Ann Surg Oncol 2022;29:3170-86.
27. Brenkman HJF, Päeva M, van Hillegersberg R, et al. Prophylactic Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Gastric Cancer-A Systematic Review. J Clin Med 2019;8:1685.
28. Canbay E, Mizumoto A, Ichinose M, et al. Outcome data of patients with peritoneal carcinomatosis from gastric origin treated by a strategy of bidirectional chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a single specialized center in Japan. Ann Surg Oncol 2014;21:1147-52.
29. Yonemura Y, Bandou E, Sawa T, et al. Neoadjuvant treatment of gastric cancer with peritoneal dissemination. Eur J Surg Oncol 2006;32:661-5.
30. Badgwell B, Blum M, Das P, et al. Phase II Trial of Laparoscopic Hyperthermic Intraperitoneal Chemoperfusion for Peritoneal Carcinomatosis or Positive Peritoneal Cytology in Patients with Gastric

Adenocarcinoma. Ann Surg Oncol 2017;24:3338–3344.
31. Newhook TE, Agnes A, Blum M, et al. Laparoscopic Hyperthermic Intraperitoneal Chemotherapy is Safe for Patients with Peritoneal Metastases from Gastric Cancer and May Lead to Gastrectomy. Ann Surg Oncol 2019;26:1394-400.
32. Yu W, Whang I, Chung HY, et al. Indications for early postoperative intraperitoneal chemotherapy of advanced gastric cancer: results of a prospective randomized trial. World J Surg 2001;25:985-90.
33. Hultman B, Lind P, Glimelius B, et al. Phase II study of patients with peritoneal carcinomatosis from gastric cancer treated with preoperative systemic chemotherapy followed by peritonectomy and intraperitoneal chemotherapy. Acta Oncol 2013;52:824-30.
34. Reutovich MY, Krasko OV, Sukonko OG. Hyperthermic intraperitoneal chemotherapy in serosa-invasive gastric cancer patients. Eur J Surg Oncol 2019;45:2405-11.
35. Sun J, Song Y, Wang Z, et al. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. BMC Cancer 2012;12:526.
36. Cui HB, Ge HE, Bai XY, et al. Effect of neoadjuvant chemotherapy combined with hyperthermic intraperitoneal perfusion chemotherapy on advanced gastric cancer. Exp Ther Med 2014;7:1083-8.
37. Zhan H, Liang H, Wang B, et al. Efficacy of intraoperative hyperthermic peritoneal perfusion on 60 patients with advanced gastric carcinoma. Chinese Journal of Clinical Oncology 2010;37:229-33.
38. Fan B, Bu Z, Zhang J, et al. Phase II trial of prophylactic hyperthermic intraperitoneal chemotherapy in patients with locally advanced gastric cancer after curative surgery. BMC Cancer 2021;21:216.
39. Rudloff U, Langan RC, Mullinax JE, et al. Impact of maximal cytoreductive surgery plus regional heated intraperitoneal chemotherapy (HIPEC) on outcome of patients with peritoneal carcinomatosis of gastric origin: results of the GYMSSA trial. J Surg Oncol 2014;110:275-84.
40. Yang XJ, Huang CQ, Suo T, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol 2011;18:1575-81.
41. Rau B, Lang H, Königsrainer A, et al. 1376O The effect of hyperthermic intraperitoneal chemotherapy (HIPEC) upon cytoreductive surgery (CRS) in gastric cancer (GC) with synchronous peritoneal metastasis (PM): A randomized multicentre phase III trial (GASTRIPEC-I-trial). Ann Oncol 2021;32:S1040.
42. Koemans WJ, Lurvink RJ, Grootscholten C, et al. Synchronous peritoneal metastases of gastric cancer origin: incidence, treatment and survival of a nationwide Dutch cohort. Gastric Cancer 2021;24:800-9.
43. Glehen O, Passot G, Villeneuve L, et al. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. BMC Cancer 2014;14:183.
44. Diniz TP, da Costa WL Jr, Fonseca de Jesus VH, et al. Does hipec improve outcomes in gastric cancer patients treated with perioperative chemotherapy and radical surgery? A propensity-score matched analysis. J Surg Oncol 2020;121:823-32.
45. Koga S, Hamazoe R, Maeta M, et al. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. Cancer 1988;61:232-7.
46. Zhu L, Xu Z, Wu Y, et al. Prophylactic chemotherapeutic hyperthermic intraperitoneal perfusion reduces peritoneal metastasis in gastric cancer: a retrospective clinical study. BMC Cancer 2020;20:827.
47. Yarema RR, Ohorchak MA, Zubarev GP, et al. Hyperthermic intraperitoneal chemoperfusion in combined treatment of locally advanced and disseminated gastric cancer: results of a single-centre retrospective study. Int J Hyperthermia 2014;30:159-65.
48. Hall JJ, Loggie BW, Shen P, et al. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for advanced gastric cancer. J Gastrointest Surg 2004;8:454-63.
49. Bonnot PE, Piessen G, Kepenekian V, et al. Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer With Peritoneal Metastases (CYTO-CHIP study): A Propensity Score Analysis. J Clin Oncol 2019;37:2028-40.
50. Rosa F, Galiandro F, Ricci R, et al. Survival advantage of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for advanced gastric cancer: experience from a Western tertiary referral center. Langenbecks Arch Surg 2021;406:1071-80.
51. Granieri S, Bonomi A, Frassini S, et al. Prognostic impact of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer

patients: A meta-analysis of randomized controlled trials. Eur J Surg Oncol 2021;47:2757-67.
52. Martins M, Santos-Sousa H, Araújo F, et al. Impact of Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy in the Treatment of Gastric Cancer with Peritoneal Carcinomatosis: A Systematic Review and Meta-analysis. Ann Surg Oncol 2022;29:7528-37.

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