Review Article

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for gastric cancer and other less common disease histologies: is it time?

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Abstract: Gastric cancer is the fourth most commonly diagnosed cancer worldwide, and once spread to the peritoneum, has a 5-year survival of less than 5%. Recent years have demonstrated advances in the use of cytoreductive surgery (CRS) in combination with heated intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis due to various malignancies. The frequent desmoplastic stroma and poor vascularization impeding drug delivery particularly in the diffuse form of gastric cancer is thought to provide a sound rationale for a regionalized treatment approach in this disease. Here, we seek to review the available data to define the role of CRS and HIPEC in gastric cancer metastatic to the peritoneal surface, and furthermore, analyze the use of CRS and HIPEC in malignancies less commonly treated with the regionalized perfusion approach.

Keywords: Metastatic gastric cancer; peritoneal carcinomatosis; cytoreductive surgery (CRS); heated intraperitoneal chemotherapy (HIPEC); systematic review

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Introduction

Gastric cancer, the fourth most common newly diagnosed cancer worldwide, carries an incontrovertible mortality burden with a five-year survival rate of ~25% for all stages (1,2). Up to 40% of gastric cancer patients develop some type of peritoneal spread during the course of their disease, after which their 5-year survival drops to less than 5% (3-5). Those afflicted by peritoneal carcinomatosis from gastric cancer are currently treated as stage IV, receiving systemic chemotherapies with generally bleak results. Indeed, only a minority of patients survive longer than one year and nearly all present challenges to palliation, frequently exacerbated due to common GI failure, in the final weeks of life (6).

The need for therapies addressing peritoneal carcinomatosis in gastric cancer, combined with an emergence of cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) in other GI cancers, has led to a number of clinical trials seeking to establish a role for this modality in gastric cancer. This regionally focused approach is built on the concept of maximizing drug delivery to the afflicted surfaces while simultaneously elongating the therapeutic window by reducing systemic toxicity. Indeed, in a large phase III clinical trial in colorectal cancer spread to the peritoneum, HIPEC and CRS extended median survival from 12.6 to 22.3 months (P=0.032) (7). Likewise, small trials and a meta-analysis have indicated an association with prolonged survival when applying this technique to stage IV gastric cancer with

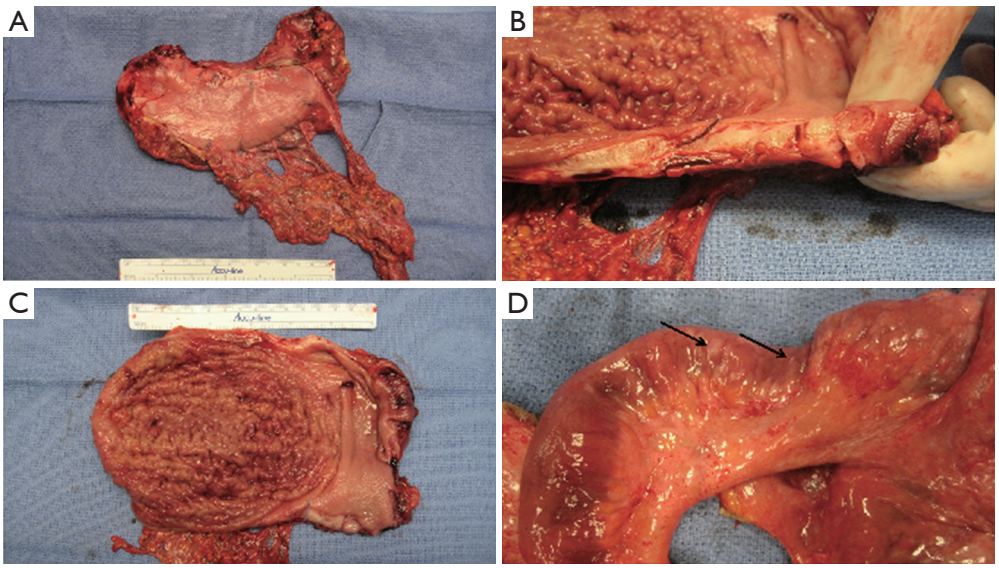

Figure 1 Diffuse gastric cancer with peritoneal surface involvement. (A) Thickened and 'rigid' gastric walls of surgical specimen; (B,C) thickened stomach wall without mucosal involvement; (D) peritoneal implants involving ileum and small bowel mesentery (arrows).

peritoneal carcinomatosis (8-10). High procedure-related morbidity and mortality associated with the CRS-HIPEC approach, however, have sparked a debate on its merit. With the advent of regulatory approval of more effective as well as novel, more personalized treatment options in stage IV gastric cancer, along with advances in tailoring investigational agents specifically for peritoneal delivery, there clearly is a need to outline the appropriate role of CRS-HIPEC in this disease (1,11,12).

The primary rational for a regional perfusion approach is the ability to target the tumor burden with up to 20-times higher concentrations of drug measured in the intraperitoneal compartment compared to plasma drug level (13,14). The issue of drug penetration and delivery is particularly important in the diffuse form of gastric cancer, which, together with pancreatic adenocarcinoma, is a prime example of a malignancy with a desmoplastic inflammatory stroma, high interstitial pressures and poor vascularization (15,16). On one hand, pharmacological manipulation has been shown to exploit a tumor's natural enhanced permeability and retention effect (EPR) by increasing leakage, extravasation, and retention of drug in the tumor tissue via greater permeability due to reduced fibrosis and interstitial pressure (16). On the other hand, direct exposure of tumor deposits to chemotherapy is thought to penetrate superficial cell layers only, and the effect of intraperitoneal chemotherapy may be mediated through rapid systemic absorption and recirculation, potentially achieving higher intratumoral concentrations than direct drug penetration (16-18).

Additionally, the evolving understanding of the heterogenetic landscape of cancer may soon require an approach individualized to metastatic site. Whole genome sequencing (WGS) studies in pancreas and renal cell cancer for example, have sampled multiple metastatic sites and elicited considerable genetic heterogeneity in both somatic mutations as well as chromosomal structural variants at different organ sites within individual patients (19,20). Further recent work has used WGS to identify patients that will have a robust or complete response to platinum-based chemotherapy (21), and it is conceivable that the choice of regional chemotherapy should be guided in the future by unique genotypic signatures of metastatic sites to optimize drug selection. Hence, the merit of individualization based on both histopathology and genotype in the selection of regional drug approaches might be particularly important in metastatic gastric cancer involving the peritoneal surface. *Figure 1* shows an example of the diffuse form of gastric cancer, which is more commonly associated with peritoneal spread than the intestinal subtype of gastric adenocarcinoma. *Figure 2* shows the considerable variability in cytoarchitecture, tumor cellularity, stromal expansion, and E-cadherin expression across a number of peritoneal surface lesions removed from different patients during CRS.

Hence, it is unlikely that a 'one size fits all' is the most

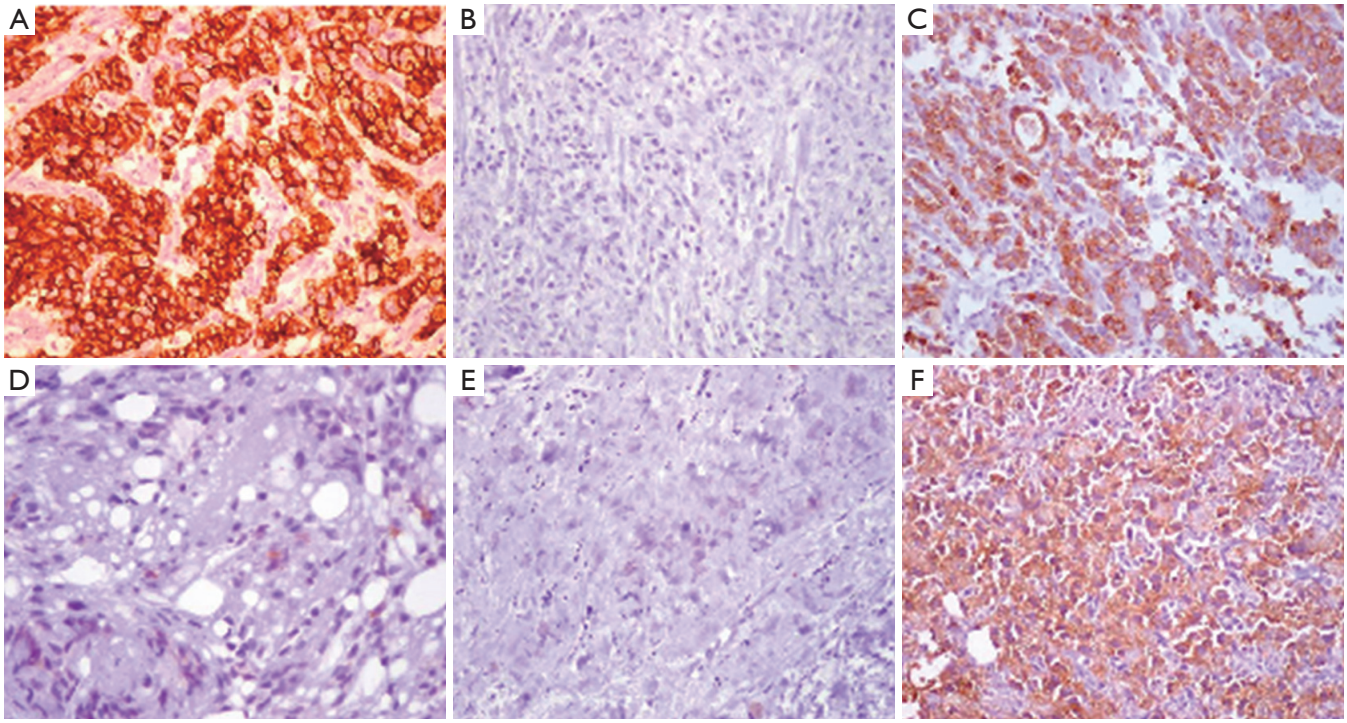

Figure 2 Variability in tumor-stroma ratio, gland formation, stromal and tumor cellularity, and CDH1 expression of peritoneal surface involvement of metastatic gastric cancer. (A-F) Immunohistochemical anti-CDH1 staining of peritoneal deposits of six patients enrolled onto the RECLAP study (22) (magnification, 20×).

effective approach, and the choice of chemotherapeutic regimens, including intraperitoneal therapy for peritoneal involvement, may soon depend on the genetic make-up of both primary and metastatic lesions. Here, we review the currently available data on the use of CRS in combination with HIPEC in gastric cancer, efforts to select patients and reduce morbidity of these procedures, as well as highlight advances of regional chemotherapy approaches in less common histologies, such as adrenocortical cancer (ACC) and abdominal sarcomatosis.

Retrospective evaluations of cytoreductive surgery (CRS) and HIPEC versus systemic chemotherapy for peritoneal carcinomatosis from gastric cancer

Given the rarity and frailty of patients with gastric cancer metastatic to the peritoneum, it is inherently difficult to study such cases clinically. It is thus important to first demonstrate that a new treatment modality can achieve outcomes superior to historical controls receiving standard of care. Indeed, in other GI cancers, retrospective experiences that have to date not been subjected to randomized controlled have led to accepted standards in treatment. Such was the case with the introduction of surgery for the management of colorectal liver metastases in the 1990s, as well as the use of CRS and HIPEC in the management of apppendiceal carcinoma or peritoneal mesothelioma through the pivotal work of Dr. Sugarbaker (23). Accordingly, there are a number of well-conducted retrospective series from high-volume peritoneal surface malignancy centers reporting on outcome of patients with gastric cancer with peritoneal carcinomatosis being treated with CRS and HIPEC. *Table 1* details these reports including number of patients per study, median follow-up, regional chemotherapy used, treatment related complications, and clinical outcome.

Two studies deserve to be highlighted: in the largest study with the most comprehensive follow-up French investigators describe a multi-institutional series of 159 patients treated with CRS and HIPEC and reported 1-, 2-, and 5-year survival rates of 43 %, 18%, and 13%, respectively (26). Also, the study by Hall *et al*. from a high-volume peritoneal surface malignancy center is remarkable as it reported equal 1- and 2-year outcomes between patients with peritoneal

Table 1 Selected non-randomized studies reporting outcome of patients with peritoneal carcinomatosis due to metastatic gastric cancer

Authors (trial design)	Publication year	Total/HIPEC/other	Agent (dose)	Toxicity	Median follow-up	Clinical outcome
Hultman *et al.* (24) (Ph II)	2013	18	CRS/HIPEC/EPIC (5 patients CDDP at 50 mg/m^2, 3 patients oxaliplatin 460 mg/m^2 with IV 5-FU and LV)	62.5% grade II-IV adverse event	14.3 months	8 patients received entire treatment. OS =14.3 months (95% CI, 6.6-20.3)
Wu *et al.* (25) (RS: ovarian metastasis and peritoneal dissemination)	2013	64, 32	Oxaliplatin 460 mg/m^2	No difference in grade III/IV AE in HIPEC and non-HIPEC group	11 months	MS CRS + HIPEC *vs.* CRS only 15.5 and 10.4 months, P=0.018
Glehen *et al.* (26) (RS, multicenter)	2010	159 (77 CRS + HIPEC closed, 67 CRS + HIPEC open, 12 CRS + HIPEC + EPIC closed)	(I) MMC 30-150 mg/m^2 + CDDP 50-100 mg/m^2; (II) OHP 360-460 mg/m^2 ± irinotecan 100-200 mg/m^2 ± IV 5-FU and leucovorin	Post-op mortality 6.5%; grade 3-4 morbidity 27.8%	20.4 months	MS 9.2 months; overall 1-, 3-, 5-year survival of 43%, 18%, 13%
Hall *et al.* (27) (RS)	2004	60, 34	HIPEC with MMC (10 μg/mL, ~40 mg)	35% HIPEC morbidity *vs.* 17.5% control	ND	NS, HIPEC 8.0 *vs.* 7.8 months (P=0.29)
Yonemura *et al.* (28) (RS)	2005	107	MMC, cisplatin, etoposide at 30, 300, and 150 mg	Not discussed	46 months	MS 11.5 months, 5-year survival 6.7%
Scaringi *et al.* (29) (RS)	2008	37 (26 with PC, 11 prophylactic)	MMC 120 mg, cisplatin 200 mg/m^2	10 patients had complications, pulmonary most frequent	ND	MS 23.4 and 6.6 months in prophylactic and PC group, P<0.05
Yonemura *et al.* (30) (CS)	1996	83	MMC 30 mg, etoposide 150 mg, cisplatin 300 mg	3.6% bowel perforation, 2.4% bone marrow suppression, 1.2% renal dysfunction	46 months	1- and 5-year survival rates of 43% and 11%
Yonemura *et al.* (31) (CS)	1991	41	MMC 50 mg, cisplatin 300 mg	Renal insufficiency 5%, leukopenia 5%, bowel perforation 2%	41.6 months	MS 14.6 months, 3-year survival rate was 28.5%

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; EPIC, early post-operative intraperitoneal chemotherapy; CDDP, cisplatin; LV, leucovorin; OS, overall survival; RS, retrospective series; MS, median survival; MMC, mitomycin; MS, median survival; ND, not discussed; NS, not significant; PC, peritoneal carcinamotosis; CS, case series.

carcinomatosis that underwent resection with complete CRS followed by HIPEC and patients who underwent radical gastrectomy without peritoneal involvement (27). Both studies reported that outcome was most favorable when a complete surgical cytoreduction could be accomplished.

For the majority of patients listed in *Table 1*, patients had already received at least one line of systemic chemotherapy. The observed results are thus in contrast to those in which the majority of patients treated with systemic chemotherapy only succumb to their disease within the first year. Data from Memorial Sloan Kettering Cancer Center, for example, has shown a median survival of less than 12 months for metastatic gastric cancer treated with chemotherapy only. Furthermore, metastatic disease evidenced by cytology only was not associated with improved survival (32). Other investigators have shown a similarly significant detriment to survival conferred by isolated positive peritoneal cytology (33). Subsequent work from the Memorial group, however, suggests that a multimodality approach of neoadjuvant systemic chemotherapy and surgical resection in patients with M1Cyt+ disease that reverts to negative cytology might be associated with improved disease specific survival (34). Efforts to sterilize the peritoneal compartment in combination with curative resection have been tested in a multicenter randomized trial, which implemented intraperitoneal chemotherapy along with high volume peritoneal lavage in 88 M1Cyt+ patients and is discussed in *Table 2* and the next section "HIPEC as an adjuvant treatment for patients with resectable gastric cancer" (45).

Overall, acknowledging the shortcomings of retrospective series with their inherent selection bias, the data suggests a subset of patients treated with the multimodality approach of CRS combined with HIPEC whose outcome is different from that expected for stage IV patients treated with systemic chemotherapy only.

HIPEC as an adjuvant treatment for patients with resectable gastric cancer

CRS and perfusion of the peritoneal compartment with heated chemotherapy as part of a multimodality approach are likely synergistic therapies. It is well established that smaller tumor burdens aid the efficacy of a sterilizing cytotoxic chemotherapy—a guiding principle of adjuvant chemotherapy (46). Indeed, several studies in *Table 1* support the observation that complete cytoreduction prior to HIPEC is associated with improved survival. Further, several phase II studies looking at HIPEC administered at time of potentially curative resections for gastric cancer have indicated that regional chemotherapy carries therapeutic activity. *Table 2* lists characteristics and outcomes of patients, without preoperatively confirmed peritoneal disease, that were randomized to peritoneal perfusion at time of gastrectomy (either as hyper- or normothermic regional chemotherapy; and in one series as early post-operative perfusion) versus gastrectomy alone.

In summary, despite the inclusion of some stage IV patients that had peritoneal involvement, the majority of these studies demonstrate improved outcomes including overall survival in patients receiving intraoperative peritoneal chemotherapy. When analyzed in a recent meta-analysis, even patients with limited peritoneal carcinomatosis that randomized to CRS and HIPEC seemed to fare better than those that received curative gastrectomy only (47). The most common morbidity of the addition of peritoneal regional chemotherapy included neutropenia and thrombocytopenia. There were no associated mortalities. This data supports an emerging role for intraoperative peritoneal chemotherapy in gastric cancer, including in patients with both a low and high risk for future peritoneal involvement as well as a limited peritoneal surface disease burden.

Cytoreductive surgery (CRS) and HIPEC in patients with known peritoneal carcinomatosis from gastric cancer

There are now promising results from long term follow-up studies on the outcomes of CRS and HIPEC in patients with peritoneal carcinomatosis from colorectal cancer available (48). These data show improved outcomes in patients treated with the multimodality approach together with the studies on the use of intraperitoneal chemotherapy in the adjuvant setting, provide a solid rationale for a prospective randomized evaluation of CRS and HIPEC for gastric cancer. *Table 3* summarizes clinical studies which randomized gastric cancer patients with stage IV disease to CRS and HIPEC (or early post-operative perfusion) versus standard of care.

Some of these studies, while initially designed to evaluate HIPEC in the adjuvant setting in patients who could undergo a potentially curative resection, include separate analyses of patients that were unexpectedly found to be stage IV at operation but still underwent resection of serosal deposits followed by HIPEC. Some of these stage IV patients only had positive cytology (M1Cyt+). Both 1- and 2-year mortality rates were superior in those who

Table 2 Characteristics and outcomes of patients enrolled in randomized studies of peritoneal perfusion at gastrectomy versus gastrectomy alone

Authors	Year	Total/HIPEC/ other	Stage I-III	Stage IV	Agent (dose)	Toxicity	Median follow-up	Clinical outcome
Koga *et al.* (35)	1988	60 26 0	24	2	HIPEC: MMC (64-100 mg in 8-12 L)	Anastomotic leak 3.1% HIPEC *vs.* 7.1% Sx alone; adhesive ileus 3.1% HIPEC *vs.* 7.1% Sx alone	30 months	NS* OS 83% HIPEC *vs.* 67.3% Sx alone
Hamazoe *et al.* (36)	1993	82 42 0	38	4	HIPEC: MMC (10 μg/mL in 8-12 L)	Thrombocytopenia, transaminitis, anastomotic break 4.8% HIPEC *vs.* 7.5% surgery alone	6 years	NS 5-year OS 64.2% HIPEC *vs.* 52.5% Sx alone (P=0.247)
Fujimura *et al.* (37)	1994	58 22 18	17 13	5 5	HIPEC: MMC (30 mg/kg) & CDDP (300 mg/kg) in 10 L; NIC: MMC (30 mg/kg) & CDDP (300 mg/kg) in 10 L	Decreased BM, renal dysfunction, intestinal perforation	31-37 months	3-year OS 68% HIPEC *vs.* 51% NIC *vs.* 23% Sx alone (P<0.001)
Sautner *et al.* (38)	1994	67 34 0	40	27	EPIC: treatment between 10th and 28th postop day	Nausea, vomiting, diarrhea present in 24 patients (73%)	72.5 months	NS MS 17.3 months HIPEC *vs.* 16.0 months control (P=0.6)
Ikeguchi *et al.* (39)	1995	174 78 0	78	0	HIPEC: MMC (80-100 mg/m^2) in 8-10 L (post-op MMC & UFT)	ND	6 years	NS* 5-year OS 51% HIPEC *vs.* 46% Sx alone
Rosen *et al.* (40)	1998	91 46 0	46	0	Perfusion: MMC (50 mg) & CH (375 mg)	Morbidity: 35% perfusion vs 16% Sx alone (P<0.02); mortality (60 days): 11% *vs.* 2%	597 days	NS OS 738.9 days HIPEC *vs.* 515.4 days Sx alone (P=0.44)
Fujimoto *et al.* (41)	1999	141 71 0	58	13	HIPEC: MMC (10 μg/mL) in 3-4 L (post-op chemo)	No difference in rate of duodenal stump leak	ND	8-year OS 62% HIPEC *vs.* 49% Sx alone (P=0.0362)
Shimoyama *et al.* (42)	1999	29 30 24	30 24	0 0	Perfusion: MMC (10 mg) in 500 mL; regional perfusion: MMC (10 mg) in 500 mL (post op chemo: CDDP, UFT)	No difference in rate of anastomotic leak or pancreatic leak	47 months	OS improved for perfusion *vs.* regional perfusion *vs.* Sx alone (P=0.049)
Yonemura *et al.* (43)	2001	139 48 44	35 29	13 15	HIPC: MMC (30 mg) & CDDP (300 mg) in 8-10 L; NIC: MMC (30 mg) & CDDP (300 mg) in 8-10 L	No difference in rate of leak, pneumonia, renal dysfunction, mortality	5.5 years	OS* 61% HIPEC *vs.* 43% NIC & 42% Sx alone (NS btw NIC & surgery alone)
Miyashiro *et al.* (44)	2011	268 135	ND	ND	Perfusion: CDDP (70 mg/m^2) in 1 L (post op chemo: CDDP, 5FU)	Mortality 3 *vs.* 1 patients; grade 4 AE: 2 *vs.* 3 patients	6 years	NS OS 62.0% perfusion *vs.* 60.9% Sx alone (P=0.482)

*P value not stated. Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin C; Sx, surgery; EPIC, early postoperative intraperitoneal chemotherapy;NS, not significant; OS, overall survival; CDDP, cisplatin; NIC, normothermic intraperitoneal chemotherapy; MS, median survival; UFT, Tegafur/uracil; ND, not declared; CH, activated carbon.

Table 3 Randomized controlled trials of patients with peritoneal carcinomatosis or serosal involvement from gastric carcinoma

Author	Year	Total/HIPEC/other	Stage	Agent (dose)	Toxicity	Median follow-up	Clinical outcome
Hagiwara[¶] *et al.* (49)	1992	49, 25	Stage IV: 49; S2: 37/19; S3: 12/5	HIPEC: MMC-CH 500 μg/mL	Leukopenia and thrombocytopenia resolved within 1 month	ND	Survival improvement of 34.6% at 1.5 years, and 41.7% at 2, 2.5, and 3.0 years (P<0.01)
Sautner* *et al.* (38)	1994	67, 33	T3[^]: 21/21, T4: 13/12, LN-: 10/10, LN+: 24/23	EPIC: treatment between 10th and 28th postop day	Nausea, vomiting, diarrhea present in 24 pts (73%)	72.5 months	T4 *vs.* T3 RR 2.4 (P=0.001), OS 42%, 13%, 8% *vs.* 73.8%, 42.8%, 30.0% at 1-, 3-, and 5-years. Local carcinosis present *vs.* absent NS-RR 0.95 (P=0.89)
Takahashi* *et al.* (50)	1995	113, 56	Stage IV: 113; S2: 76/39; S3: 37/17	Perfusion: MMC (50 mg) & CH (375 mg) in 100 mL	NS morbidity except 2 colocutaneous fistulas in HIPEC group	3 years	3-year OS 38% perfusion *vs.* 20% Sx alone (P<0.05)
Kuramoto *et al.* (46)	2009	88, 29, 30 (EIPL)	Stage IV: 88	NIC: CDDP (100 mg) in 1.5 & 3 L lavage; NIC + EIPL: CDDP (100 mg) in 1.5 & 10 L lavage; adjuvant 5-FU PO ×2 years	ND	5 years	5-year OS 43.8% for EIPL-NIC, 4.6% NIC alone, 0% Sx alone (P<0.0001)
Yang *et al.* (51)	2011	68, 34	Stage IV: 68	HIPEC: CDDP 120 mg and MMC 30 mg	SAE in 4 CRS only, 5 CRS + HIPEC	32 months	MS in CRS + HIPEC *vs.* CRS was 11 and 6.5 months (P=0.046)
Rudloff *et al.* (8)	2014	16, 9	Stage IV: 16	HIPEC: oxaliplatin 460 mg/m^2 + IV 5-FU 400 mg/m^2 and IV leucovorin 20 mg/m^2; all received adjuvant FOLFOXIRI	1 mortality septic shock POD 49	ND	MS 11.3 in HIPEC *vs.* 4.3 in chemo alone

[¶], included only patients with S2 or S3 disease; *, included stage III and stage IV; [^], stage not provided. Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin C; CH, activated carbon; ND, not declared; EPIC, early postoperative intraperitoneal chemotherapy; OS, overall survival; NS, not significant; Sx, surgery; NIC, normothermic intraperitoneal chemotherapy; CDDP, cisplatin; EIPL, extensive intraoperative peritoneal lavage; SAE, serious adverse events; CRS, cytoreductive surgery; MS, median survival.

received intraoperative intraperitoneal chemotherapy while 5-year mortality rates did not differ between the groups (47). These findings are affirmed by the results of the so far largest randomized clinical trial on the subject: Yang and coworkers randomized 68 patients with peritoneal carcinomatosis due to gastric cancer to either CRS alone versus CRS plus HIPEC and showed a small but statistically significant survival improvement in those with peritoneal involvement that received both CRS and HIPEC (51). The design of Yang's and co-workers study was different from the recently presented GYMSSA study where patients were randomized to gastrectomy, CRS, and HIPEC followed by 2nd line FOLFOXFIRI versus FOLFOXIRI chemotherapy alone (8). These patients had all undergone diagnostic laparoscopy before randomization to assess peritoneal disease burden. While this study did not meet its accrual target and thus remains underpowered, the findings of several patients living beyond one year (one beyond 4 years) in the multimodality arm compared to all patients dying of their disease within one year in the chemotherapy only arm is noteworthy.

Complications associated with CRS and HIPEC in gastric cancer patients

While the above early, albeit immature, data might point to an emerging role of this approach in the management of metastatic gastric cancer with peritoneal involvement, a concept of clinical equipoise between potentially promising findings and the related risks and burden of the procedure—which are substantial—should be applied. It should also be noted that there is likely a publication bias leading to underreporting of negative findings, however, these reports do exist (52). The main toxicities reported from this approach are neutropenia, particularly in the early post-operative period, as well as GI toxicity, including leaks and fistulas. A number of studies suggest surgical techniques to reduce the likelihood of GI complications. These include (I) complete drainage of the peritoneal chemotherapy effluent followed by extensive washing prior to reestablishing GI continuity or closure; (II) the re-resection of intestinal ends (up to 1 cm) prior to anastomosis in order to join fresh ends which were not exposed to the regional chemotherapy; or (III) avoidance of excessive peritoneal stripping (53).

Despite a relatively common surgical approach there was considerable heterogeneity in the toxicities in these studies. Some reported hardly any leaks or no severe GI toxicity while others, such as the GYMSSA trial, had a high (≥20 percent) 90-day mortality rate with a limited number of patients receiving the planned adjuvant FOLFOXIRI chemotherapy. The reason for toxicity variation is unknown; potential causes include higher peritoneal disease burden, greater proportion of total gastrectomies compared to partial gastrectomies, or the administration of another 2nd line adjuvant chemotherapy regimen (FOLFOXIRI). There was no detectable correlation identifiable between the type of intraperitoneal chemotherapy administered and post-procedure complications. All studies do recommend for these procedures to be performed at high volume peritoneal surface malignancy centers.

Cytoreductive surgery (CRS) and HIPEC in less common diseases

CRS with HIPEC has been associated with improved outcomes for peritoneal carcinomatosis caused by various histologies such as peritoneal mesothelioma, appendiceal, ovarian, and colorectal cancer (48,51,54-56). However, there are still other histologies, such as those cancers that tend to have confined peritoneal disease without signs of systemic metastasis, which may benefit from HIPEC and warrant further study.

CRS and HIPEC in abdominal sarcomatosis

One such example is abdominal soft tissue sarcoma, which tends to present with early peritoneal recurrence and no distant metastasis (57). These patients have a median survival of 13 months and both surgical resection and chemotherapy have failed to show durable responses (58). In a study by Hunt *et al.*, 28 patients underwent CRS and HIPEC over a 5-year period with either cisplatin or a cisplatin/mitoxantrone combination in two separate phase I trials (59). In patients that received HIPEC with cisplatin, the median survival was 16.9 months, while patients who received HIPEC with the combination treatment had a median survival of 5.5 months only. Complication rates were significant, 60% of the cisplatin group and 90% of the combination group developed grade 3/4 toxicities. Another study by Choudry *et al.* examined CRS and HIPEC in 15 patients with recurrent sarcomatosis of varying histologies (60). After CRS and chemoperfusion with mitomycin, cisplatin or doxorubicin, overall survival was 22.6 months. Grade 3/4 complications occurred in 24% of the patients. There has also been interest in exploring the role of CRS and HIPEC in a specific type of abdominal sarcoma, gastrointestinal stromal

tumors. Bryan *et al.* retrospectively reviewed 16 patients that received CRS/HIPEC for GIST-induced sarcomatosis and found a median overall survival of 3.33 years (61). The authors, and others, speculate that debulking followed by first- and second-line tyrosine kinase inhibitor therapy in the form of imatinib (Gleevec®) or sunitinib (Sutent®) reduces, or delays, the risk of relapse due to the delayed formation of resistant clones in the tumor.

Taken together, these results might support the use of the multimodality CRS and HIPEC approach in some patients afflicted by abdominal sarcomatosis, however, toxicity can be substantial and indicates a need for diligent patient selection in future clinical trials. Critically, a randomized study with a non-HIPEC control arm has not yet been performed and additional trials are warranted.

CRS and HIPEC in adrenocortical cancer (ACC)

ACC is a rare tumor with a poor prognosis. Mortality is in the 75-90% range over 5 years, and average survival from time of diagnosis is 14.5 months with 60% of patients eventually developing with unresectable intrabdominal disease (62,63). Systemic therapy for these patients is associated with a poor response and no effect on overall survival (64,65). Indeed, the largest randomized trial for metastatic ACC with etoposide, doxorubicin, and cisplatin showed a progression free survival of 5 months and a 23% response rate (66). Considering the lack of effective systemic treatments for patients with metastatic disease, more effective therapies are needed.

At the National Cancer Institute (NCI), a retrospective analysis was performed of 14 patients with peritoneal recurrence from ACC who were treated with post-operative EDP chemotherapy. Patients who did and did not respond to chemotherapy had an average survival of 30 and 14 months, respectively. This suggests that response to chemotherapy may correlate with an increase in survival. Furthermore, considering the advantages of the regional chemotherapy approach it gives reason to believe that there may be added benefit for these patients that respond, when HIPEC is applied directly to the tumor bed. Given these findings, a trial is currently being conducted at the NCI to establish the efficacy of CRS and HIPEC for peritoneal recurrence of ACC (67). Given the efficacy of systemic cisplatin in ACC, as well as the higher tolerated dosing when given as a heated perfusate, the investigators of the trial hypothesize that patients will achieve prolonged disease free and overall survival.

Conclusions

Currently, there is still limited available data and literature defining a role for CRS and HIPEC in the management of patients with advanced gastric cancer, and further clinical research on this approach is still needed. Results thus far have suggested that CRS and HIPEC may have a role in select patients; those with a low peritoneal disease burden that can be completely reduced, or with disease that is positive by cytology only, are likely the best candidates for the approach. Clinical decisions should be made with the knowledge that toxicities can be substantial, and it is unlikely a curative option. Studies on CRS and HIPEC applied to less common diseases like soft tissue sarcomas or ACC metastatic to the peritoneal surface, while hampered by an inherent heterogeneity of included patients and histologies, mirror the trend observed in management of metastatic gastric cancer experiences but remain too scarce to give any general recommendations. Further development will require the establishment of a robust clinical trial framework at cooperating centers of excellence and more meaningful improvement in outcome will likely require the addition of novel drugs, or drug combinations, taking the unique site-specific genotype of metastases to different organs and compartments into account.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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