Review Article

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in treatment of gastric cancer with peritoneal carcinomatosis

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Abstract

Although gastric cancer with peritoneal carcinomatosis is associated with poor prognosis and is generally treated with palliative systemic therapy, recent studies have shown that cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) may prove to be an efficacious treatment option. In addition to reviewing the natural history of gastric cancer with peritoneal carcinomatosis, this mini-review examines literature on the efficacy of CRS and HIPEC as compared to chemotherapy and surgical options. Both randomized and non-randomized studies were summarized with the emphasis focused on overall survival. In summary, CRS and HIPEC are indeed a promising treatment option for gastric cancer with peritoneal carcinomatosis and large randomized clinical trials are warranted.

Keywords: Cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; peritoneal carcinomatosis

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Introduction

Although the incidence of gastric cancer has decreased over the years, it is the fifth leading cause of cancer worldwide after lung, breast, colorectal and prostate cancers and it is the third most common cause of cancer deaths worldwide after lung and liver cancers (1,2). Gastric cancer accounted for 10% of the total cancer-related deaths and 8% of the total cancer cases in 2008 with over 70% of new cases and deaths occurring in developing countries (3). Asia and Eastern Europe have the highest rates of disease (4). The 5-year overall survival (OS) for gastric cancer is approximately 15%–20% and the survival rate drops steeply as the staging progresses. When localized to the stomach the 5-year OS is approximately 55%, but by stage IV the 5-year OS decreases to 4%.

Peritoneal carcinomatosis arising from gastric cancer is generally associated with poor prognosis. Risk factors found to be significantly associated with peritoneal carcinomatosis in literature include tumor stage T3/T4 (5-9), age ≤60 years (9), histological type (including signet-ring cell features) (6,10), nodal invasion (7,8), vascular invasion (6), ascites (5), liver metastasis (5), and female gender (10). The median survival rates for peritoneal carcinomatosis range from 1 to 9 months with no survival at the 5th year (11).

Recently, Thomassen *et al*. (10) did a population-based study to investigate the morbidity and mortality among patients with peritoneal carcinomatosis of gastric origin and found the median survival of patients with peritoneal

metastasis to be 4 months as compared to 14 months in patients without metastasis. Out of the 5,220 patients studied, 39% of them presented with metastatic disease and 35% of them had peritoneal carcinomatosis. Similarly, Sadeghi *et al.* (5) found the OS was 3.1 months and over half were diagnosed with peritoneal carcinomatosis at the time of primary gastric cancer diagnosis in their prospective trial.

Surgery along with adjuvant chemotherapy or chemo-radiation has been the mainstay treatment of non-metastatic gastric cancer over the years with palliative systemic chemotherapy being the standard of care in advanced or recurrent gastric cancer. Within the last three decades, there has been an increasing interest in cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in treating advanced gastric carcinoma with peritoneal carcinomatosis with the goal of killing any residual microscopic disease that may be present after completely removing the macroscopic disease. The intent of this article is to review literature dealing with treatments for gastric cancer with peritoneal carcinomatosis including chemotherapy, surgery, and HIPEC.

Current approaches for gastric cancer with peritoneal carcinomatosis

Chemotherapy and surgery

Palliative chemotherapy is the standard of care in advanced or recurrent gastric cancer. Wagner *et al.* (12) published a systematic review in 2010 that evaluated the effect of chemotherapy in patients with advanced gastric cancer as compared to best supportive care. They found a 6.7 month improvement in median survival (from 4.3 to 11.0 months) in the chemotherapy group when compared with the best supportive care (*Table 1*). In 2013, Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) (13) did a meta-analysis on the efficacy of chemotherapy on OS and progression-free survival (PFS) in advanced/recurrent gastric cancer. When comparing the experimental chemotherapy arms with the corresponding control arms, the hazard ratio was 0.88 and 0.81 in regards to OS and PFS. These hazard ratios equated to a median OS difference of 3 weeks (37.6 and 34.4 median in weeks) and a PFS difference of 4 weeks (20.4 and 16.4 median in weeks). The GASTRIC study exemplified how chemotherapy in addition to standard regimens has yielded minimal improvement in OS and progression-free intervals with no certain chemotherapy regimen emerging as a better standard (13). Although chemotherapy is the mainstay treatment for advanced gastric cancer, there does not seem to be any set consensus on the overall efficacy of treatment.

The outcome of surgical intervention is often predicated by the progression of gastric cancer. Hioki *et al.* (14) found that gastrectomy increased survival in patients with metastasis to adjacent peritoneum (P1) and few scattered metastasis to adjacent peritoneum (P2) but not in patients with numerous distant peritoneal metastasis (P3). They found that the OS in P1, P2 and P3 groups was 18 months, 15 months and 9 months, respectively. Furthermore, the 1-year survival was found to be 64.7%, 69.2% and 35.2%, respectively. However, Kim *et al.* (9) found that there was no significant trend of improved survival after surgical management of HIPEC.

Currently, there are no large randomized studies examining the efficacy of surgery and systemic therapy versus systemic therapy alone in patients with advanced metastatic gastric cancer. The GYMSSA trial will be conducted by the National Cancer Institute and will compare gastrectomy, metastectomy plus systemic therapy versus systemic chemotherapy alone in metastatic gastric cancer patients (15). This trial will highlight whether or not there is a benefit to aggressive surgical intervention in addition to the current chemotherapeutic standard of care.

CRS plus HIPEC versus chemotherapy

Hultman *et al.* (16) compared systemic chemotherapy followed by CRS and HIPEC with systemic chemotherapy only in patients with peritoneal carcinomatosis from gastric

Table 1 Comparison of median survival times of chemotherapy versus surgery

Treatment	Case No. (Ref No.)	Median survival (month)		P
		Experimental group	Control group	
Chemotherapy	103 (12)	11.0	4.3	0.19
	4,214 (13)	9.4	8.6	<0.0001
Surgery	101 (14)	11.0	Not provided	<0.001

cancer and found the mean OS in the experimental group was 20.5 months as compared to 11.1 months in the control group (*Table 2*).

Table 2 Comparison of mean and median survival of CRS+HIPEC+EPIC versus chemotherapy groups (Ref 16)

Treatment	Case No.	Survival (month)	
		Mean	Median
Chemotherapy	10	11.1	10.4
CRS+HIPEC+EPIC	7	20.5	15.3

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy. P values were not provided.

CRS plus HIPEC versus surgery

It has been shown that if intraperitoneal free cancer cells are present after curative surgery in advanced gastric patients, the 5-year survival rate is only 15.4%, as compared to 49.4% if no intraperitoneal cancer cells are found (17). Furthermore, Kuramoto *et al.* (18) found that extensive intraoperative peritoneal lavage followed by intraperitoneal chemotherapy (EIPL-IPC) significantly increased the 5-year survival rate on patients with intraperitoneal free cancer cells without overt peritoneal metastasis (CY+/P) as compared to surgery plus IPC and surgery alone groups. The 5-year survival rate was 43.8%, 4.6% and 0% in the EIPL-IPC, IPC and surgery alone groups, respectively (18). The goal of HIPEC in killing off microscopic tumor cells that may be present after CRS is a promising treatment modality for gastric cancer with peritoneal carcinomatosis.

There are a limited amount of randomized trials on CRS and HIPEC in gastric cancer with peritoneal carcinomatosis. Yang *et al.* (19) completed a randomized phase III study and found the median survival for the CRS+HIPEC group was 11.0 months as compared to 6.5 months in the CRS alone group. Yonemura *et al.* (20) did a prospective randomized study on 139 patients with advanced gastric cancer who were treated with either chemohyperthermic peritoneal perfusion (CHPP) and surgery, chemonormothermic peritoneal perfusion (CNPP) and surgery, or surgery alone. They found that the 5-year OS rates for CHPP, CNPP and surgery alone groups were 61%, 43% and 42%, respectively. Fujimura *et al.* (21) did a randomized study that showed improved survival in patients receiving continuous hyperthermic peritoneal perfusion or continuous normothermic peritoneal perfusion as compared to the gastric surgery without perfusion group. Furthermore, the significant differences in the survival curves showed that peritoneal perfusion, whether hyperthermic or normothermic, is an effective procedure for preventing peritoneal recurrence. Yu *et al.* (22) did a prospective randomized trial which showed that gastric resection plus early postoperative intraperitoneal chemotherapy improved the 5-year OS compared with surgery only in patients with stage IV gastric cancer (28% and 5%, respectively).

There are many nonrandomized studies dealing with CRS and HIPEC. Fujimoto *et al.* (23) did a nonrandomized study and found increased survival rate for gastric cancer patients with peritoneal carcinomatosis receiving intraperitoneal hyperthermic chemoperfusion and aggressive surgery as compared to surgery alone. Hirose *et al.* (24) did a nonrandomized study to investigate the efficacy of continuous hyperthermic peritoneal perfusion with surgery as compared to surgery alone by a multivariate regression analysis. The continuous hyperthermic peritoneal perfusion group had higher median survival time and 1-year survival rate as compared to the control group: 11 months and 44.4% versus 6 months and 15.8%, respectively. Similarly, Yonemura *et al.* (25) found the median survival of 11.5 months in the patients who received cytoreduction and intraperitoneal hyperthermic chemotherapy (IPHC). Glehen *et al.* (26) found the median survival of patients receiving CRS followed by IPC to be 10.3 months with the median survival increasing to 21.3 months when a completeness of cytoreduction (CCR) score of CCR-0 or CCR-1 was obtained (*Table 3*).

Complete versus incomplete cytoreduction

While CRS and HIPEC are promising treatment modalities for gastric cancer with peritoneal carcino-

Table 3 Comparison of median survival of CRS+HIPEC versus surgery alone

Treatment	Case No. (Ref No.)	Median survival (month)	P
CRS+HIPEC	34 (19)	11.0	0.046
	17 (24)	11.0	0.0455
	107 (25)	11.5	0.001
	49 (26)	10.3	Not provided
Surgery alone	34 (19)	6.5	0.046
	20 (24)	6.0	0.0455

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

matosis, the success of the treatment is largely dependent on the resection status. Hall *et al.* (27) evaluated CRS and IPHC with peritoneal carcinomatosis from gastric cancer. The study investigated the outcomes of patients who underwent gastric resection with CRS followed by IPHC with mitomycin C, while the control group underwent radical gastrectomy without extended nodal resection. The OS was similar between the experimental and control groups (7.8 months and 8.0 months, respectively), and the OS time in the IPHC group was dependent on resection status. Within the IPHC group, a median survival time was 11.2 months if R0/R1 resection was completed as compared to 3.3 months if R2 resection was completed. Yonemura *et al.* (25) completed a retrospective study on 107 patients with peritoneal dissemination of gastric cancer who had intraoperative CHPP after CRS to see whether or not CCR or peritonectomy had an effect on OS and they found that the overall median survival was 11.5 months. The median survival was 15.5 months and 7.9 months in the complete and incomplete cytoreduction groups, respectively. The 5-year survival rate was 6.7% overall, and in the peritonectomy group, it was 27%. Scaringi *et al.* (28) found a 23.4 month median survival in patients without demonstrable peritoneal carcinomtosis who received CRS+HIPEC while the peritoneal carcinomatosis group had a median survival of 6.6 months. The median survival was 15 months when curative CRS was performed versus the median survival of 3.9 months in the palliative group. Similarly, Yang *et al.* (29) found that the median survival of patients with peritoneal cancer index (PCI) ≤20 undergoing CRS+HIPEC was 27.7 months while a PCI>20 had a median survival of 6.4 months. Thus, PCI>20 is an absolute contraindication for CRS-HIPEC in gastric cancer. Furthermore, PCI was found to predict the ability to achieve CCR-0, and thus survival. Yonemura *et al.* (30) determined that the best results are obtained with PCI<6. In another investigation, Chia *et al.* (31) also confirmed PCI<6 as a predictor of CCR-0. The estimated median survival for patients with CCR-0, CCR-1 and CCR-2/3 were 43.4 months, 9.5 months and 7.5 months, respectively (29). Glehen *et al.* (32) did a retrospective multicenter study to evaluate the treatment of CRS combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from gastric cancer. The study found an overall median survival of 9.2 months, while the median survival for completeness of CRS scores of CC-0, CC-1 and CC-2/3 was 15 months, 6 months and 4 months, respectively (*Table 4*).

Table 4 Comparison of median survival on cytoreduction status

Treatment	Case No. (Ref No.)	Median survival (month)	P
R0	7 (27)	36.3	0.05
R0/R1	12 (27)	11.2	0.015
R2	19 (27)	3.3	0.015
CCR-0	11(29)	43.4	0.001
	8 (28)	15.0	0.007
	85 (30)	15.0	<0.001
CCR-1	6 (29)	9.4	0.001
	37 (30)	6.0	<0.001
CCR-0/1	25 (26)	21.3	<0.01
CCR-2	24 (26)	6.6	<0.01
	18 (28)	3.9	0.007
CCR-2/3	11 (29)	8.3	0.001
	30 (30)	30.0	<0.001
Complete cytoreduction	47 (25)	15.5	<0.001
Incomplete cytoreduction	60 (25)	7.9	<0.001

CCR, completeness of cytoreduction.

Quality of life (QOL)

Many practitioners argue that QOL after CRS-HIPEC is prohibitive. Tsilimparis *et al.* investigated QOL after CRS-HIPEC (33) and found that pre- and post-operative QOL did not differ statistically with most of the reduced elements recovering after 6–12 months. Zhu *et al.* (34) in a comprehensive review of QOL after CRS-HIPEC concluded that within 3 months 50% of patients returned to baseline QOL. We agree with other authors that reduced QOL of patients after CRS and HIPEC should not be used as an argument to deny surgical therapy to these patients.

Conclusions

Gastric cancer with peritoneal carcinomatosis has long been associated with a poor prognosis and is usually treated with palliative systemic chemotherapy. The state of the art treatment regimen including CRS and HIPEC has shown to increase OS rates. Gill *et al.* (35) did a systematic review of non-randomized, randomized, and prospective cohort trials regarding the effectiveness of CRS and HIPEC in patients with gastric cancer and peritoneal carcinomatosis and found that the overall median survival was 7.9 (range:

6.1–9.2) months and improved to 15 months if the patients had a CCR score of 0 or 1. They also found that the 1-year survival rate was 43% (range: 22%–68%). Although there is a higher perioperative morbidity and mortality associated with CRS and HIPEC, patients should not be dissuaded because it has been found that the postoperative QOL was similar to that of preoperative by 6–12 months (36). Surgeons' proficiency has a major impact on outcomes in CRS-HIPEC. Rahul *et al*. (37) reviewed extensively the subject and concluded that the learning curve for a center is approximately 140–220 cases, and for individual surgeons about 33–70 cases. Our recommendations are: CRS-HIPEC for gastric cancer should be contemplated in a multidisciplinary manner for physically fit patients [Eastern Cooperative Oncology Group (ECOG) performance status score of 0/1 without significant comorbidities] who underwent staging laparoscopy with PCI<6 and to be performed by experienced surgeons.

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Footnote

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

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