Published in final edited form as:

Ann Surg Oncol. 2014 May ; 21(5): 1448–1455. doi:10.1245/s10434-013-3327-5.

Aggressive Locoregional Surgical Therapy for Gastric Peritoneal Carcinomatosis

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Abstract

Background—Peritoneal carcinomatosis from gastric cancer (GPC) responds poorly to systemic chemotherapy. Limited published data demonstrate improved outcomes after aggressive locoregional therapies. We assessed the efficacy of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC) in GPC.

Methods—We prospectively analyzed 23 patients with GPC undergoing CRS/HIPEC between 2001 and 2010. Kaplan–Meier survival curves and multivariate Cox regression models identified prognostic factors affecting oncologic outcomes.

Results—CRS/HIPEC was performed for synchronous GPC in 20 patients and metachronous GPC in 3 patients. Adequate CRS was achieved in 22 patients (CC-0 = 17; CC-1 = 5) and median peritoneal cancer index was 10.5. Most patients received preoperative chemotherapy (83 %) and total gastrectomy (78 %). Pathology revealed diffuse histology (65 %), signet cells (65 %) and LN involvement (64 %). Major postoperative morbidity occurred in 12 patients, with 1 in-hospital mortality at postoperative day 66. With median follow-up of 52 months, median overall survival (OS) was 9.5 months (95 % confidence interval 4.7–17.3), with 1- and 3- year OS rates of 50 and 18 %. Median progression-free survival (PFS) was 6.8 months (95 % confidence interval 3.9–14.6). In a multivariate Cox regression model, male gender [hazard ratio (HR) 6.3], LN involvement (HR 1.2), residual tumor nodules (HR 2.4), and >2 anastomoses (HR 2.8) were joint significant predictors of poor OS ($\chi^2 = 18.2$, $p = 0.001$), while signet cells (HR 8.9), anastomoses >2 (HR 5.5), and male gender (HR 2.4) were joint significant predictors of poor progression ($\chi^2 = 16.3$, $p = 0.001$).

Conclusions—Aggressive CRS/HIPEC for GPC may confer a survival benefit in select patients with limited lymph node involvement and completely resectable disease requiring less extensive visceral resections.

DISCLOSURE

The authors declare no conflict of interest.

Gastric adenocarcinoma is frequently associated with synchronous or metachronous peritoneal dissemination. Positive peritoneal cytology and/or macroscopic peritoneal carcinomatosis (PC) are identified in 5–50 % of patients presenting with gastric cancer; especially with serosal involvement by large tumors, extensive lymph node involvement, diffuse infiltrative growth pattern and scirrhous-type reaction of the primary tumor.^{1–5} Disease recurrence after curative resection of gastric cancer occurs in approximately 25–50 % of patients. Disease recurrence is isolated to the abdominal cavity in approximately 50 % of patients and is responsible for the majority of deaths after curative resection.^{6–9} Locoregional recurrence may be minimized to less than 20 % by optimizing gastric resection margins, performing adequate D2 or greater extended lymph node dissections or by providing adjuvant radiation to the surgical field after inadequate regional lymph node dissection.^{10,11} However, the incidence of peritoneal recurrence (10–30 %) is not affected by the extent of gastric resection or adjuvant systemic therapies.

Patients with gastric peritoneal carcinomatosis (GPC) have a poor prognosis, with a median survival of less than 6 months and no long-term survivors.¹² Systemic chemotherapy has demonstrated some short-term survival benefit of up to 7–10 months in patients with distant metastatic gastric cancer, but not in the setting of PC.^{13,14} A number of experts consider cytoreductive surgery with hyperthermic intraperitoneal chemoperfusion (CRS/HIPEC) as the standard of care for the treatment of pseudomyxoma peritonei, malignant peritoneal mesothelioma and resectable colorectal carcinomatosis.^{15–17} However, the role of CRS/HIPEC in GPC remains controversial.^{18,19} Randomized controlled trials of curative gastrectomy in conjunction with CRS/HIPEC have demonstrated significant long-term survival benefit and decreased peritoneal recurrence in patients with advanced gastric cancer without visible carcinomatosis.^{20–26} Although some prospective trials have demonstrated limited improvement in median survival after curative gastrectomy plus CRS/HIPEC for macroscopic GPC, especially in patients with limited peritoneal disease, long-term survival benefit in this setting has been minimal.^{27–31} We present our institutional experience with CRS/HIPEC for the management of synchronous or metachronous macroscopic GPC and provide a review of the literature.

MATERIALS AND METHODS

We analyzed 23 consecutive patients with GPC who underwent CRS/HIPEC between May 2001 and July 2010 from a prospective database. One patient was lost to follow-up and was excluded from survival analyses. The study was approved by the University of Pittsburgh institutional review board. Intraoperatively, volume of disease was quantified by the peritoneal cancer index (PCI).^{32,33} Cytoreductive surgery (CRS) was performed in accordance with techniques, described by Bao and Bartlett. Completeness of cytoreduction (CC) score assessed adequacy of resection, as follows: CC-0, no visible residual disease; CC-1, residual tumors ≤ 2.5 mm; CC-2, residual tumors 2.5 mm to 2.5 cm; CC-3, residual tumors ≥ 2.5 cm.³⁴ A standard institutional protocol for HIPEC was initiated after CRS.³⁵ Using the closed technique, a roller-pump heat exchanger perfusion machine (ThermoChem HT-100, ThermoSolutions, Melbourne, FL, USA) allowed adequate saline flow (>800 ml/min) and a target intraperitoneal tissue temperature of 42 °C. Mitomycin C 30 mg was added to the perfusate initially for 60 min, followed by an additional 10 mg for a further 40 min.

Postoperative morbidity was classified according to the Dindo–Clavien grading system.³⁶ For the purposes of analysis, grades 3 and 4 were considered major complications.

Statistical analysis was performed by Stata software, version 10 (StataCorp, College Station, TX, USA). *p* values <0.05 were considered significant. Overall survival (OS) was calculated from the date of surgery to the date of death. If a patient did not die, they were censored at the time of their last follow-up. Time to progression was calculated from the date of surgery to the date of tumor recurrence. If a patient did not experience progression or recurrence, they were censored on the date of their last follow-up or death when the cause of death is clearly not related to gastric cancer. When progression or recurrence records were missing and cancer could not be ruled out as a cause for death, these patients were included as having disease progression. Survival times were estimated using the Kaplan–Meier method. One patient was lost to follow-up and was excluded from survival analyses. Proportional hazards Cox regression was used to examine both univariate and multivariate associations with mortality and progression. In univariate analyses, Bonferroni adjustments were made to *p* values to account for multiple comparisons. All factors that were examined in univariate analysis were considered for entry into the model for multivariate analysis. Variables were selected for the final multivariate model on the basis of a stepwise selection method with the use of clinical judgment and cumulative knowledge for proper selection of predictors.

RESULTS

Patient Characteristics and Clinical Presentation

The median time interval from initial disease diagnosis until surgical resection at our institution was 5.5 months (range 0.3–58.2 months). The mean age of our patients was 51.5 years, and most patients were women (56.5 %). Most patients presented with synchronous PC (87 %), and almost half of the patients (47.8 %) were symptomatic. Before surgical resection at our institution, 20 patients received chemotherapy (Table 1). The most commonly used drugs included combinations of platinum-based drugs 79 %, fluoropyrimidines 74 %, taxanes 47 %, and anthracyclines 37 %, with one patient each receiving bevacizumab and trastuzumab. The median number of cycles of neoadjuvant therapy was 4 (range 3–12 cycles). Data regarding response to neoadjuvant chemotherapy were not available.

Operative Characteristics and Pathology

Adequate cytoreduction (CC-0/1) was achieved in 22 patients despite a median PCI of 10.5. The majority of patients underwent total gastrectomy (18 patients), 2 patients had partial gastrectomy, 2 patients did not undergo gastrectomy as a result of extensive carcinomatosis, and 1 patient had previously undergone a total gastrectomy. Median operative time and estimated blood loss were 494 min and 500 ml, respectively. All patients received HIPEC with mitomycin C (98 %). Table 2 demonstrates the distribution of T and N stage for the primary gastric cancer according to the American Joint Committee on Cancer 7th edition staging system. Pathologic assessment revealed diffuse histology in 15 patients and high-grade tumors in 20 patients. High-grade tumors were defined as those meeting any one of the following histologic criteria, including poor cellular differentiation or the presence of

signet ring cells or diffuse histology. Positive lymph nodes, signet ring cells, and perineural/perivascular invasion were seen in 63.6, 65.2, and 65.2 % of patients, respectively (Table 2). D2 lymph node dissections were routinely performed in our patients with GPC. The mean number of lymph nodes collected at the time of gastrectomy was 17, and the mean number of positive lymph nodes was 8.

Postoperative Characteristics

Median intensive care unit and hospital length of stay were 2–20 days, respectively. The most common postoperative complications overall included minor infections (34.8 %), pulmonary complications (30.4 %), and cardiac complications (30.4 %), while major 60-day postoperative morbidity (grade III/IV) occurred in 52.2 % of patients. Of the 7 patients undergoing formal distal pancreatic resection, 2 developed a pancreatic leak. Four patients underwent reoperation for enterocutaneous fistulae, wound, or anastomotic complications. Of the 19 patients with available data, adjuvant chemotherapy was administered to 9 (47.4 %) patients. There were no postoperative deaths within 60 days of surgery; however, 1 patient died at postoperative day 66 (Table 3).

Oncologic Outcomes

Median follow-up time (based on time to end of study) was 4.4 years (range 9.0 months to 9.9 years). Death occurred in 18 patients and tumor progression occurred in 13 patients. Disease progression involved the peritoneum in 7 patients and occurred systemically in 10 patients. Two patients had either an unknown date of progression or unknown progression status. The median OS was 9.5 months [95 % confidence interval (CI) 4.7–17.3], with 1- and 3-year OS probabilities of 49.6 and 17.9 % (Fig. 1a). The median progression-free survival (PFS) was 6.8 months (95 % CI 3.9–14.6), with 1- and 3-year PFS probability of 42.8 and 10.7 % (Fig. 1b).

Univariate associations with poor survival were examined for gender, synchronous versus metachronous presentation, symptoms, completeness of cytoreduction, PCI, blood loss, specific visceral resection, number of anastomoses, tumor histology/grade/differentiation, signet ring cell features, lymph node involvement, and postoperative morbidity. On univariate analysis, significant predictors of poor survival included number of positive lymph nodes ($p = 0.008$) and delayed return of bowel function of >3 weeks ($p = 0.02$). There was a trend toward poor survival in male patients ($p = 0.08$), in those undergoing incomplete CC-1 cytoreductive surgery ($p = 0.09$), in patients with multiple bowel anastomoses ($p = 0.16$), and in patients with higher estimated blood loss ($p = 0.13$). In a multivariate Cox regression model, male gender, number of anastomoses, number of positive lymph nodes, and incompleteness of cytoreduction (CC-1) were joint significant predictors of poor survival ($\chi^2 = 18.2$; $p = 0.001$) (Table 4). Significant predictors of poor progression on univariate analysis included signet cells ($p = 0.03$). There was a trend toward worse progression in men ($p = 0.09$), higher number of positive lymph nodes ($p = 0.07$), incompleteness of cytoreduction CC-1 ($p = 0.11$), and patients with multiple visceral anastomoses ($p = 0.12$). In a multivariate Cox regression model, signet cells, >2 visceral anastomoses, and male gender were joint significant predictors of poor progression ($\chi^2 = 16.3$; $p = 0.001$) (Table 4).

DISCUSSION

On the basis of the EVOCAPE 1 study, patients with GPC generally have advanced T stage, high peritoneal tumor burden, and liver metastases, and they demonstrate a median OS of 3 months after palliative surgery and systemic chemotherapy.¹² Randomized trials comparing combination chemotherapy regimens to best supportive care alone for advanced, recurrent, or metastatic unresectable gastric cancer have demonstrated response rates of 25–50 % and median survival of 7–10 months, with no long-term survivors. However, a majority of the patients in these trials had non-peritoneal-based metastatic disease.^{37–39} The addition of targeted drugs to combination chemotherapy regimens has further improved survival.^{40,41} However, the response rate of measurable GPC to systemic chemotherapy is only 14–25 %, most likely attributable to poor penetration of systemic chemotherapy across the blood–peritoneal barrier.^{13,14, 42–44} In patients with isolated GPC, systemic chemotherapy benefits those patients without measurable disease and those with low-grade PC (defined by lack of PC on preoperative imaging, or lack of bowel involvement and minimal ascites on preoperatively imageable disease), as opposed to patients with measurable disease or high-grade PC. This benefit from systemic chemotherapy in patients with nonmeasurable peritoneal disease or low-grade PC is especially evident when combined with gastrectomy and D1/D2 lymphadenectomy, demonstrating median survival of 18–30 months.⁴⁵ This provides a rationale for aggressive CRS surgery to achieve macroscopic disease clearance and HIPEC to target microscopic disease.

Recent systematic reviews of CRS/HIPEC for gastric cancer with isolated macroscopic PC demonstrate a median survival of 8 months and a 5-year survival up to 13 %. Survival advantage is especially evident after complete cytoreduction in patients with low PCI, demonstrating median survival of 15 months (range 10–43 months) and 5-year survival rate of up to 27 %. This was achieved with morbidity and mortality rates of 22 and 5 %, respectively.^{18,30} Independent prognostic factors for improved survival after CRS/HIPEC include synchronous PC, complete cytoreduction (CC-0), systemic chemotherapy, no significant postoperative adverse events, surgery at a high-volume center, and low burden of peritoneal carcinomatosis.^{27–29,31,46–48} In our study, a limited subset of patients demonstrated a modest survival benefit to CRS/HIPEC. Complete cytoreduction (CC-0) was achieved in 74 % of patients and they demonstrated a favorable survival of 15 months, similar to published data. Any amount of macroscopic residual disease after CRS (>CC-0) portends poor survival, probably reflecting the ineffectiveness of currently available chemotherapeutic regimens in this aggressive malignancy. Although PCI did not correlate with survival in our cohort of patients, the extent of surgery based on the number of visceral anastomoses predicted survival and may be a surrogate for tumor burden and our ability to achieve complete cytoreduction. Additionally, male gender and number of positive lymph nodes were significant independent predictors of poor OS. However, the results of the multivariate analysis should be considered with some caution, given the small sample size in this study.

Our major morbidity rate is higher than previously published series. However, we have reported our 60-day major (grade III/IV) postoperative morbidity rate (52 %), as opposed to most published studies, which have reported 30-day morbidity rates or which have not

defined this period specifically. We think that 30-day morbidity does not adequately capture the often delayed complications associated with these complex procedures. In addition, we considered ileus >3 weeks (3 patients) and any readmission within 60 days of surgery (2 patients) as a major morbidity because these factors significantly affect patient quality of life. In light of this modest survival benefit in a small subset of patients and the significant morbidity associated with CRS/HIPEC, rigorous selection criteria and neoadjuvant/adjuvant therapeutic modalities must be considered when contemplating aggressive CRS/HIPEC in this patient population with advanced GPC. Currently at our institution, all patients with T3T4N1 gastric cancer first undergo CT imaging and laparoscopic staging including peritoneal washings. We do not currently offer CRS/HIPEC to patients with macroscopic PC, except in rare situations where very limited, focal, small-volume disease is encountered and is isolated to the peritoneal cavity. Even in this situation, patients first receive neoadjuvant chemotherapy and preferably should have a disease-free interval of >1 year for metachronous presentation. Patients with microscopic disease in the peritoneal cavity at laparoscopic staging also receive neoadjuvant chemotherapy followed by CRS/HIPEC for stable disease. Ideally, all gastric cancer patients being considered for CRS/HIPEC should be enrolled onto prospective clinical trials. However, until such clinical trials can be implemented, a highly selective approach is recommended.

Neoadjuvant systemic chemotherapy demonstrates response rates of up to 79 % at the primary tumor site in patients with locally advanced gastric cancer.⁴⁹ However, the response rate of peritoneal nodules is only 14–25 %.⁴⁴ Positive peritoneal cytology is an independent predictor of poor survival after curative gastrectomy, with survival rates similar to patients with gross peritoneal disease. Conversion of positive peritoneal cytology to negative cytology occurs in over 50 % of patients after neoadjuvant systemic chemotherapy, and these patients demonstrate significantly improved survival after curative gastrectomy.^{1,2} Bidirectional chemotherapy, consisting of combination neoadjuvant systemic and intraperitoneal chemotherapy, has been demonstrated to convert positive peritoneal washing cytology to negative in 63 % of patients with advanced gastric cancer, with corresponding ability to increase CC-0 resection.⁵⁰ However, despite cytologic conversion, long-term survival after curative resection in these patients is rare, and more than two-thirds experience disease recurrence within the peritoneal cavity, which is the major cause of death. The most promising survival outcomes for CRS/HIPEC have been demonstrated in patients with locally advanced gastric cancer without microscopic or macroscopic peritoneal dissemination.^{17,24–26} In our patient cohort, 83 % of patients received neoadjuvant chemotherapy immediately before surgical resection. Conversely, adjuvant chemotherapy was provided to only 9 of 19 patients (47.4 %) with available data. Of the 10 patients who did not receive adjuvant chemotherapy, 1 patient died at postoperative day 66, 5 patients had major postoperative morbidity that prevented further therapy, 2 patients had metachronous carcinomatosis for which they received preoperative chemotherapy only, and 2 patients had no documented reason for the lack of adjuvant therapy.

In summary, aggressive CRS/HIPEC may be selectively offered to gastric cancer patients with low peritoneal tumor burden in whom complete cytoreduction can be achieved. In fact, given the limited survival benefit even in this select subgroup of patients, a multidisciplinary protocol-based approach is warranted. CRS/HIPEC may be most beneficial in a prophylactic

setting for patients with locally advanced gastric cancer without peritoneal dissemination and possibly those with positive peritoneal cytology that demonstrate favorable response to neoadjuvant systemic or bidirectional chemotherapy.

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FIG. 1.

a Kaplan–Meier OS curve for patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion ($n = 22$). Median survival was 9.5 months (95 % CI 4.7–17.3), with 1- and 3-year OS probability of 49.6 and 17.9 %, respectively. **b** Kaplan–Meier curve for time to progression for patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion ($n = 21$). Median time to progression was 6.8 months (95 % CI 3.9–14.6), with 1- and 3-year PFS probability of 42.8 and 10.7 %, respectively

TABLE 1Preoperative patient characteristics and presentation ($n = 23$)

Characteristic	Value
Age at surgery, year, mean $\pm$ SD	51.5 $\pm$ 15
BMI, kg/m ² , median (range) ($n = 21$)	25.2 (16.9–39.3)
Age-adjusted Charlson comorbidity index, median (range) ^a	0 (0–5)
Preoperative albumin, g/dl, median (range) ($n = 19$)	3.9 (1.9–4.3)
Gender, n (%)	
Male	10 (43.5)
Female	13 (56.5)
Race, n (%)	
White	21 (91.3)
Not white	1 (4.3)
Unknown	1 (4.3)
Disease status, n (%)	
Synchronous GPC	20 (87)
Metachronous GPC	3 (13)
Prior surgical therapy, n (%)	
CRS	2 (8.7)
Chemoperfusion	1 (4.3)
Clinical parameter, n (%)	
Symptomatic	11 (47.8)
Abdominal pain	8 (34.8)
Ascites	3 (13)
Bowel obstruction	2 (8.7)
Prior chemotherapy, n (%) ($n = 20$)	
Adjuvant	1 (4.3)
Neoadjuvant	19 (82.6)

BMI body mass index, *GPC* gastric peritoneal carcinomatosis, *CRS* cryoreductive surgery^aExcluding index gastric cancer diagnosis

TABLE 2

Operative characteristics and pathology ($n = 23$)

Characteristic	Value
Operative time, min, median (range) ($n = 21$)	494 (287–780)
Estimated blood loss, ml, median (IQR) ($n = 19$)	500 (200–900)
Peritoneal cancer index, median (range) ($n = 22$)	10.5 (0–29)
Completeness of cytoreduction, n (%)	
CC-0	17 (73.9)
CC-1	5 (21.7)
Unknown	1 (4.3)
Surgical resection, n (%)	
Peritoneal stripping	10 (43.5)
Omentectomy	21 (91.3)
Distal pancreatectomy	7 (30.4)
Splenectomy	13 (56.5)
Diaphragmatic resection	5 (21.7)
Hepatectomy	1 (4.4)
Cholecystectomy	6 (26.1)
Low anterior resection	3 (13)
Partial colectomy	6 (26.1)
Small bowel resection	16 (69.6)
Partial gastrectomy	2 (8.7)
Total gastrectomy	18 (78.3)
Ureterolysis	5 (21.7)
Hysterectomy	5 (21.7)
Ostomy	3 (13)
No. of anastomoses, median (range)	2 (0–5)
Location of primary tumor, n (%) ($n = 19$)	
Proximal	12 (63.2)
Mid/distal	3 (15.8)
Diffuse	4 (21.1)
AJCC 7th edition TN stage, n (%) ($n = 19$)	
T2N0	1 (5.3)
T2N1	4 (21.1)
T3N1	5 (26.3)
T2N3	5 (26.3)
T4N1	3 (15.8)
T4N3	1 (5.3)
Histologic classification, n (%)	
Intestinal	7 (30.4)
Diffuse	15 (65.2)
Unknown	1 (4.3)

Characteristic	Value
Tumor grade, <i>n</i> (%)	
Low grade	3 (13)
High grade	20 (87)
Differentiation, <i>n</i> (%)	
Well differentiated	1 (4.3)
Moderately differentiated	4 (17.4)
Poorly differentiated	18 (78.3)
Signet ring cells present, <i>n</i> (%)	15 (65.2)
Perineural/perivascular involvement, <i>n</i> (%) (<i>n</i> = 20)	15 (65.2)
Positive lymph node status, <i>n</i> (%) (<i>n</i> = 22)	14 (63.6)

IQR interquartile range, *CC* completeness of cryoreduction, *AJCC* American Joint Committee on Cancer

TABLE 3Postoperative characteristics ($n = 23$)

Characteristic	Value
Overall morbidity, n (%) ($n = 22$)	
Minor morbidity	10 (43.5)
Major morbidity	12 (52.2)
Overall mortality, n (%)	
30 day	0
60 day	0
In hospital (day 66)	1 (4.3)
Minor wound infection, n (%)	8 (34.8)
Major wound infection, n (%)	0
Sepsis, n (%)	5 (21.7)
Postoperative, bleeding n (%)	1 (4.3)
Cardiac, n (%)	7 (30.4)
Pulmonary, n (%)	7 (30.4)
Ileus, n (%)	4 (17.4)
Delayed gastric emptying, n (%)	6 (26.1)
Pancreatic leak, n (%)	2 (8.7)
Enterocutaneous fistula, n (%)	1 (4.3)
Anastomotic leak, n (%)	3 (13)
Hospital length of stay, day, median (range)	20 (9–120)
ICU length of stay, d, median (range) ($n = 22$)	2 (0–110)
Return to OR, n (%)	4 (17.4)
Return to ICU, n (%)	4 (17.4)

ICU intensive care unit, *OR* operating room

TABLE 4

Multivariate predictors of mortality and poor progression

Predictor	HR	Comparison group	SE	95 % CI for HR	p value
Predictors of mortality ($\chi^2 = 18.2$; $p = 0.001$)					
Sex (male)	6.2		4.8	1.4–27.9	0.016
No. of positive lymph nodes	1.2		0.1	1.1–1.4	0.003
No. of anastomoses > 2	2.8		1.9	0.7–10.8	0.14
Completeness of cytoreduction > CC-0	2.4		1.8	0.6–10.4	0.25
Predictors of progression ($\chi^2 = 16.3$; $p = 0.001$)					
Signet cells	9.9		6.2	2.3–35.1	0.002
Visceral anastomoses > 2	5.5		4.2	1.2–24.1	0.03
Sex (male)	1.5		0.4	0.8–7.6	1.48

HR hazard ratio, SE standard error, CI confidence interval