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Cytoreductive surgery and heated intraperitoneal chemotherapy for peritoneal carcinomatosis from rare etiologies

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ABSTRACT

Background: Cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) are commonly used in the treatment of peritoneal carcinomatosis (PC) originating from colorectal, appendiceal and ovarian cancers. It is unclear what benefit CRS/HIPEC might have for PC from uncommon etiologies, therefore we sought to describe local practice patterns and evaluate overall survival (OS).
Methods: All patients who had CRS/HIPEC between 2000 and 2016 were identified using our institutional cancer database. Patients with appendiceal, colorectal, and ovarian pathologies were excluded. Kaplan-Meier curves were used to estimate and demonstrate 5-year OS. Cox regression analysis was performed to determine factors associated with OS.
Results: Of all patients treated with CRS/HIPEC at our institution, 38 were treated for PC of rare origin. Etiologies included 23 patients with mesothelioma, 8 with primary peritoneal carcinoma, 4 with small bowel tumours and 3 with gastric cancer. Median OS of 35.4, 20.8, 25.4, and 20.2 months were obtained for each group respectively. 5-year OS for each pathology was 8.7%, 0.0%, 25.0%, and 33.3% respectively with corresponding mean PCI of 31.3, 23.6, 21.5, and 12.7. No independent prognostic factors were significant on Cox regression analysis. Median length of stay was 19 days. Readmission rate within 30 days of discharge was 7.9%. Rate of Grade III/IV complications was 34.2%. No thirty-day mortality.
Conclusion: Survivals beyond 20 months can be obtained with the use of CRS/HIPEC for rare PC etiologies aligning with results of other groups. CRS/HIPEC in well-selected patients demonstrates a clinical benefit and this could be confirmed with a multi-institutional study.

Introduction

Peritoneal carcinomatosis (PC) is defined by the presence of metastatic malignant deposits on the peritoneal surface. The incidence of PC in gastric cancer (GC) is 14–35%. Heated intraperitoneal chemotherapy (HIPEC) is rarely used for GC but the three main indications where it is utilized include: prophylactically when there is no PC but a locally advanced primary increases the risk of developing future PC, when there is a very limited amount of PC, and for palliation of refractory ascites.[1] Small bowel tumours are a rare entity comprising less than 5% of gastrointestinal cancers with adenocarcinoma and neuroendocrine tumours accounting for up to 37% and 30% respectively.[2] Carcinomatosis comprises 33% of small bowel cancer recurrences.[3] Mesothelioma in itself is uncommon and peritoneal mesothelioma accounts for only 30% of cases.[4] Primary peritoneal cancer is very rare occurring in the range of 1 per one million women and is histologically identical and clinically similar to epithelial ovarian cancer but develops along a different etiological pathway.[5,6]

In general, PC portends poor prognosis even if treated with systemic chemotherapy. The cytoreductive surgery (CRS) and HIPEC procedure was developed to combat this unique locoregional disease with the complete surgical removal of PC implants ≥1 mm coupled with perfusion of heated chemotherapy at temperatures of 40–42 degrees Celsius.[7] This procedure is now the standard of care for PC originating from colorectal, appendiceal and epithelial ovarian cancers in appropriately selected patients.[8–12] It is unclear what role CRS/HIPEC has to play for uncommon etiologies including GC, small bowel tumours, mesothelioma, and other rare cancers. Therefore, the use of this treatment modality for PC from these uncommon etiologies is controversial and typically performed at

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only experienced centres.

The primary objective of this study was to describe local practice patterns and technical feasibility for the use of CRS/HIPEC in patients with PC from rare etiologies. Our secondary objectives were to evaluate the median overall survival, calculate 5-year overall survival, perioperative morbidity and mortality, and identify prognostic factors for overall survival.

Methods

Study design

This is a single centre retrospective cohort study that was conducted at the Foothills Medical Center (Calgary, Alberta). This is a university-affiliated tertiary care referral centre for the treatment of PC with CRS/HIPEC, currently performing more than 60 procedures per year. We included all patients who had both CRS and HIPEC for PC for an etiology other than colorectal, appendiceal and ovarian between January 2000 and December 2016. The observation period for follow up concluded at end of the month of April 2018. Exclusion criteria consisted of patients with gastric cancer treated prophylactically (PCI of zero), those who had missing information regarding CCR or PCI, those with previous HIPEC, or patients immediately lost to follow up.

Data collection

To identify patients for this study, we used the Cancer Surgery Alberta Peritoneal Database. This is the institutional database at the University of Calgary containing the majority of oncology patients with colorectal, hepatobiliary, and advanced gastrointestinal malignancy with diagnosed peritoneal disease that were referred for surgical resection or palliative treatment. Data collected consisted of operative reports, pathology reports, and markers of morbidity and mortality (specifically any mortality within 30 days of index operation, grade III/IV complications, length of stay, and readmission rates). Follow up consultation clinic notes were reviewed to obtain additional data. When electronic records were insufficient, chart reviews were performed and referral centres contacted to obtain follow up data. Peritoneal Carcinomatosis Index (PCI) and Completeness of Cytoreduction (CCR) were utilized for stratifying the extent of disease and quality of surgical resection. No standardized guidelines exist for the selection of appropriate candidates with PC from rare etiologies to undergo CRS/HIPEC, thus selection criteria were extrapolated from standard criteria used for selection of patients with established indications (e.g. colorectal cancer). Patients at our centre must be deemed medically fit to have CRS/HIPEC (without significant comorbidities and with reasonable physiologic reserve to tolerate a radical surgery with long operative time under general anesthesia), good ECOG[13] functional status scores 0 or 1 (at most restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), reasonable likelihood that complete cytoreduction could be performed (utilizing preoperative cross-sectional imaging), absence of extraperitoneal disease, no bulky retroperitoneal disease, and disease responsive to chemotherapy. All patients treated with CRS/HIPEC were reviewed at multi-disciplinary Tumour Board Rounds and treatment was agreed upon by group consensus.

Operative details

Patients underwent CRS as initially described by Sugarbaker et al.[14] A laparotomy incision was created, followed by complete lysis of adhesions, and the PCI was calculated preoperatively to assess the extent and size of tumour implants. One or more peritonectomy procedures were then undertaken to remove all visible disease, as well as electrofulguration of tumour nodules on the small bowel and visceral resections where necessary to remove primary tumours or sites of metastases. Subsequently, a treatment of HIPEC was undertaken. Table 1 summarizes the chemotherapy agents utilized for each pathology type. 3L of Dianeal peritoneal dialysis solution was used for HIPEC, and 1.5L of the same solution was used for early postoperative intraperitoneal chemotherapy (EPIC) for patients with mesothelioma. Circulating time for all intraperitoneal agents was 60 min at temperature of 40–42 degrees Celsius. Any visceral anastomoses were then undertaken, and PCI and Completeness of Cytoreduction Score (CCR) were calculated at the conclusion of the procedure. CCR-0 was defined as no visible residual tumour, CCR-1 as tumour nodules no greater than 2.5 mm in size remaining, and CCR-2 as tumour nodules between 2.5 mm and 2.5 cm remaining. CCR-3 was defined as tumour nodules greater than 2.5 cm remaining or the presence of confluent unresectable nodules.[15] No HIPEC was undertaken when the resulting CCR score was 2 or more, and these patients were not included in the final analysis.

Statistical analysis

We used descriptive statistics to evaluate patients and tumour characteristics. Means were compared using paired-sample Student's T-test. Cox regression analysis was used to determine if any continuous and categorical variables were prognostic of the dependent variable overall survival (OS). OS analysis was performed using the Kaplan-Meier method for each subgroup and the entire group. A p-value of <0.05 was defined as statistically significant. All data was analyzed using IBM SPSS Statistical software version 24.0 (International Business Machines, Armonk, NY).

Results

A review of the institutional database yielded 503 patients with peritoneal disease. This was narrowed down to 104 possible patients after exclusion of the patients with PC of colorectal, appendiceal, and ovarian origin. After review of pathology and operative reports, 56 patients were brought to the operating room with intent to perform CRS/HIPEC; however significant burden of disease and inability to achieve complete cytoreduction resulted in a handful of patients receiving palliative procedures without any intraoperative chemotherapy drug administered. Fig. 1 demonstrates a breakdown by pathology. In total, 45 patients underwent CRS/HIPEC for PC from rare etiologies; however, one mesothelioma patient and one primary peritoneal patient were excluded from the study due to incomplete reporting of PCI and CCR. For gastric cancer, 5 patients had PCI of zero (no evidence of PC intra-operatively, or on pathology/cytology reports) and were deemed to have been treated prophylactically and thus were excluded from the analysis.

Table 1
HIPEC regimens utilized for each pathology.

Pathology	Regimen
Mesothelioma	Doxorubicin 15 mg and Cisplatin 50 mg, EPIC paclitaxel 25 mg × 5 days
Peritoneal	Doxorubicin 15 mg and Cisplatin 50 mg or Cisplatin 40 mg only or Mitomycin C 15 mg or Oxaliplatin 400 mg and 5-FU 800 mg IV
SB adenoCA	Oxaliplatin 400 mg and 5-FU 800 mg IV
SB NET	Mitomycin C 15 mg
Gastric	Mitomycin C 15 mg

*EPIC: early postoperative intraperitoneal chemotherapy, 5-FU: 5-fluorouracil, SB: small bowel, adenoCA: adenocarcinoma, NET: neuroendocrine tumour.

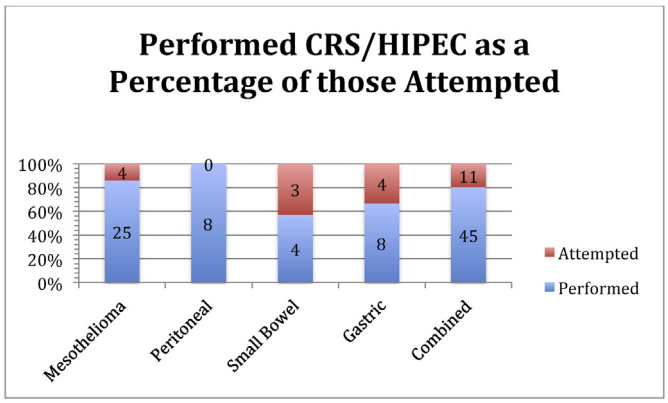

Fig. 1. Performed CRS/HIPEC as a percentage of those attempted per pathology.

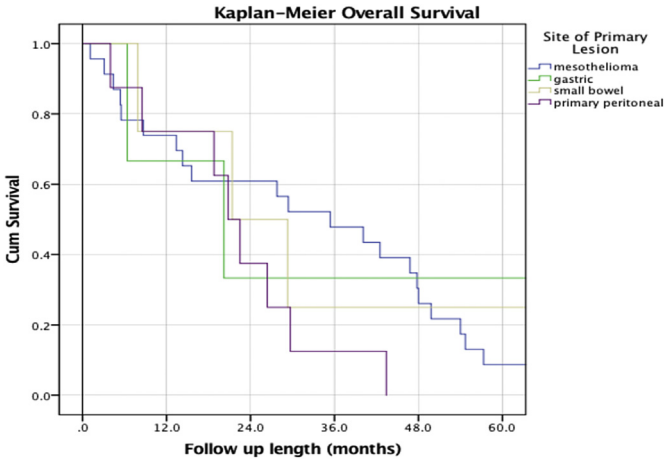

Fig. 2. Kaplan-Meier Graph of 5-year Overall Survival for each primary etiology.

In summary, 38 patients underwent CRS/HIPEC for PC of uncommon etiology and were within our inclusion criteria. There were 24 female (63%) and 14 male (37%) patients. The median age was 56 (range 20–81). Mesothelioma comprised over half (23) of pathology followed by primary peritoneal (8), small bowel (4) and gastric (3). Median overall survival times of 35.4, 20.8, 25.4, and 20.2 months were calculated for each of these groups respectively (Table 2). Five-year OS for each pathology was 8.7%, 0.0%, 25.0%, and 33.3% respectively. This information is presented in a Kaplan-Meier survival graph at 1, 2, 3, 4, and 5-year intervals (Fig. 2). Mean PCI was 31.3, 23.6, 21.5, and 12.7 respectively. A CCR score of zero was achieved in 56.5% of patients with mesothelioma, 87.5% of patients with primary peritoneal, and 100% of patients with gastric and small bowel tumours. The median OS of our 38 patients collectively was 26.4 months. Cox regression analysis was performed with the covariates including age at the time of surgery, gender, PCI, CCR, and site of primary lesion; however, none were statistically significant independent prognostic factors. The mean and median length of stay for our patients was 22.6 days and 19 days respectively. The rate of readmission to hospital within 30 days of discharge was 7.9%. The rate of Clavien-Dindo Grade III/IV complications was 34.2%, and no patients died within 30 days of their procedure.

Discussion

To date, limited data has been published to validate use of CRS/HIPEC in these small patient populations with PC from sites of rare origin, simply due to the infrequent nature of these diseases. The exception to this is gastric cancer (GC). The majority of the literature surrounding PC from gastric origin arises from high volume centres in Asia where GC is more prevalent than in the Western population. The results are so far promising but controversy still exists surrounding this topic with the majority of patients receiving CRS/HIPEC only if enrolled in a clinical trial. One published RCT by Yang et al. comparing CRS/HIPEC versus surgery alone for treatment of PC from GC reported a median OS of 11 months in the treatment arm compared to 6.5 months in the control arm.[16] A review of the literature is supportive of the aforementioned RCT with median OS for GC with PC treated with CRS/HIPEC to be in the range of 11–15 months compared to 7–11 months with systemic chemotherapy alone.[1,17–19] One area of consideration is that many studies included patients treated prophylactically in their analysis.[1] In these studies, patients underwent curative gastric resection and intraoperatively had no evidence of PC but had high risk features of metastasis or recurrence (advanced T stage, advanced N stage, signet ring cell histology, large tumour size, young age, or positive peritoneal lavage cytology). Not surprisingly, these patients have better outcomes compared to their PC counterparts due to decreased morbidity in the absence of peritoneal stripping procedures.[1] At our institution, the median OS for GC with PC was 20.2 months. Given that only three patients were included in the analysis, the small sample size makes it difficult to compare with other studies.

A systematic review of 7 prospective observational studies for PC from mesothelioma reported a median OS range of 34.9 months.[20] In their review of peritoneal mesothelioma, Chua et al. reported a median OS of 28–35 months for patients treated with CRS/HIPEC.[4] Our group achieved similar results with median OS 35.4 months. Given the rare incidence of this disease, treatment of our patients was adapted from original protocols described by Mohamed and Sugarbaker[21] who included EPIC in their procedure; thus there is no HIPEC only comparison group. The rationale behind addition of EPIC is to further supplement microscopic tumour removal, thus decreasing future recurrence.

One multi-institutional study of CRS/HIPEC for primary peritoneal serous carcinoma included 32 patients.[5] The median DFS was 16.7 months with OS at 1, 3, and 5-years reported as 93.6%, 71.5%, and 57.4% respectively. PCI was a prognostic factor in this study. Of note our primary peritoneal group was heterogeneous including two patients with exclusively omental disease. A median OS of 20.8 in our patients is similar to that of published studies. Keeping in mind that all of our patients with primary peritoneal disease had

Table 2
Median, mean, range, and 5-year overall survival for each site of primary lesion.

Site of Primary Lesion	Median OS (months)	Mean OS (months)	OS Range (months)	5-year OS (%)
Mesothelioma	35.4	32.6	1.1–70.6	8.7
Primary Peritoneal	20.8	21.8	4.0–43.4	0.0
Small Bowel	25.4	45.0	7.9–121.4	25.0
Gastric	20.2	55.5	6.4–139.9	33.3

Note: No patients with PC from primary peritoneal etiology have been followed long enough to have 5-year data.

their surgeries performed between 2012 and 2016, we were unable to follow them long enough to obtain 5-year data; however the Kaplan-Meier curve estimate of 5-year OS is 0%. To place things in perspective, a more descriptive representation of our results is the 2-year OS of 37.5%. During the study period two patients demonstrated recurrence (one death) and the remaining are alive without evidence of recurrence or were censored due to loss to follow up.

A recent multi-institutional study by Liu et al. of CRS/HIPEC for PC from small bowel adenocarcinoma reported median OS of 32 months.[22] This study included 152 patients of which mean PCI was 12 with CCR score 0 or 1 achieved in 88.2% of patients. Goéré et al. report a 5-year OS of 39.9% for their patients with small bowel neuroendocrine tumour.[23] While these two entities have different tumour biologies, our smaller sample groups were analyzed together due to each demonstrating a wide range of OS (7.9–29.3 and 21.4–121.4 months for adenocarcinoma and neuroendocrine tumour respectively). Patients at our institution had a lower median OS of 25.4 months and a higher mean PCI in this group (21.5), but all four of our patients had CCR 0.

The observed 34.2% rate of Grade III/IV complications is within the range reported by several large series assessing morbidity and mortality in CRS/HIPEC.[24] This was similar to another study from our institution which found a 43.2% and 19.6% rate for colorectal/appendiceal carcinomatosis treated with HIPEC + EPIC and HIPEC alone respectively.[25] We know from both the literature and experience that higher PCI is directly related to increased surgical morbidity in CRS/HIPEC.[24,26] It is worthy to note that the patients in our study with grade III/IV complications all had a large burden of disease with mean PCI score of 29.4. Three patients were readmitted to hospital within 30 days of their discharge, demonstrating that delayed complications were not common and likely to be observed within the duration of their operative admission. Readmission diagnoses included one patient with an abscess requiring percutaneous drain insertion, one for management of *C. difficile* colitis, and one for workup of a seizure.

These multi-institutional studies referred to above aim to increase the sample size for analysis, but we should remember that these studies suffer from the heterogeneity that exists in treatment protocols between institutions. Strengths of our study include long duration of the study at 16 years, high volume experienced tertiary care centre, referral centre for western Canada, tumour board review of all patients, and no thirty-day mortality for all patients meeting inclusion criteria. Retrospective analysis, single centre, small sample size, heterogeneous histology, and missing data are among the limitations of this study. In the analysis only 12 patients were confirmed to have died during follow up. This leaves 26 patients who were censored due to not reaching the terminal event (death) within the observation period or else were lost to follow up (some of these patients had last documented appointments greater then 24 months ago, thus the true OS is less than ideal for these patients). We must also be cognizant that our study patients were a highly selected cohort representing only a subset of those with PC from sites of rare origin. We predict that with increased sample size, PCI will be shown to be an independent prognostic factor.

Conclusion

Our institution achieved overall survival beyond 20 months for patients with peritoneal carcinomatosis from rare etiologies treated with CRS and HIPEC, aligning with results of the greater surgical community. In conclusion PC of rare etiology treated with CRS/HIPEC is technically feasible, with acceptable perioperative morbidity and mortality, when performed at an expert centre for appropriately selected patients. It should continue to be a treatment option for patients, balancing the expected survival benefit with perioperative risks and patient quality of life. Additional studies comparing systemic chemotherapy versus CRS/HIPEC, and quality of life assessments may help confirm an overall clinical benefit for these patients. This would be best accomplished through a multi-institutional study. With the growing body of literature supporting CRS/HIPEC as a safe and effective treatment modality we anticipate further knowledge procurement, and efforts made to standardize treatment protocols may allow for better reproducibility and analysis of outcomes.

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The authors have no conflicts of interest to disclose, and this study had no external funding source.

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