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Secondary Cytoreductive Surgery ± Hyperthermic Intraperitoneal Chemotherapy for Recurrent Colorectal Cancer Peritoneal Metastases

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Abstract

Background Most patients who have colorectal cancer peritoneal metastases (CRC-PM) treated with cytoreductive surgery ± hyperthermic intraperitoneal chemotherapy (CRS±HIPEC) experience recurrence within 1 year. This study assessed the safety and oncologic value of secondary CRS±HIPEC for patients with CRC-PM.

Methods A multi-institutional database of patients treated for CRC-PM (2000–2024) was reviewed. Patients who underwent curative-intent initial CRS±HIPEC alone were compared with those who underwent secondary CRS±HIPEC for recurrent disease. Patients who received more than two procedures were excluded. The primary objective was to evaluate the safety of secondary CRS±HIPEC for CRC-PM as measured by perioperative outcomes. The secondary objective was to examine the association between overall survival (OS) and secondary CRS±HIPEC.

Results The study included 136 patients, 17 of whom underwent secondary CRS±HIPEC. There was no difference in postoperative complications between secondary and initial CRS±HIPEC. When OS was defined from the date of the index operation, secondary CRS±HIPEC was associated with improved OS versus initial CRS±HIPEC alone (51.0 months [95% confidence interval {CI}, 39.8–62.2 months] vs. 24.0 months [95 % CI, 19.4–28.6) months]). To assess the value of secondary CRS±HIPEC, OS was compared from the date of the second procedure for the secondary cohort. Overall survival measured after secondary CRS±HIPEC was similar to that after initial CRS±HIPEC (27.0 months [95 % CI, 17.3–36.7 months] vs. 24.0 months [95 % CI, 19.4–28.6 months]). Among the patients with recurrence after their index CRS±HIPEC, secondary

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CRS±HIPEC remained associated with better OS than that of those who received only one procedure (27.0 months [95 % CI, 17.3–36.7 months] vs. 12.0 months [95 % CI, 9.2–14.8 months]).
Conclusion Secondary CRS±HIPEC should be considered for well-selected patients with CRC-PM recurrence.

Keywords Colorectal cancer peritoneal metastases · Cytoreductive surgery ± hyperthermic intraperitoneal chemotherapy · Secondary surgery

Approximately 8 % of patients with colorectal cancer (CRC) present with synchronous or experience metachronous peritoneal metastases (PM).[1] Compared with non-peritoneal metastases, peritoneal metastases are associated with significantly worse overall survival: lung only (24.6 months; 95% CI, 22.7–26.4 months), liver only (19.1 months; 95% CI, 18.3–19.8 months), and peritoneal only (16.3 months; 95% CI, 13.5–18.8 months).[2] Relative to systemic therapy alone, cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (CRS±HIPEC) has been associated with improved survival in both retrospective studies[3–5] and randomized trials[6–8] for patients with colorectal cancer peritoneal metastases (CRC-PM). When complete cytoreduction can be achieved, median survival after CRS±HIPEC approaches 3 to 5-years.[7]

Although CRS±HIPEC is considered an established treatment strategy for this patient population, the majority of patients with CRC-PM experience recurrence within 1 year, with about one-third of these recurrences isolated to the peritoneal cavity.[3,9–12] To date, no randomized controlled trials have explored the role of secondary CRS±HIPEC for recurrent CRC-PM. Currently, data are limited to single-institution, international, or mixed-histology retrospective studies.[13,14] Thus, the goal of the current study was to assess the safety and oncologic utility of secondary CRS±HIPEC for patients with CRC histology using a large, multi-institutional database that includes patients undergoing surgery at high-volume centers across the United States.

The primary objective of this study was to evaluate the safety of secondary CRS±HIPEC specifically for CRC-PM, as measured by perioperative outcomes. The secondary objective was to examine the association between overall survival (OS) and secondary CRS±HIPEC versus index CRS±HIPEC alone plus systemic therapy and/or best supportive care.

Patients and Methods

Patient Selection

The US HIPEC Collaborative is a multi-institutional retrospective database composed of patients from 12 academic medical centers.[15] After institutional review board approval was obtained at all sites, we performed a retrospective cohort study including patients from 2000–2017. The Emory University cohort was updated through 2024. The study included patients with CRC histology who underwent curative-intent initial CRS±HIPEC alone or secondary CRS±HIPEC with complete cytoreduction. Complete cytoreduction was defined as a completeness of cytoreduction (CCR) score of 0 or 1. The study excluded patients who underwent emergent, non–curative-intent CRS±HIPEC with a CCR score greater than 1, had unavailable surgery date(s) and/or death status. Patients who underwent a single CRS±HIPEC were included in the index CRS±HIPEC-alone cohort. Patients who underwent a previous CRS±HIPEC followed by a second CRS±HIPEC were included in the secondary CRS±HIPEC cohort. Those who underwent more than two CRS±HIPEC treatments were excluded.

Primary Objective: Perioperative Outcomes

Clinicodemographic, histopathologic, and perioperative data were collected and compared between the index-alone and secondary CRS±HIPEC cohorts. For the secondary CRS±HIPEC cohort, only data pertaining to their second surgery were available and analyzed. The clinicodemographic data collected included age, gender, race, location of primary tumor, presence of non-peritoneal metastases on preoperative imaging, and neoadjuvant/adjuvant therapies (including receipt of chemotherapy, immunotherapy, bevacizumab, and radiation). The histopathologic data collected included primary tumor-node-metastasis (TNM) stage, tumor differentiation, lymphovascular invasion (LVI), perineural invasion (PNI), presence of perforation, and/or obstruction.

Preoperative lab values were collected within 90-days after surgery, were the last documented, and included carcinoembryonic antigen (CEA; mg/dL), creatinine (mg/dL), glycated hemoglobin (HbA1c), and albumin (g/dL). Preoperative clinical characteristics such as body mass index (BMI) and American Society of Anesthesiologists (ASA) physical status class also were assessed between cohorts.

Operative characteristics explored included operative time (h), estimated blood loss (mL), intraoperative peritoneal carcinomatosis index (PCI), CCR score, and intraoperative transfusion requirements (including red blood cells, fresh frozen plasma, platelet, and cryoprecipitate transfusions). To ensure that secondary surgeries were comparable

with index operations, a compositive variable that included the total number of visceral organs removed at the time of CRS±HIPEC was calculated. Resections used to generate this continuous variable were as follows: cholecystectomy, diaphragmatic resection, gastrectomy, splenectomy, pancreatectomy, omentectomy, hysterectomy, oophorectomy, partial cystectomy, colectomy, small bowel resection, appendectomy, nephrectomy, ureteral resection, and formal liver resection.

For our primary objective, postoperative clinically significant complications, requirement of postoperative red blood cell (RBC) transfusion, length of stay, need for readmission, and 30-day mortality were compared between cohorts. Clinically significant complications were defined as grades III to V adverse events based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 terminology[16] and included presence of deep surgical-site infection, intraabdominal infection, intraoperative death, cardiac arrest, unplanned intubation, ventilator requirement longer than 48 h, need for tracheostomy, pulmonary embolism, bleeding requiring an intervention, need for a postoperative drainage procedure, postoperative sepsis, reoperation, acute renal failure, chest tube placement/thoracentesis, postoperative total parenteral nutrition, postoperative tube feeds, readmission, and/or postoperative RBC transfusion of more than three units.

Secondary Objective: Overall Survival

For our second objective, OS was compared between the index-alone and secondary CRS±HIPEC cohorts for all analyses, but was defined and evaluated in four distinct ways. For both cohorts, OS was first defined as time from date of index operation to death or last follow-up. Next, to assess the value of secondary CRS±HIPEC, OS was redefined as time from date of second operation to death or last follow-up for the secondary CRS±HIPEC cohort. Immortal time is an interval during a study period in which an outcome event cannot occur.[17] With respect to this study, immortal time was defined as the period between CRC-PM diagnosis and secondary CRS±HIPEC. To receive a secondary CRS±HIPEC, a patient must survive this immortal time. In an attempt to account for this potential selection bias, a landmark survival analysis was performed only among patients with disease recurrence, as previously described.[18,19] For the index CRS±HIPEC-alone cohort, OS was redefined as time from date of recurrence to death or last follow-up. For the secondary CRS±HIPEC cohort, OS remained defined as time from date of second operation to death or last follow-up. Finally, in an attempt to ensure that those in the index CRS±HIPEC-alone cohort represented patients with recurrent disease potentially eligible for CRS±HIPEC, this analysis was repeated after exclusion of patients with extra-abdominal disease recurrence (those with bone, chest, lung, or retroperitoneal disease recurrence).

Statistical Analysis

All analyses were performed using IBM SPSS Statistics version 29.0 (SPSS, Inc., Chicago, IL, USA). Chi-square or Fisher's exact tests were used for comparison of categorical variables, as appropriate. Distributions of continuous variables were compared using Mann-Whitney *U* tests. The association between secondary CRS±HIPEC and experience of a clinically significant postoperative complication was assessed using binary logistic regression. Covariates that were statistically significant, defined by a p value lower than 0.05 in univariate analyses, were selected for inclusion in multivariable binary logistic regression models. Covariates missing more than 20% of data were excluded from multivariable logistic regression models.

The association between secondary CRS±HIPEC and OS was assessed using log-rank Kaplan Meier, univariate, and multivariate Cox regression survival analyses. Covariates significantly associated with secondary CRS±HIPEC and/or death in bivariate analyses were explored using univariate Cox regression models. Covariates statistically significant, defined by a p value lower than 0.05 in univariate analyses were then selected for inclusion in multivariable Cox regression models. Covariates missing more than 20% of data were excluded from multivariable Cox regression models.

Results

Study Population

Within the US HIPEC Collaborative, 521 patients with colorectal histology were identified, and 136 met the inclusion and exclusion criteria, had appropriate data available, and were included in the final analysis (Fig. 1). Of these patients, 119 (87.5%) underwent index CRS±HIPEC alone, and 17 (12.5%) received secondary CRS±HIPEC. Among the index CRS±HIPEC cohort, 114 (95.8%) patients received intraperitoneal chemotherapy and thus underwent index CRS+HIPEC. The remaining 5 (4.2%) patients underwent index CRS alone. All the patients in the secondary CRS±HIPEC cohort underwent CRS alone for their index operation. At the time of their second operation, 16 (94.1%) of the patients received intraperitoneal chemotherapy and thus underwent secondary CRS+HIPEC. The remaining patient (5.9%) received secondary CRS alone.

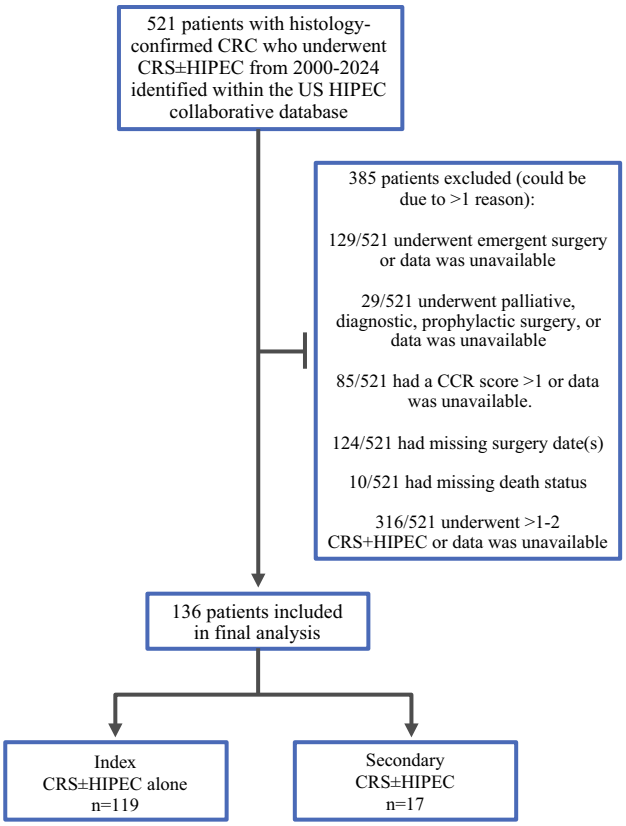


Fig. 1 Study consort diagram. CCR, completeness of cytoreduction. CRS±HIPEC, cytoreductive surgery ± hyperthermic intraperitoneal chemotherapy

Perioperative Outcomes

Patient clinicodemographic and histopathologic factors did not differ between the cohorts (Table 1). Similarly, preoperative characteristics including labs, BMI, and ASA status did not differ significantly between the index-alone and secondary CRS±HIPEC cohorts (Table 2). The median operative time was significantly longer for the index CRS±HIPEC-alone cohort than for the secondary CRS±HIPEC cohort (index CRS±HIPEC alone, 9.3 h [IQR, 4.2 h] vs. secondary CRS±HIPEC, 7.8 h [IQR, 3.7 h]; $p = 0.03$]. Important to note, number of visceral organs resected, rates of diverting ileostomy, end ileostomy, or colostomy creation did not differ significantly between the cohorts. Likewise, estimated blood loss, intraoperative transfusion requirements, and PCI were similar among the index-alone and secondary CRS±HIPEC cohorts. Of the patients who received intraperitoneal chemotherapy, a majority received mitomycin, whereas the remaining patients received oxaliplatin (Table 2).

The rates of CTCAE grades III to IV (clinically significant adverse events) were similar between the cohorts (Table 2). In both uni- and multivariable logistic regression, secondary CRS±HIPEC was not significantly associated with experience of a clinically significant postoperative complication, although this study likely was underpowered for such an analysis (Table S1). Furthermore, length of stay, rates of readmission, and 30-day mortality did not differ significantly between the cohort that had an index CRS±HIPEC alone and the secondary CRS±HIPEC cohort (Table 2).

Survival Outcomes

Among the entire study cohort, there were 81 deaths. Mortality rates did differ across cohorts (index CRS±HIPEC alone, 72 [60.5%] vs. secondary CRS±HIPEC, 9 [52.9%]; $p = 0.75$). Overall survival was first explored among the entire cohort and defined as the time from the date of the index operation to death or last follow-up visit. This showed an associated improved median OS among the patients who underwent secondary CRS±HIPEC compared with those who underwent only one procedure (index CRS±HIPEC alone, 24.0 months [95% CI, 19.4–28.6 months] vs. secondary CRS±HIPEC, 51.0 months [95% CI, 39.8–62.2 months]; $p = 0.008$; Fig. 2A).

To assess the oncologic value of a secondary versus the index CRS±HIPEC, OS was redefined as the time from the date of the second operation to death or last follow-up visit for the secondary CRS±HIPEC cohort. This demonstrated that the median OS after a secondary CRS±HIPEC was similar to that after the initial CRS±HIPEC (index CRS±HIPEC alone, 24.0 months [95% CI, 19.4–28.6 months] vs. secondary CRS±HIPEC, 27.0 months [95% CI, 17.3–36.7 months]; $p = 0.388$; Fig. 2B).

Accounting for immortal time bias, we then performed a subset analysis that included only the patients with recurrent disease. For this analysis OS was redefined as the time from the date of recurrence to death or last follow-up visit for the index CRS±HIPEC-alone cohort. Among the patients with recurrent disease, the secondary CRS±HIPEC was associated with better OS than systemic therapy alone and/or best supportive care (index CRS±HIPEC alone, 12.0 months [95% CI, 9.2–14.8 months] vs. secondary CRS±HIPEC, 27.0 months [95% CI, 17.3–36.7 months]; $p = 0.010$; Fig. 2C).

After exclusion of patients with extra-abdominal disease recurrence among the index CRS±HIPEC-alone cohort, the survival benefit associated with a secondary CRS±HIPEC persisted (index CRS±HIPEC alone, 12.0 months (95% CI, 10.2–13.8 months] vs. secondary CRS±HIPEC, 27.0 months (95% CI, 17.3–36.7 months]; $p = 0.003$; Fig. 2D). Notably, after inclusion of patients who underwent more than two repeat CRS±HIPEC treatments, this associated survival benefit persisted (Fig. S1A) and remained after exclusion of patients with extra-abdominal disease recurrence (Fig. 1B). The median time to recurrence was similar between the cohorts (index CRS±HIPEC alone, 6.0 months [IQR, 7.8 months] vs.

Table 1 Clinicodemographic and histopathologic characteristics of all patients, stratified by index alone or secondary CRS±HIPEC

Variable	All patients ($n = 136$) n (%)	Index CRS±HIPEC ($n = 119$) n (%)	Secondary CRS±HIPEC ($n = 17$) n (%)	p Value
Patient demographics				
Median age: years (IQR)	54.2 (19.3)	55.0 (20.0)	54.4 (15.2)	0.82
Female gender	71 (52.2)	61 (51.3)	10 (58.8)	0.75
Race[a]				
White	96 (72.7)	81 (70.4)	15 (88.2)	0.58
Black	18 (13.6)	14 (14.8)	1 (5.9)	
Latino	9 (6.8)	8 (7.0)	1 (5.9)	
Asian	5 (3.8)	5 (4.3)	0 (0)	
Other	4 (3.0)	4 (3.5)	0 (0)	
Clinical characteristics				
Location of primary tumor[b]				
Right	63 (48.5)	52 (46.0)	11 (64.7)	0.67
Transverse	6 (4.6)	6 (5.3)	0 (0)	
Left	16 (12.3)	15 (13.3)	1 (5.9)	
Sigmoid	33 (24.6)	28 (24.8)	4 (23.5)	
Rectosigmoid	3 (2.3)	3 (2.7)	0 (0)	
Rectum	10 (7.7)	9 (8.0)	1 (5.9)	
Preoperative imaging demonstrating				
Lung metastases[c]	13 (9.6)	11 (9.2)	2 (11.8)	0.65
Liver metastases[d]	13 (9.6)	13 (10.9)	1 (5.9)	0.36
Extraperitoneal metastases[e]	47 (34.8)	40 (33.6)	7 (43.8)	0.60
Neoadjuvant				
Chemotherapy	108 (79.4)	98 (82.4)	10 (58.8)	0.05
Immunotherapy[f]	12 (8.8)	10 (8.8)	2 (11.8)	0.66
Bevacizumab[g]	58 (45.0)	51 (45.5)	7 (41.2)	0.94
Radiation[h]	5 (3.7)	5 (4.2)	0 (0)	1.0
Adjuvant				
Chemotherapy[i]	42 (32.8)	38 (33.9)	4 (25.0)	0.58
Radiation[j]	1 (.8)	1 (1.0)	0 (0)	1.0
Histopathologic factors				
Primary tumor stage[k]				
T0	0 (0)	0 (0)	0 (0)	0.70
T1	0 (0)	0 (0)	0 (0)	
T2	5 (4.1)	4 (3.8)	1 (7.1)	
T3	35 (29.2)	32 (30.2)	3 (21.4)	
T4	80 (66.7)	70 (66.0)	10 (71.4)	
Lymph node positivity[l]	91 (75.2)	78 (72.9)	13 (92.9)	0.19
Tumor differentiation[m]				
Well	14 (12.7)	12 (12.5)	2 (14.3)	0.72
Moderate	68 (61.8)	61 (63.5)	7 (50.0)	
Poor	27 (24.5)	22 (22.9)	5 (35.7)	
Undifferentiated	1 (.9)	1 (1.0)	0 (0)	
LVI[n]	41 (39.4)	33 (35.9)	8 (66.7)	0.06
PNI[o]	25 (25.5)	20 (23.3)	5 (41.7)	0.18
Perforated[p]	25 (21.7)	21 (20.8)	4 (28.6)	0.50
Obstructed[q]	18 (15.4)	16 (15.5)	2 (14.3)	1.0

CRS±HIPEC, cytoreductive surgery ± hyperthermic intraperitoneal chemotherapy; IQR, interquartile range; LVI, lymphovascular invasion; PNI, perineural invasion

The following numbers of patients had unavailable data and were excluded from respective analyses: [a]race (4/136), [b]location of primary tumor (6/136), preoperative imaging demonstrating [c]lung metastases (1/136), [d]liver metastases (1/136), [e]extraperitoneal metastases (1/136), neoadjuvant [f] bevacizumab (5/136), [g]immunotherapy (6/136), [h]radiation, adjuvant [i]chemotherapy (8/136), [j]radiation (16/136), [k]primary tumor stage (16/136), [l]lymph node positivity (15/136), [m]tumor differentiation (26/136), [n]LVI (32/136),[o]PNI (38/136), [p]perforation (21/136), and [q]obstructed (19/136)

Table 2 Perioperative characteristics of all patients, stratified by index alone or secondary CRS±HIPEC

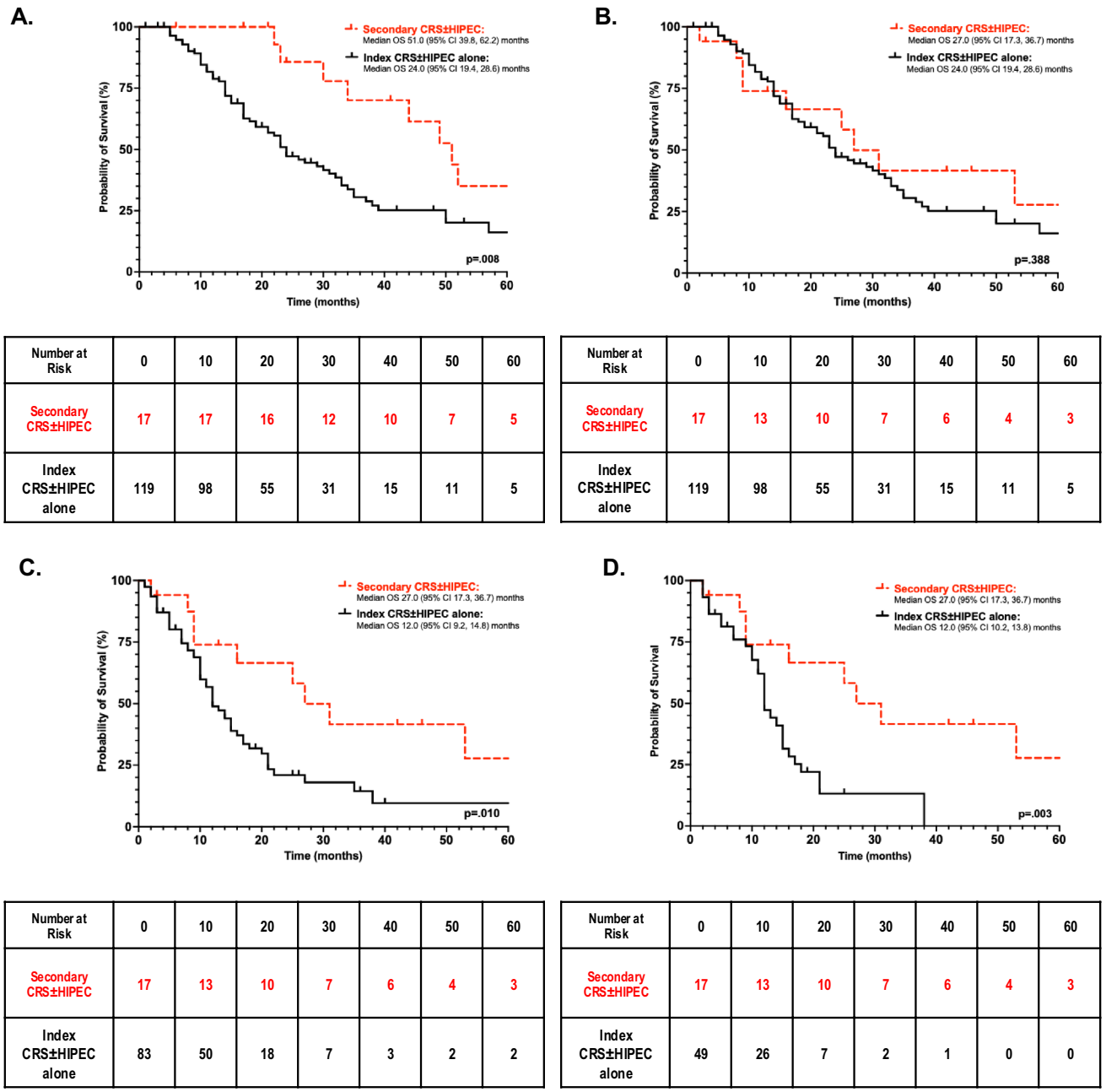
Variable	All patients ($n = 136$) n (%)	Index CRS±HIPEC ($n = 119$) n (%)	Secondary CRS±HIPEC ($n = 17$) n (%)	p Value
Preoperative characteristics				
Labs				
Median CEA: ng/mL (IQR)[a]	3.5 (7.4)	3.4 (7.6)	5.5 (5.6)	0.76
Median creatinine: mg/dL (IQR)[b]	.7 (.3)	.8 (.3)	.7 (.3)	0.52
Median HbA1C: mg/dL (IQR)[c]	5.4 (1.3)	5.4 (1.3)	5.4 (.95)	0.93
Median albumin: mg/dL (IQR)[d]	4.0 (.5)	4.0 (.50)	3.8 (.8)	0.54
Median BMI: kg/m^2 (IQR)[e]	26.5 (6.0)	26.7 (7.3)	25.0 (5.7)	0.77
ASA class[f]				
I	0 (0)	0 (0)	0 (0)	0.90
II	12 (8.9)	10 (8.5)	2 (11.8)	
III	106 (78.5)	93 (78.8)	13 (76.5)	
IV	17 (12.6)	15 (12.7)	2 (11.8)	
Operative characteristics				
Median operative time: h (IQR)[g]	9.0 (4.2)	9.3 (4.2)	7.8 (3.7)	**0.03**
Median no. of visceral organs removed (IQR)	4.0 (2.0)	4.0 (2.0)	3.0 (3.0)	0.30
Diverting loop ileostomy creation[h]	19 (15.8)	17 (15.7)	2 (16.7)	1.0
End ileostomy or colostomy creation[i]	22 (17.3)	21 (19.1)	1 (5.9)	0.30
Median EBL: mL (IQR)[j]	500 (400)	500 (413)	400 (425)	0.44
Intraoperative transfusion				
RBC[k]	28 (28.3)	23 (27.4)	5 (38.5)	0.51
FFP[l]	5 (5.3)	5 (6.3)	0 (0)	1.0
Platelets[m]	1 (1.1)	1 (1.3)	0 (0)	1.0
Cryoprecipitate[n]	1 (1.1)	1 (1.3)	0 (0)	1.0
Median PCI (IQR)[o]	11.0 (8.0)	11 (8.0)	10 (10.0)	0.30
CCR				
0	111 (81.6)	99 (83.2)	12 (70.6)	0.31
1	25 (18.4)	20 (16.8)	5 (29.4)	
Intraperitoneal chemotherapy	130 (95.6)	114 (95.8)	16 (94.1)	0.55
Mitomycin[p]	121 (89.0)	107 (94.7)	14 (87.5)	0.26
Oxaliplatin	8 (5.9)	6 (5.3)	2 (12.5)	
Postoperative characteristics				
CTCAE grades III–V complication[q]	83 (61.9)	73 (62.4)	10 (58.8)	0.99
Postoperative RBC transfusion[r]	36 (36.7)	28 (23.5)	8 (61.5)	0.06
Median stay: days (IQR)[s]	10.0 (7.0)	10.0 (7.0)	10.0 (8.0)	0.93
Readmission[t]	51 (38.1)	46 (39.3)	5 (29.4)	0.60
30-Day mortality	1 (.7)	1 (.8)	0 (0)	1.0
Death	81 (59.6)	72 (60.5)	9 (52.9)	0.75

CRS±HIPEC, cytoreductive surgery ± hyperthermic intraperitoneal chemotherapy; CEA, carcinoembryonic antigen; IQR, interquartile range; HbA1C, glycohemoglobin; BMI, body mass index; ASA, American Society of Anesthesiologists; EBL, estimated blood loss; RBC, red blood cell; FFP, fresh frozen plasma; PCI, peritoneal carcinoma index; CCR, completeness of cytoreduction; CTCAE, Common Terminology Criteria for Adverse Events

The following numbers of patients had unavailable data and were excluded from respective analyses: [a]CEA (54/136), [b]creatinine (2/136), [c]HbA1c (114/136), [d]albumin (13/136), [e]BMI (1/136), [f]ASA class (1/136), [g]operative time (1/136), [h]diverting loop ileostomy (16/136), [i]end ileostomy or colostomy (9/136), [j]EBL (1/136), intraoperative [k]RBC (39/136), [l]FFP (44/136), [m]platelet (45/136), [n]cryoprecipitate (44/136) transfusion, [o]PCI (10/136), [p]intraperitoneal chemotherapy agent (7/136), [q]CTCAE grades III–V complication (2/136), [r]postoperative RBC transfusion (38/136), [s]length of stay (3/136), [t]readmission (2/136)

secondary CRS±HIPEC, 5.0 months (IQR, 5.5 months]; $p = 0.20$).

Patient clinicodemographic and histopathologic factors did not differ when stratified based on mortality status (Table S2). As expected, the patients who died during the



Number at Risk	0	10	20	30	40	50	60
Secondary CRS±HIPEC	17	17	16	12	10	7	5
Index CRS±HIPEC alone	119	98	55	31	15	11	5

Number at Risk	0	10	20	30	40	50	60
Secondary CRS±HIPEC	17	13	10	7	6	4	3
Index CRS±HIPEC alone	119	98	55	31	15	11	5

Number at Risk	0	10	20	30	40	50	60
Secondary CRS±HIPEC	17	13	10	7	6	4	3
Index CRS±HIPEC alone	83	50	18	7	3	2	2

Number at Risk	0	10	20	30	40	50	60
Secondary CRS±HIPEC	17	13	10	7	6	4	3
Index CRS±HIPEC alone	49	26	7	2	1	0	0

Fig. 2 Log-rank Kaplan-Meier curves demonstrating probability of survival from (**A**) date of initial surgery for both cohorts, among the entire cohort, (**B**) date of second surgery for the secondary CRS±HIPEC cohort or initial surgery for the cohort who received only one CRS±HIPEC, among the entire cohort, (**C**) date of second surgery for the secondary CRS±HIPEC cohort or recurrence for the cohort who received only one CRS±HIPEC, among the patients with recurrent disease, (**D**) date of second surgery for the secondary CRS±HIPEC cohort or recurrence for the cohort that received only one CRS±HIPEC, among the patients with recurrent disease and after exclusion of the patients with extra-abdominal disease recurrence among the index CRS±HIPEC-alone cohort. CRS±HIPEC, cytoreductive surgery ± hyperthermic intraperitoneal chemotherapy. OS, overall survival

study period had a significantly higher median PCI, number of visceral organs resected, and rates of end ileostomy or colostomies created. Similarly, these patients had higher rates of postoperative complications (Table S3). To control for clinically significant potential confounders among those with recurrent disease (the landmark survival analysis cohort), uni- and multivariable Cox regression analyses were explored. Multiple covariates were associated with a significantly higher hazard rate of death in the univariate analysis, including the number of visceral organs resected (HR, 1.14; 95% CI, 1.00–1.29); $p = 0.038$), end ileostomy or colostomy creation (HR, 2.55; 95% CI, 1.33–4.29; $p = 0.005$), EBL

(HR 1.00; 95% CI, 1.00–1.00; $p < 0.001$), intraoperative RBC transfusion (2.05; 95% CI, 1.16–3.63; $p = 0.014$), PCI (1.08; 95% CI, 1.03–1.12; $p < 0.001$), CTCAE grades III to V complications (1.82; 95% CI, 1.07–3.09; $p = 0.027$), and readmission (2.00; 95% CI, 1.21–3.31; $p = 0.007$].

Consistent with the Kaplan-Meier log-rank analyses reported earlier, in the univariate analysis, the hazard ratio for death among the patients who received a secondary CRS±HIPEC was 0.40 (95% CI, 0.19–0.83) times less than among those who underwent only an index CRS±HIPEC ($p = 0.014$). After control for potential confounders, the hazard ratio for death among the patients who received a secondary CRS±HIPEC remained 0.43 (95% CI, 0.19–0.97) times less than among those who underwent only an index CRS±HIPEC ($p = 0.042$; Table 3).

Discussion

This retrospective cohort study used a multi-institutional database from a geographically diverse collection of high-volume centers across the United States to compare perioperative and survival outcomes between patients who underwent index-alone or secondary CRS±HIPEC for CRC-PM. The rates of clinically significant postoperative complications, readmissions, 30-day mortalities, and median length of stay did not differ significantly between those who had an index CRS±HIPEC alone and those who underwent a secondary CRS±HIPEC. These findings are consistent with previously published literature from international multi-institution or single-center retrospective studies.[20–24] Altogether, these data suggest that secondary CRS±HIPEC is safe for appropriately selected patients with CRC-PM recurrence.

In the absence of randomized data, the role of secondary CRS±HIPEC remains controversial. In the current study and others,[20,22] when OS was timed from the date of the first CRS±HIPEC, there was an associated improved OS among the patients who underwent secondary CRS±HIPEC compared with those who received only one CRS±HIPEC. Certainly, one potential explanation for these findings is that patients who underwent a repeat surgery were a highly selected population comprising those with less aggressive tumor biology and lower volume of disease. Although likely a contributing factor, in bivariate analyses, our cohorts demonstrated no differences in factors suggestive of more aggressive tumor biology including tumor stage, lymph node positivity, tumor differentiation, LVI, PNI, and median time to recurrence.

To further account for this explanation and potential selection biases such as immortal time bias, landmark survival analyses[19] were performed only among patients with disease recurrence. For these analyses, OS was defined from date of recurrence for the index CRS±HIPEC-alone cohort and date of the second CRS±HIPEC for the secondary CRS±HIPEC cohort. Among the patients with recurrent

Table 3 Uni- and multivariable Cox regression survival analyses among patients with recurrent disease ($n = 100$)

Covariate	Univariate HR (95 % CI)	p Value	Multivariable[a] HR (95 % CI) ($n = 84$; censored = 27)	p Value
Operative time[b]	1.00 (1.00–1.00)	0.472		
No. of visceral organs resected	1.14 (1.00–1.29)	**0.038**	.99 (0.82–1.19)	0.891
End ileostomy or colostomy creation[c]	2.55 (1.33–4.90)	**0.005**	2.68 (1.31–5.50)	**0.007**
EBL	1.00 (1.00–1.00)	**< 0.001**	1.00 (1.00–1.00)	0.298
Intraoperative RBC transfusion[d]	2.05 (1.16–3.63)	**0.014**		
PCI[e]	1.08 (1.03–1.12)	**< 0.001**	1.07 (1.01–1.13)	**0.017**
CCR	1.48 (0.85–2.58)	0.171		
CTCAE grades III–V complication[f]	1.82 (1.07–3.09)	**0.027**	1.00 (0.46–2.18)	0.989
Postoperative RBC transfusion[g]	1.48 (0.85–2.58)	0.170		
Readmission[h]	2.00 (1.21–3.31)	**0.007**	2.28 (1.16–4.48)	**0.016**
Secondary CRS±HIPEC	.40 (0.19–0.83)	**0.014**	.43 (0.19–0.97)	**0.042**

Bold values are statistically significant ($p < 0.05$)

HR, hazard ratio; CI, confidence interval; EBL, estimated blood loss; PCI, peritoneal carcinoma index; CCR, completeness of cytoreduction; CTCAE, grades III–V complications; RBC, red blood cell; CRS±HIPEC, cytoreductive surgery ± hyperthermic intraperitoneal chemotherapy

[a]Controlling for number of visceral organs resected, end ileostomy or colostomy creation, EBL, PCI, CTCAE grades III–V complication, and readmission

The following numbers of patients had unavailable data and were excluded from respective analyses: [b]operative time (1/100), [c]end ileostomy or colostomy creation (8/100), [d]intraoperative RBC transfusion (24/100), [e]PCI (7/100), [f]CTCAE grades III–V complication (2/100), [g]postoperative RBC transfusion (24/100), and [h]readmission (2/100)

disease, repeat surgery was associated with improved OS compared with systemic therapy alone and/or best supportive care in the log-rank Kaplan-Meier as well as the uni- and multivariable Cox regression analyses. The observed survival benefit among the secondary cohort may remain, in part, due to patient selection, given that the patients who did not receive a secondary CRS±HIPEC likely had poor functional status, more extensive peritoneal disease recurrence, and/or extra-peritoneal recurrence.

Acknowledging that the aforementioned cohorts likely were not equivalent or comparable, we next excluded patients with extra-abdominal disease recurrence and demonstrated that improved OS associated with secondary CRS±HIPEC persisted. Finally, after inclusion of patients who underwent more than two CRS±HIPEC procedures, this associated survival benefit remained. Even if tumor biology is somewhat driving these observed improved outcomes, these data suggest the existence of a subset of CRC-PM patients with whom we should be more aggressive and offer iterative CRS±HIPEC.

As outlined in a 2016 review by Mogal et al.[14] and a more recent systematic review by Sarofim et al.,[13] many surgeons are performing repeat CRS±HIPEC for patients with recurrent peritoneal disease for CRC as well as other primary tumor histology types despite the lack of prospective data or guidelines[25] to support this treatment strategy. Previous work using the US HIPEC Collaborative by Powers et al.[18] reported similar safety and efficacy profiles for repeat CRS±HIPEC used to treat a mixed-histology and appendiceal-specific cohort. The current study expanded on on this prior work by focusing on repeat CRS±HIPEC among the CRC histology cohort within the US HIPEC Collaborative.

Interestingly, much of the literature on repeat CRS±HIPEC for CRC-PM aligns with the results of the current study. For example, Laks et al.[20] reported that among 232 patients who underwent an index CRS+HIPEC for CRC-PM, 30 had a repeat CRS+HIPEC at their institutions. These authors compared perioperative outcomes for initial CRS+HIPEC between the two cohorts and likewise found no differences in rates of postoperative complications between the cohorts. Similar to the results of our study, among patients with peritoneal recurrence, when OS was timed from the index CRS+HIPEC, the patients who underwent a repeat CRS+HIPEC had an associated better median OS than those who did not receive an iterative CRS+HIPEC (repeat CRS+HIPEC, 68 months vs. single CRS+HIPEC, 51 months; $p = 0.03$).[20]

Among 287 patients included in another study by Braam et al.,[26] 132 patients experienced disease recurrence after index CRS+HIPEC, 32 of whom were treated with iterative curative-intent resection. These authors likewise found that among patients with intrabdominal recurrence, repeat CRS±HIPEC was associated with improved median OS compared with palliative therapies (repeat CRS±HIPEC, 42.9 months vs. palliative therapies, 11.8 months; $p < 0.001$).[26] Tidandini et al.,[27] found that among their mixed-histology CRS+HIPEC cohort of 63 patients, 55 had CRC, with a median OS of 82.3 months after the initial treatment, 53.9 months after the second treatment ($n = 58$), and 74.5 months after the third treatment ($n = 4$) with CRS+HIPEC.

In another retrospective study, Chua et al.[24] identified 545 CRS procedures performed in 466 patients for mixed primary tumor histology. Of these procedures, 79 were repeat surgeries for disease recurrence, with more than 80 % of the patients receiving HIPEC. In multivariable Cox-regression, these authors identified an interval longer than 18 months between index and repeat CRS and use of HIPEC as independent predictors of improved survival after repeat CRS.[24]

Finally, a more recent study by Cashin et al.[28] used propensity score-matching to address the inherent selection bias that accompanies receipt of a second CRS±HIPEC. These findings showed that secondary CRS+HIPEC remained significantly associated with survival after matching factors the authors found to be significantly associated with receipt of a second CRS+HIPEC (sex, PCI at index surgery, disease-free interval, and extra-peritoneal metastases).[28] Until clinical trials are conducted to study the safety and efficacy of repeat CRS±HIPEC, clinicians must rely on retrospective data such as these and multidisciplinary discussions to identify optimal candidates for iterative CRS±HIPEC.

To date, prospective data for this patient population focuses on the safety and efficacy of an index CRS±HIPEC or the addition of perioperative systemic therapies to this treatment algorithim.[6–8,29] For example, in a recent phase 3 clinical trial, termed PRODIGE7,[8] the authors sought to explore the benefit of adding HIPEC to CRS compared with CRS alone. Interestingly, no survival benefit was observed among patients who received CRS+HIPEC (CRS+HIPEC: median OS, 41.7 months (95% CI, 36.2–53.8 months) vs. CRS alone: median OS, 41.2 months (95% CI, 35.1–49.7 months),[8] although some question the legitimacy of these results due to identified design flaws and concerns regarding the efficacy of the chosen intraperitoneal oxaliplatin regimen.[30,31] Given the results of PRODIGE7,[8] the current retrospective study, and others,[13,14] prospective studies exploring the value of secondary CRS and/or CRS+HIPEC for this patient population are justified.

Limitations of this study included its retrospective design, exclusion of patients with unavailable data, and patients who underwent more than two iterations of CRS±HIPEC. In an attempt to account for selection biases and control for confounding variables, several uni- and multivariable survival analyses were performed, as detailed earlier. Another limitation pertained to the constraints of retrospective analyses. For example, among patients who underwent iterative CRS±HIPEC, only data pertaining to the second operations

were available. Similarly, the rationale surrounding clinical decision-making, such as whether HIPEC was administered or not, could not be explored.

The strengths of this study included use of the US HIPEC Collaborative database and inclusion of patients treated with index and/or secondary CRS±HIPEC at 12 high-volume institutions across the United States. Finally, to our knowledge, this study represents the first, to date, to explore the safety and efficacy of secondary CRS±HIPEC specifically for CRC-PM using a non-international, multi-institutional database.

Conclusions

Among patients with CRC-PM, secondary CRS±HIPEC for disease recurrence is associated with similar rates of perioperative complications but improved survival compared with those who underwent only one procedure and were treated with systemic therapy and/or best supportive care. Furthermore, these data suggest that survival gained after a secondary CRS±HIPEC parallels the survival gained after an index operation. Thus, secondary CRS±HIPEC should be considered for well-selected patients with CRC-PM recurrence. Finally, pragmatic prospective trials exploring the safety and oncologic value of secondary CRS, CRS+HIPEC, or both are warranted for patients with CRC-PM.

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