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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Repeat Cytoreductive Surgery-Hyperthermic Intraperitoneal Chemoperfusion is Feasible and Offers Survival Benefit in Select Patients with Peritoneal Metastases

Haroon A. Choudry, MD[1], Filip Bednar, MD[1], Yongli Shuai, MS[3], Heather L. Jones, MPA-C[1], Reetesh K. Pai, MD[2], James F. Pingpank, MD[1], Steven S. Ahrendt, MD[1], Matthew P. Holtzman, MD[1], Herbert J. Zeh, MD[1], and David L. Bartlett, MD[1]

[1]Division of Surgical Oncology, Koch Regional Perfusion Center, University of Pittsburgh, Pittsburgh, PA; [2]Department of Pathology, University of Pittsburgh, Pittsburgh, PA; [3]The University of Pittsburgh Cancer Institute Biostatistics Facility, Pittsburgh, PA

ABSTRACT

Introduction. We hypothesized that repeat cytoreductive surgery-hyperthermic intraperitoneal chemoperfusion (CRS-HIPEC) for peritoneal metastases (PM) may be associated with suboptimal resection, more frequent postoperative complications, and worse oncologic outcomes.

Methods. Using a prospectively maintained database, we compared clinicopathologic, perioperative, and oncologic outcome data in patients undergoing single or repeat CRS-HIPEC procedures. The Kaplan–Meier method was used to estimate survival. Multivariate analyses identified associations with perioperative and oncologic outcomes.

Results. Of the 1294 patients undergoing CRS-HIPEC procedures at our institution, only one CRS-HIPEC procedure (single HIPEC cohort) was performed in 1169 patients (90.3%), whereas 125 patients (9.7%) underwent repeat CRS-HIPEC procedures (repeat HIPEC cohort). Of the 1440 CRS-HIPEC procedures at our institution, a first CRS-HIPEC procedure was performed in 1294 patients (89.9%), whereas subsequent second, third, and fourth CRS-HIPEC procedures were performed in 125 patients (8.7%), 18 patients (1.3%), and 3 patients (0.2%), respectively. Progression-free survival (PFS) following the second CRS-HIPEC procedure was negatively impacted by shorter PFS following the first CRS-HIPEC procedure, independent of other significant variables related to the second procedure, including completeness of cytoreduction and postoperative complications. Patients undergoing multiple CRS-HIPEC procedures were not at higher risk for suboptimal resection or postoperative complications and demonstrated equivalent PFS following each successive procedure compared to the first procedure.

Conclusions. Repeat CRS-HIPEC procedures for PM were not associated with suboptimal perioperative and oncologic outcomes. Our data confirmed our ability to select patients appropriately for repeat CRS-HIPEC procedures.

Cytoreductive surgery-hyperthermic intraperitoneal chemoperfusion (CRS-HIPEC) has gained acceptance as a locoregional surgical therapy, usually in the context of multimodality systemic treatment, for select patients with peritoneal metastases (PM) from a variety of malignancies.[1–5] Disease recurrence remains common, which may or may not be amenable to further surgery.[6–11] A limited number of published series have evaluated the feasibility of repeat CRS-HIPEC procedures for recurrent PM. Mogal et al. recently provided a review of the data.[10,12–17] These small studies generally demonstrate safety and long-term survival benefit from repeat CRS-HIPEC procedures.

Patients with PM offer unique challenges, including frequent malnutrition, extensive chemotherapy exposure, variable histology (grades, subtypes, differentiation), and organ dysfunction from compressive/infiltrative effects of intra-abdominal disease. Major considerations for repeat CRS-HIPEC include patient-related factors, such as performance status, tumor-related factors like histology/grade, and procedure-related factors, such as resectability, disease

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H. A. Choudry, MD
e-mail: choudrymh@upmc.edu

burden, and the potential for postoperative complications. The potential survival benefits of aggressive surgical procedures, such as CRS-HIPEC, must be weighed against risks associated with long operative times, surgery/hyperthermia-related tissue injury, massive fluid shifts, frequent blood transfusions, and postoperative complications, which may negatively impact survival.[18–22]

We hypothesized that repeat CRS-HIPEC procedures for PM may be associated with poorer surgical success, more frequent postoperative complications, and worse oncologic outcomes after each successive CRS-HIPEC procedure.

METHODS

Using a prospective database (2002–2017), we reviewed clinicopathologic, perioperative, and oncologic outcomes in patients undergoing one or more CRS-HIPEC procedures at our institution. This study was approved by the Institutional Review Board at the University of Pittsburgh. Patients were excluded from undergoing CRS-HIPEC if they had extra-abdominal metastatic disease, poor performance status (ECOG 3-5), or unresectable disease on preoperative imaging or intraoperative assessment. There were no staged CRS-HIPEC procedures included in this study.

Intraoperatively, volume of disease was quantified by the peritoneal cancer index (PCI).[23] Cytoreductive surgery (CRS) was performed as described by Bao and Bartlett; and post-CRS residual disease was categorized as CC-0 (no residual macroscopic disease) or CC-1 (residual tumor nodule < 2.5 mm) resection; CC-2 (residual tumor nodule 2.5 mm to 2.5 cm); CC-3 (residual tumor nodule > 2.5 cm or confluent sheets of tumor).[24] A standard institutional protocol for HIPEC was initiated after CRS to maintain a target intraperitoneal tissue temperature of 42 °C. Postoperative morbidity was classified according to the Clavien-Dindo (CDC) grading system (grades 3–4 were considered major complications).[25] Tumor grades for each primary diagnosis were analyzed individually and also as a combined tumor grade, categorized into low combined tumor grade (including AJCC grade G1 mucinous appendix neoplasms; well-differentiated papillary and benign multicystic mesothelioma; low-grade serous and mucinous borderline ovarian cancer); intermediate combined tumor grade (including AJCC grade G2 mucinous appendix neoplasms; appendiceal goblet cell carcinoid Tang group A; well-moderately differentiated colorectal cancer; epithelioid mesothelioma; endometrioid and granulosa cell ovarian cancers); and high combined tumor grade (including AJCC grade G3 mucinous appendix neoplasms; appendiceal goblet cell carcinoid Tang groups B and C; poorly differentiated colorectal cancer; sarcomatoid and biphasic mesothelioma; high-grade serous and small cell and clear cell and carcinosarcoma of the ovary).[26,27]

Overall survival (OS) was calculated from date of diagnosis of PM or CRS-HIPEC to date of death. We also compared OS after the first CRS-HIPEC procedure between single and repeat HIPEC cohorts following propensity score matching of CC-score and PCI, and stratified by primary tumor diagnosis and tumor grade. Progression-free survival (PFS) was calculated from date of CRS-HIPEC (for each CRS-HIPEC procedure) to the date of progression or death. Kaplan–Meier method was used to estimate survival distributions and log-rank test was used to assess the difference. The relationship of OS to patients' clinical and pathologic characteristics was further assessed by Cox proportional hazards regression. The univariate Cox regression was first used to assess the mortality rate in relation to the available explanatory variables in exploratory fashion. Based on this univariate analysis, the potential significant predictors were evaluated further to find prognostic factors in the multiple covariates Cox model via stepwise procedures. For predictive modeling of PFS after the second CRS-HIPEC procedure, we included standard clinic-pathologic variables associated with the second operation (including age, body mass index [BMI], AA-CCI, diagnosis, tumor grade, postoperative complications and grade, post-discharge morbidity and grade, PCI, and CC-score), as well as PFS after the first CRS-HIPEC procedure and the gap-time between the first and second CRS-HIPEC procedures (defined as the duration between date of disease progression after the first CRS-HIPEC procedure and performance of the second CRS-HIPEC procedure). The corresponding relative mortality rates are summarized as hazard ratios (HR), with $HR > 1.0$ corresponding to increased mortality. A significance level was set at 0.05, and all reported p values were two-sided. We used generalized linear mixed model to identify predictors of incomplete resection and postoperative complications across multiple HIPEC procedures. Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

Of the 1294 patients undergoing CRS-HIPEC procedures at our institution, only one CRS-HIPEC procedure (single HIPEC cohort) was performed in 1169 patients (90.3%), whereas 125 patients (9.7%) underwent repeat CRS-HIPEC procedures (repeat HIPEC cohort).

Clinicopathologic and Perioperative Characteristics Related to the First CRS-HIPEC Procedure for Patients in the Single HIPEC Versus Repeat HIPEC Cohorts

Repeat CRS-HIPEC procedures were more likely to be performed in patients with PM from appendix cancer (12%) compared with those with malignant peritoneal mesothelioma (10%), colorectal cancer (7%), or ovarian cancer (3%; $p = 0.006$). Similarly, repeat CRS-HIPEC procedures were more likely to be performed in patients with low (14%) and intermediate (11%) combined tumor grade tumors compared with those with high combined tumor grade tumors (6%; $p = 0.005$). Patients in the repeat HIPEC cohort were younger, with higher intraoperative PCI, and were less likely to receive complete macroscopic resection (CC-0) at the time of the initial CRS-HIPEC procedure compared with those in the single HIPEC cohort. Major in-hospital postoperative complications following the first CRS-HIPEC procedure were more common in the repeat HIPEC cohort (Table 1).

Oncologic Outcome Analysis for Patients in Single and Repeat HIPEC Cohorts With and Without Propensity Score Matching

Overall survival calculated from diagnosis of PM was 104 months (95% confidence interval [CI] 78.4, 129.4 months) for the repeat HIPEC cohort and 55 months (95% CI 49.9, 60.1 months) for the single HIPEC cohort ($p < 0.0001$). Overall survival calculated from the first CRS-HIPEC procedure was 82.9 months (95% CI 64.9, 111.9 months) for the repeat HIPEC cohort and 32.9 months (95% CI 28.8, 38.0 months) for the single HIPEC cohort ($p < 0.0001$). Progression-free survival following the first CRS-HIPEC procedure was 21.5 months (95% CI 19, 23.6 months) for the repeat HIPEC cohort and 13.7 months (12.6, 14.9 months) for the single HIPEC cohort ($p > 0.05$).

We compared OS after the first CRS-HIPEC procedure between single and repeat HIPEC cohorts following propensity score matching of CC-score and PCI, and

TABLE 1 Clinicopathologic and perioperative characteristics related to the first CRS-HIPEC procedure for patients in the single and repeat CRS-HIPEC cohorts

Variable		Single CRS-HIPEC cohort ($n = 1169$)	Repeat CRS-HIPEC cohort ($n = 125$)
Diagnosis; *n* (%)	Appendix	563 (48.2)	78 (62.4)
	Colorectal	360 (30.8)	29 (23.2)
	Mesothelioma	142 (12.1)	15 (12)
	Ovarian	104 (8.9)	3 (2.4)
Combined tumor grade; *n* (%)	Low	293 (28.2)	46 (37.7)
	Intermediate	426 (41)	55 (45.1)
	High	319 (30.7)	21 (17.2)
Appendix tumor grade; *n* (%)	Grade G1	268 (54)	41 (58.6)
	Grade G2	133 (26.8)	23 (32.9)
	Grade G3	95 (19.2)	6 (8.6)
Colorectal tumor grade; *n* (%)	Well-diff	18 (7.1)	3 (10.7)
	Mod-diff	152 (60.3)	16 (57.1)
	Poorly-diff	80 (31.7)	9 (32.1)
Mesothelioma tumor grade; *n* (%)	Low	14 (10.2)	0
	Intermediate	109 (79.6)	12 (80)
	High	14 (10.2)	3 (20)
Ovarian tumor grade; *n* (%)	Low	10 (9.6)	1 (33.3)
	Intermediate	9 (8.7)	1 (33.3)
	High	85 (81.7)	1 (33.3)
Age at first CRS-HIPEC (yr); mean (SD)		55.5 (12.2)	52.2 (10.6)
CC-0 resection; %		68.1	51.6
CC-0/1 resection; %		93.4	92.7
PCI at first CRS-HIPEC; mean (SD)		16.2 (8.7)	18.5 (9.2)
Major in-hospital Clavien-Dindo grades 3–4 complications; %		23.4	31.2

CRS-HIPEC cytoreductive surgery-hyperthermic intraperitoneal chemoperfusion; *CC* completion of cytoreduction score; *PCI* peritoneal cancer index

stratification by primary tumor diagnosis and tumor grade (Fig. 1). For patients with appendix cancer, overall survival calculated from the first CRS-HIPEC was significantly longer for the repeat HIPEC cohort compared with the single HIPEC cohort ($p = 0.0007$). When stratified by tumor grade, this survival difference was only statistically significant for AJCC grade G2 ($p = 0.005$) or combined AJCC grades G2/G3 appendix cancers ($p = 0.001$). However, the Kaplan–Meier survival curves for each grade crossed only after long-term follow, suggesting a prolonged clinically significant benefit for all grades. For patients with colorectal cancer, overall survival calculated from the first CRS-HIPEC procedure was significantly longer for patients in the repeat HIPEC cohort compared with those in the single HIPEC cohort ($p < 0.0001$). This survival difference was only significant for moderately differentiated colorectal cancer ($p = 0.002$), although there were very few cases of well-differentiated colorectal cancer in this study. There was no difference in overall survival calculated from the first CRS-HIPEC procedure in patients with intermediate/high-grade malignant peritoneal mesothelioma ($p = 0.24$) in the single versus repeat HIPEC

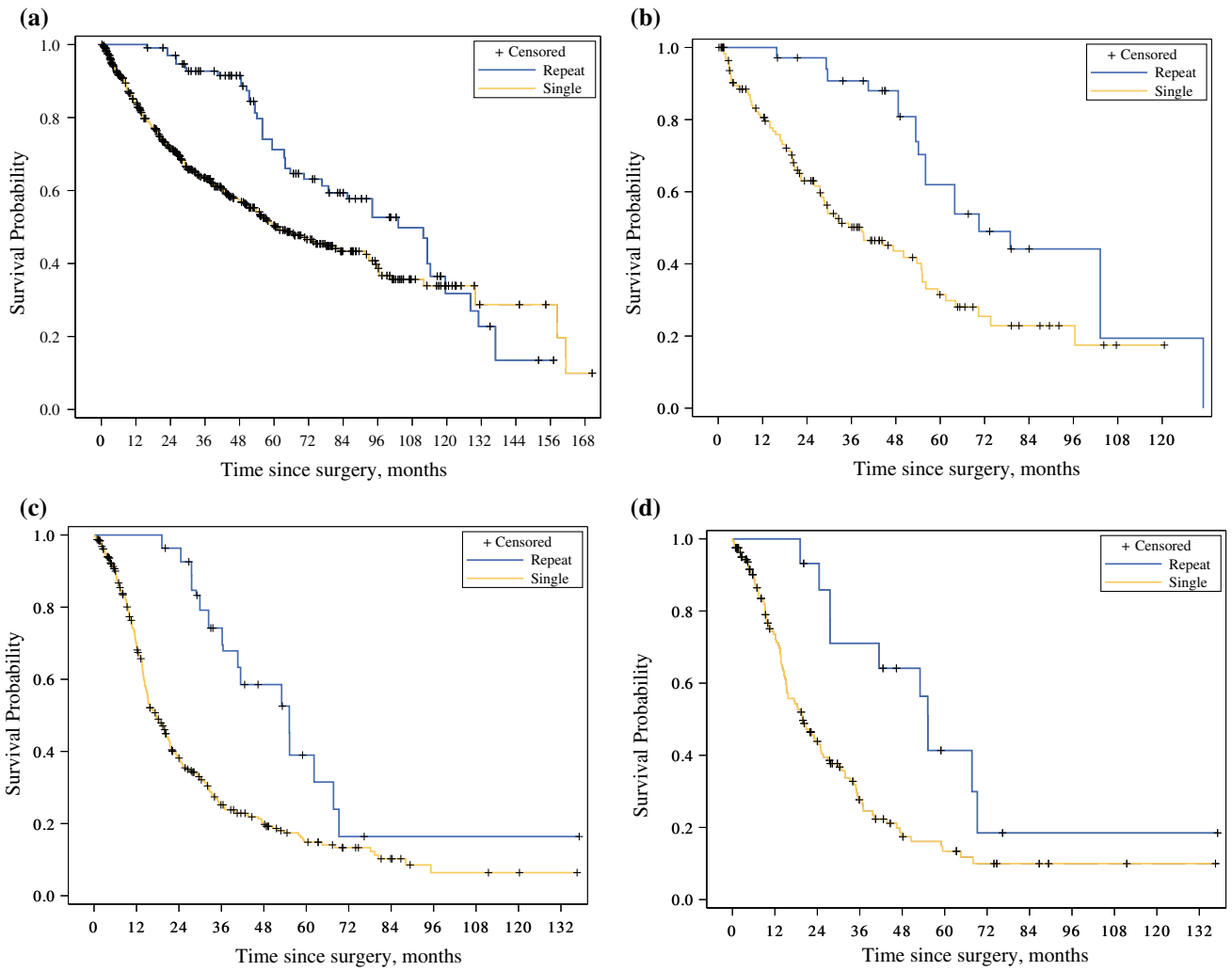

FIG. 1 Comparison of overall survival (Kaplan–Meier) between patients in single versus repeat HIPEC cohorts. OS was calculated from the first CRS-HIPEC procedure. Propensity score matching was performed for CC-score and PCI, and patients were stratified by primary tumor diagnosis and tumor grade. **a** For patients with appendix cancer, overall survival calculated from the first CRS-HIPEC was significantly longer for the repeat HIPEC cohort compared with the single HIPEC cohort (log-rank test, $p = 0.0007$). **b** When stratified by tumor grade, this survival difference was statistically significant for AJCC grades G2 appendix cancers (log-rank test, $p = 0.005$); (also significant for combined AJCC grade G2/G3, log-rank test, $p = 0.001$; figure not shown). **c** For patients with colorectal cancer, overall survival calculated from the first CRS-HIPEC procedure was significantly longer for patients in the repeat HIPEC cohort compared with those in the single HIPEC cohort (log-rank test, $p < 0.0001$). **d** When stratified by tumor differentiation, this survival difference was significant for moderately differentiated colorectal cancer (log-rank test, $p = 0.002$)

cohorts (none of the 14 patients with low-grade mesothelioma required repeat CRS-HIPEC).

Predictive Modeling for PFS After the Second CRS-HIPEC Procedure in the Repeat HIPEC Cohort

In our Cox-proportional hazards model, completeness of cytoreduction, major in-hospital postoperative complications (CDC grades 3–4), morbidity within 30 days of discharge, and duration of PFS after the first CRS-HIPEC procedure were independent predictors of PFS following the second CRS-HIPEC procedure (Table 2). Of note, the gap-time between the first and second CRS-HIPEC procedures was not a predictor of PFS after the second CRS-HIPEC procedure.

Clinicopathologic, Perioperative, and Oncologic Outcomes Across All CRS-HIPEC Procedures

Of the 1440 CRS-HIPEC procedures at our institution, a first CRS-HIPEC procedure was performed in 1294 patients (89.9%), whereas subsequent second, third, and fourth CRS-HIPEC procedures were performed in 125 patients (8.7%), 18 patients (1.3%), and 3 patients (0.2%), respectively. The mean time-interval was 32.2 months (range 5.9–124.8) between the first and second CRS-HIPEC procedures, 42.5 months (range 12.2–123.9) between the second and third procedures, and 32.4 months (range 12–47.9) between the third and fourth procedures. Multiple CRS-HIPEC procedures were more likely to be performed for PM from appendix cancer than other diagnoses (appendix: 12.9%, colorectal: 7.4%, mesothelioma: 8.7%, ovarian: 4.5%; $p = 0.007$) and for low and intermediate combined tumor grade tumors than high-grade tumors (low grade: 13.3%, intermediate grade: 11.4%, high grade: 6.8%, $p = 0.03$). The rates of complete macroscopic resection (CC-0), optimal cytoreduction (CC-0/1), and major in-hospital Clavien-Dindo postoperative grades 3–4 complications were similar after the second and third CRS-HIPEC procedures compared with the first CRS-HIPEC procedure (Table 3). Stomas were created in 35%, 29%, 29%, and 50% of patients undergoing first, second, third, and fourth CRS-HIPEC procedures, respectively.

There was no statistically significant difference in PFS following the second or third CRS-HIPEC procedures compared with the first CRS-HIPEC procedure for all tumor diagnoses combined or for each individual tumor diagnosis (Table 3). There was a statistically significant reduction in PFS following the third CRS-HIPEC procedure compared with the first and second CRS-HIPEC procedures for patients with low combined tumor grade and for AJCC grade G1 appendix cancers. For intermediate/high-grade appendix, colorectal and ovarian cancers, and malignant peritoneal mesothelioma, PFS was similar following the first and second CRS-HIPEC procedures.

Of the 32 AJCC grade G1 appendix cancers undergoing suboptimal cytoreduction (CC-2/3), 11 patients (34%) underwent a subsequent CRS-HIPEC procedure in which CC-0/1 resection was achieved in 10 patients. Despite suboptimal resection at the initial procedure (PFS 14.3 months; 95% CI 1.4, 27.2), OS for these patients was 136.9 months (95% CI 88.9, 184.9). Median PCI was 25 and major postoperative complications occurred in 55% of this small cohort of patients.

Predictive Modeling for Clinical Outcomes Across All CRS-HIPEC Procedures

Using generalized linear mixed model, we found that the odds of achieving a complete macroscopic (CC-0) resection was dependent on the intraoperative PCI and primary tumor diagnosis. Similarly, major in-hospital complications (CDC grades 3–4) was more likely to occur in patients undergoing suboptimal resection (Table 4).

TABLE 2 Multivariate Cox proportional hazards model for progression-free survival following the second CRS-HIPEC procedure

Variable		*p* value	Hazard ratio	95% CI
CC-score (referent: CC-0)	CC-1	0.008	0.53	0.26, 1.07
	CC-2		1.65	0.78, 3.5
	CC-3		–	–
In-hospital postoperative complications (Clavien-Dindo grades) (referent: no complications)	Grade 1	0.002	1.41	0.53, 3.8
	Grade 2		0.94	0.5, 1.8
	Grade 3		4.0	1.7, 9.1
	Grade 4		4.5	1.4, 14.6
Morbidity within 30 days of discharge (referent: no)	Yes	0.01	2.15	1.2, 3.8
PFS after first CRS-HIPEC-months (per one unit increase)		0.01	0.98	0.96, 0.99

CRS-HIPEC cytoreductive surgery-hyperthermic intraperitoneal chemoperfusion; *CC* completion of cytoreduction score

TABLE 3 Clinicopathologic and perioperative characteristics across multiple CRS-HIPEC procedures

Variable		First CRS-HIPEC (n = 1294)	Second CRS-HIPEC (n = 125)	Third CRS-HIPEC (n = 18)	Fourth CRS-HIPEC (n = 3)
Clinicopathologic and perioperative characteristics					
Diagnosis; n (%)	Appendix	641 (49.5)	78 (62.4)	15 (83.3)	2 (66.7)
	Colorectal	389 (30.1)	29 (23.2)	2 (11.1)	0
	Mesothelioma	157 (12.1)	15 (12)	0	0
	Ovarian	107 (8.3)	3 (2.4)	1 (5.6)	1 (33.3)
Combined tumor grade; n (%)	Low	339 (29.2)	41 (34.5)	10 (58.8)	1 (33.3)
	Intermediate	481 (41.5)	55 (46.2)	5 (29.4)	2 (66.7)
	High	340 (29.3)	23 (19.3)	2 (11.8)	0
Appendix tumor grade; n (%)	Grade G1	309 (54.6)	39 (54.9)	10 (66.7)	1 (50)
	Grade G2	156 (27.6)	26 (36.6)	4 (26.7)	1 (50)
	Grade G3	101 (17.8)	6 (8.5)	1 (6.7)	0
Colorectal tumor grade; n (%)	Well-diff	21 (7.5)	1 (3.6)	0	0
	Mod-diff	168 (60)	16 (57.1)	0	0
	Poorly-diff	89 (31.8)	11 (39.3)	1(100)	0
Mesothelioma tumor grade; n (%)	Low	14 (9.2)	0	0	0
	Intermediate	121 (79.6)	10 (76.9)	0	0
	High	17 (11.2)	3 (23.1)	0	0
Ovarian tumor grade; n (%)	Low	11 (10.3)	0	0	0
	Intermediate	10 (9.3)	1 (33.3)	1 (100)	1 (100)
	High	86 (80.4)	2 (66.7)	0	0
CC-0 resection; %		66.5	61.9	70.6	100
CC-0/1 resection; %		93.3	90.3	94.1	100
PCI; mean (SD)		16.5 (8.8)	13.3 (6.9)	15.6 (9.2)	18 (14.1)
Major in-hospital CDC grades 3–4 complications; %		24.2	24.3	29.4	50
Progression-free survival; mo (95% CI)					
Overall (all diagnoses)		13.7 (12.6, 14.9)	13.7 (11.5, 15.9)	19.7 (11.3, 28.1)	–
Appendix cancer		21.2 (18.7, 23.7)	19.6 (10.2, 28.9)	–	–
Colorectal cancer		10.4 (9.1, 11.7)	9.1 (3.9, 14.3)	–	–
Mesothelioma		13.7 (9.4, 18.1)	10.6 (5.5, 15.8)	–	–
Ovarian cancer		14.3 (8.3, 20.2)	8.1 (0, 16.4)	–	–
Combined tumor grade	Low	40.4 (30.5, 50.3)	28.9 (7.6, 50.3)	19.6 (8.7, 30.6)	–
	Intermediate	13.3 (11.8, 14.8)	12.2 (9.4, 14.9)	–	–
	High	10.5 (9.0, 11.9)	8.6 (3.7, 13.6)	6.5 (–, –)	–
Appendix tumor grade	Grade G1	39.9 (30.1, 49.9)	40.1 (13.5, 66.5)	19.7 (8.8, 30.6)	–
	Grade G2	13.9 (11.0, 16.9)	13.7 (8.6, 18.8)	–	–
	Grade G3	11.6 (7.4, 15.7	8.6 (0, 18.3)	6.5 (–, –)	–
Colorectal tumor grade	Well-diff	16.8 (6.5, 27.0)	–	–	–
	Mod-diff	11.0 (8.3, 13.8)	10.9 (6.3, 15.6)	–	–
	Poorly-diff	8.7 (6.8, 10.5)	6.7 (5.5, 7.8)	13.9 (–, –)	–
Mesothelioma tumor grade	Low	88.9 (–, –)	–	–	–
	Intermediate	14.9 (11.1, 18.7)	10.5 (0, 24.6)	–	–
	High	6.2 (3.2, 9.1)	14.1 (–, –)	–	–
Ovarian tumor grade	Low	45.7 (14.6, 76.8)	–	–	–
	Intermediate	28.0 (24.2, 31.8)	27.3 (–, –)	–	–
	High	11.2 (8.8, 13.6)	3.0 (–, –)	–	–

CRS-HIPEC cytoreductive surgery-hyperthermic intraperitoneal chemoperfusion; *CC* completion of cytoreduction score; *CDC* Clavien-Dindo classification; *PCI* peritoneal cancer index

TABLE 4 Generalized linear mixed model predicting CC-0 resection and major in-hospital postoperative complications across all CRS-HIPEC procedures

Variable		*p* value	Odds ratio[a]	95% CI
Predictors of CC-0 resection				
Primary tumor diagnosis (referent: appendix cancer)	Colorectal cancer	0.008	2.95	0.9, 9.3
	Mesothelioma		0.21	0.06, 75.8
	Ovarian cancer		1.74	0.1, 28.6
PCI (per one unit increase)		< 0.0001	0.87	0.8, 0.9
Predictors of major in-hospital postoperative complications (CDC grades 3–4)				
CC-score (referent: CC-0)	CC-1	0.004	2.77	1.5, 5.0
	CC-2		3.59	1.3, 10.2
	CC-3		2.0	0.2, 23.8

CRS-HIPEC cytoreductive surgery-hyperthermic intraperitoneal chemoperfusion; *CC* completion of cytoreduction score; *PCI* peritoneal cancer index; *CDC* Clavien-Dindo classification

[a]Assuming that PCI is at its mean value (16.05)

DISCUSSION

The clinical benefit and potential hazards of repeat CRS-HIPEC procedures remain poorly studied.[10,12–17] In this study, patients undergoing multiple CRS-HIPEC procedures were not at higher risk for suboptimal resection or postoperative complications and demonstrated equivalent PFS following each successive procedure compared with the first procedure.

Patients who underwent a second CRS-HIPEC procedure were more likely to have appendix cancer and non-high-grade tumors at their first CRS-HIPEC procedure, suggesting that tumor biology played an essential role in determining the feasibility of repeat CRS-HIPEC procedures. This was further highlighted by the fact that patients in the repeat HIPEC cohort were more likely to get a second CRS-HIPEC procedure despite having worse prognostic factors associated with the first procedure, including higher PCI, lower CC-0 resection, and higher incidence of postoperative complications.

Overall survival calculated from the first CRS-HIPEC procedure was significantly prolonged in the repeat HIPEC cohort compared with the single HIPEC cohort for appendix cancers (AJCC grades G2/G3) and colorectal cancer (moderately differentiated tumors). The apparent lack of OS benefit for repeat CRS-HIPEC procedures in patients with AJCC grade G1 appendix cancer was most likely due to excellent long-term survival after the first CRS-HIPEC procedure and limited follow-up in this study. There were too few patients with well-differentiated colorectal cancer to determine the impact of repeat CRS-HIPEC in such patients; however, one would expect equivalent or superior benefit to moderately differentiated cancers. Conversely, the lack of survival benefit for repeat CRS-HIPEC in patients with poorly differentiated colorectal cancers and intermediate/high-grade malignant peritoneal mesothelioma was likely related to the aggressive biology of these tumors. None of the 14 patients with low-grade mesothelioma required repeat CRS-HIPEC. We reviewed the subset of patients with AJCC grade G1 appendix cancers undergoing CC-2/3 resection at the first CRS-HIPEC procedure ($n = 32$). Despite suboptimal resection, higher PCI, and more postoperative complications associated with the first operation, a third of these patients underwent repeat CRS-HIPEC procedures (91% optimal resection) and demonstrated excellent long-term survival.

Progression-free survival after the second CRS-HIPEC procedure was negatively impacted by traditional factors, such as incomplete macroscopic resection and postoperative complications associated with the second procedure. However, we also found that shorter duration of PFS following the first CRS-HIPEC (but not time-interval between first and second procedure) was associated with shorter PFS after the second CRS-HIPEC procedure. This emphasizes the importance of surgeon experience, technical expertise, and appropriate patient selection for these challenging procedures and the potential impact of one CRS-HIPEC procedure on subsequent procedures. Our current clinical practice is to avoid repeat CRS-HIPEC procedures in patients with early disease recurrence after a CRS-HIPEC procedure. This is evident by our data demonstrating mean time-interval of 32.2 months between the first and second CRS-HIPEC procedures, 42.5 months between the second and third procedures, and 32.4 months between the third and fourth procedures. With our highly

selective approach to repeat CRS-HIPEC procedures, we found that PFS was similar across multiple procedures regardless of primary diagnosis or tumor grade.

Limitations of our study include the relatively small sample size for patients undergoing multiple (> 2) CRS-HIPEC procedures, heterogeneity of the patient populations, and inherent bias associated with the retrospective nature of the data. Patients deemed unresectable at the initial or subsequent CRS-HIPEC procedures (aborted cases) are not captured in our database; this key limitation prevents us from retrospectively commenting on intraoperative decision making. In general, cases are aborted if optimal resection (CC-0/1) cannot be achieved or if significant morbidity and impairment of quality of life would be likely to occur with an attempted CC-0/1 resection.

CONCLUSIONS

Our data for multiple HIPEC procedures confirmed our ability to select patients appropriately for repeat CRS-HIPEC procedures. Patients undergoing multiple CRS-HIPEC procedures were not at higher risk for suboptimal resection or postoperative complications and demonstrated equivalent PFS following each successive procedure compared with the first procedure. While we did not have formal guidelines to help decide for or against repeat CRS-HIPEC, our data suggest that we were more likely to perform repeat CRS-HIPEC in patients having primary appendix histology, non-high-grade tumors, and longer PFS following initial CRS-HIPEC. Time duration between the first and second CRS-HIPEC did not appear to be a predictor for undergoing a repeat CRS-HIPEC procedure. These data suggest that tumor biology plays an essential role in the feasibility of CRS-HIPEC and patient selection.

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DISCLOSURES None.

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