



High-grade complication is associated with poor overall survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Joey Wee-Shan Tan¹ · Grace Hwei Ching Tan¹ · Wai Yee Ng¹ · Chin-Ann Johnny Ong¹ · Claramae Shulyn Chia¹ · Khee Chee Soo¹ · Melissa Ching Ching Teo¹

Received: 21 September 2019 / Accepted: 21 December 2019
© Japan Society of Clinical Oncology 2020

Abstract

Background Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly used in peritoneal carcinomatosis (PC) management. This modality is criticized for its high morbidity and mortality. We evaluate the morbidity and mortality of patients undergoing this procedure in our institution.

Methods A review of our institution's database was performed. All patients who underwent CRS/HIPEC between July 2011 and March 2018 were divided into three groups: no, low-grade, and high-grade complications. Prognostic factors were determined with Cox regression, while morbidity risk factors were analyzed using multinomial logistic regression.

Results 225 consecutive patients underwent CRS/HIPEC. The most common primary cancer types were colorectal (35.1%), appendiceal (25.8%), and ovarian (22.2%). Median age was 55 years old (range 14–77), and patients were typically female (68.0%). 38.7% developed low-grade complications and 14.7% had high-grade complications. No 30-day mortality was observed. Different tumor origins are associated with significant differences in overall survival ($p < 0.001$). Patients without complications had significantly better survival than those with high-grade complications (HR 0.35, 95% CI 0.15–0.81, $p < 0.001$). Males were more likely to develop low-grade complications (OR 3.30, 95% CI 1.31–8.30, $p = 0.011$). Intra-operative blood loss was associated with greater odds of developing any post-operative complications (OR 1.001, 95% CI 1.0003–1.002, $p = 0.007$; and OR 1.002, 95% CI 1.001–1.002, $p < 0.001$, for low and high grade, respectively).

Conclusion Presence of high-grade complication was associated with poorer survival in patients after CRS/HIPEC. Pre-operative careful assessment of patients is pivotal to ensure favorable patient outcome following this complex procedure.

Keywords Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · Peritoneal disease · Morbidity · Mortality

Introduction

Peritoneal carcinomatosis (PC) is a form of metastatic disease from a number of intra-abdominal malignancies including appendiceal, gastrointestinal and gynecologic. The presence of PC has been known to portend a poor prognosis. In the presence of modern systemic chemotherapy and biologics, median survival of patients is 12–18 months for

colorectal PC [1], up to 12 months for gastric PC [2], and rarely above 30 months for platinum-sensitive ovarian PC [3]. The introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the 1980s changed the landscape for PC treatment. This multimodal therapeutic approach aims to remove all macroscopic disease, following which a heated chemotherapy perfusate is used to target all remaining viable microscopic disease [4]. CRS/HIPEC has consistently demonstrated improved survival [5–10] and quality of life [11–14] in selected patients across various malignancies. Randomized controlled trials investigating the efficacy of CRS/HIPEC in colorectal [15], gastric [16] and ovarian cancers [17, 18] have also revealed significant benefits to patient outcomes.

Despite mounting evidence of its therapeutic efficacy, CRS/HIPEC is undermined by its alleged associated

Joey Wee-Shan Tan and Grace Hwei Ching Tan contributed equally to this work.

✉ Melissa Ching Ching Teo
melissa.teo.c.c@singhealth.com.sg

¹ Division of Surgical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610, Singapore

morbidity and mortality rates. In a 2009 meta-analysis, high-risk morbidity and mortality rates for this complex procedure ranged between 0–52 and 0–17%, with an average of 28.8% and 2.9%, respectively [19]. More recently, large series consisting of patients with varied oncologic origins have reported rates of morbidity and mortality of 31–50% and 0.9–5.8%, respectively [5, 6, 19–23]. The prevention of complications and death after CRS/HIPEC continues to be an important challenge. We evaluate the post-operative 30-day morbidity and mortality of patients undergoing this procedure in our institution, after our initial experience, in an attempt to show that minimal morbidity and mortality can be a reality for this complex surgical procedure. Additionally, we sought to identify factors associated with survival and the development of morbidity in our patient cohort to guide future patient management.

Patients and methods

A prospective database containing relevant patient demographics, tumor characteristics and treatment-related data of consecutive patients who underwent CRS/HIPEC in the National Cancer Centre Singapore (NCCS) was reviewed.

The NCCS CRS/HIPEC programme was first initiated in 2001, with 64 procedures performed up to 2010. After this 10-year period, we felt that our institution had overcome our learning curve and hence selected patients treated between July 2011 and March 2018 for this study. This was supported by a preliminary analysis of our patient data that revealed patients treated prior to July 2011 had significantly higher complication rates as compared to those who underwent CRS/HIPEC after that period ($p=0.041$). The SingHealth Centralized Institutional Review Board approved the conduct of this study (CIRB 2011/917/D). The details of our institution's pre-operative and operative management have been described in greater detail previously [24].

Patient selection

Patients were deemed eligible for CRS/HIPEC if they demonstrated Eastern Cooperative Group (ECOG) score status zero or one [25] and did not present with distant metastases on pre-operative radiological imaging. All potential CRS/HIPEC cases were discussed at multidisciplinary tumor board meetings (MDTM) to determine the feasibility of complete cytoreduction and tumor clearance. During the MDTM, surgical, medical, and radiation oncologists, pathologists, and oncology radiologists gather to critically review clinical presentations and radiological scans to assess the possibility of obtaining complete cytoreduction before deciding on the treatment strategy in a consensus approach. Routine physical and blood tests, including detection of

tumor markers, were conducted for each patient prior to the surgical procedure.

CRS/HIPEC procedure

CRS was performed as described by Sugarbaker et al. [26]. Patients who undergo diaphragmatic stripping had chest tubes routinely inserted intra-operatively. If bowel anastomoses were required, they were performed after HIPEC. The extent of peritoneal disease and completeness of resection were determined intra-operatively by the peritoneal cancer index (PCI) score [27] and completeness of cytoreduction (CC) score [28, 29], respectively. Patients with a CC score of zero or one were deemed to have achieved optimal cytoreduction.

The drug used for HIPEC was prescribed according to the primary tumor origin by the treating medical oncologist. The drug of choice for colorectal and appendiceal PC was mitomycin C, while cisplatin was administered for ovarian, primary peritoneal and mesothelioma PC. HIPEC was performed via the closed technique at 41–42 °C for 60 min.

Post-operative morbidity and mortality

Morbidity was documented and graded using the Common Terminology Criteria for Adverse Events (CTCAE) classification within 30 days. Low-grade complications were described as grades 1 and 2, and high-grade complications as grades 3 and 4. Death related to the adverse event was defined as grade 5.

Follow-up

Post-operative surveillance was conducted every 3 months for the 1st year and subsequently once every 6 months. Routine tests include computed tomography (CT) imaging of the thorax, abdomen and pelvis, and blood tests of tumor markers when appropriate. Adjuvant systemic chemotherapy was prescribed when indicated by the medical oncologists.

Statistical analyses

We evaluated the demographics and clinical differences among patients who were divided into three groups: (1) no post-operative complications, (2) low-grade complications, and (3) high-grade complications. Patient demographics and perioperative details were summarized using descriptive statistics. Survival functions were estimated using Kaplan–Meier method and log-rank test was used to evaluate differences amongst groups. Cox regression was

used to investigate factors on the risk of the event of death. Variables with $p < 0.10$ on the univariate analysis were included in the multivariate Cox regression model, built using backward selection. Multinomial logistic regression was performed to identify independent risk factors for developing low- and high-grade complications using no post-operative complications group as the reference. Variables with $p < 0.10$ on univariate analysis were included in the multivariate multinomial logistic regression model, built using stepwise backward selection. Variables with $p < 0.05$ were considered statistically significant. All analyses were performed using Stata version 12.0 (StataCorp LLC, TX, USA).

Results

Patient demographics and treatment characteristics

From July 2011 and March 2018, 225 patients underwent the CRS/HIPEC procedure in our institution. Patient clinicopathologic factors, and intra- and post-operative details are listed in Table 1. The median age of our patient cohort was 55 (range 14–77) years. Patients were typically female (68.0%), Chinese (75.1%), and with ECOG status 0 (89.7%). 37.3% of our patients did not exhibit any comorbidities. The most common primary tumor types observed were colorectal (35.1%), appendiceal (25.8%) and ovarian (22.2%). Median pre-operative CEA, CA19-9, CA125 and CRP levels were 3.3 $\mu\text{g/L}$ (range 0.2–1407), 17.6 U/mL (range 0.6–6863), 21.8 U/mL (0.7–6131), and 2.6 mg/L (range 0.2–245), respectively.

Patients had a median PCI score of 10 (range 0–39) and 99.6% of them underwent optimal cytoreduction (CC score 0/1). Median duration of the CRS/HIPEC procedure was 6.9 h (range 3.3–14.7). During the surgery, patients had an estimated median blood loss of 1000 mL (range 0–11,000), required a median of 1 pint (range 0–21) of blood transfusion. Post-operatively, a median of 0 pints (range 0–25) of blood transfusion was required. Median ICU stay, time to full feed and total hospital stay were 0 (range 0–40), 5 (range 3–41) and 12 (range 6–94) days, respectively. 96.0% of our patients were warded in the ICU for 4 or less days. 1 patient had a 40-day ICU stay; this patient had extensive peritoneal disease and required a staged CRS and HIPEC. In addition, he suffered from post-operative complications which were managed in the ICU.

Following the surgery and within 30 days, 38.7% of patients developed low-grade complications, while 14.7% experienced high-grade complications. No mortality was observed. The most common complications observed

were pulmonary (19.4%), renal (14.7%), gastrointestinal (11.8%), and wound infection (11.8%) (Table 2).

Follow-up and survival analyses

With a median follow-up of 19.8 months (95% CI 17.2–25.3), median OS of our patient cohort was 54.3 months (95% CI 44.5–73.1). Overall 1-, 3- and 5-year OS rates were 92.7%, 71.1% and 44.8%, respectively. Individually, patients who experienced no post-operative, low-grade and high-grade complications had 5-year OS rates of 52.8% (95% CI 25.0–74.6), 37.0% (95% CI 19.2–54.8), and 43.0% (95% CI 20.2–64.1), respectively, where the difference amongst OS rates was statistically significant ($p = 0.016$) (Fig. 1). The multivariate OS analysis identified the primary tumor type and presence of complications as independent prognostic factors (Table 3). Patients with ovarian PC and primary peritoneal cancer (HR 0.36, 95% CI 0.17–0.76, $p = 0.008$), and appendiceal PC (HR 0.22, 95% CI 0.17–0.76, $p = 0.002$) had significantly better survival than those with colorectal PC. Patients who experienced no complications also had better survival as compared to those who experienced high-grade complications (HR 0.35, 95% CI 0.15–0.81, $p < 0.001$).

Factors associated with the development of complications

Factors associated with different post-operative complication groups were determined with multinomial logistic regression, and summarized in Table 4. The multivariate multinomial logistic regression was built using stepwise backward selection. Male patients were more likely to experience low-grade complications (OR 3.30, 95% CI 1.31–8.30, $p = 0.011$). An increase in volume of blood loss led to a higher chance of having low- (OR 1.001, 95% CI 1.0003–1.002, $p = 0.007$) and high-grade complications (OR 1.002, 95% CI 1.001–1.002, $p < 0.001$).

Discussion

As with all major surgical procedures, for CRS/HIPEC to become standard of care for the treatment of peritoneal disease, an optimal risk–benefit balance must be achieved. Skepticism for this procedure lies not in its efficacy, but its associated morbidity and mortality. We report zero CRS/HIPEC-associated mortality in our patient cohort, and acceptable low- and high-grade morbidity rates were 38.7% and 14.7%, respectively. Furthermore, surrogates of complications including short median ICU stay (0 days) and total hospital stay (12 days) indicate consistency with low morbidity rates associated with CRS/HIPEC. Therefore,

Table 1 Patient clinicopathologic factors, operative and post-operative details

Characteristics	Total (<i>n</i> = 225)	
	<i>n</i>	%
Age at CRS/HIPEC [median (range)]	55 (14–77)	
Gender		
Female	153	68.0
Male	72	31.9
Race		
Chinese	169	75.1
Malay	8	3.6
Indian	10	4.4
Others	38	16.9
ECOG status		
0	200	89.7
1	23	10.3
Comorbidities		
Yes	141	62.7
No	84	37.3
Primary tumor		
Colorectal	79	35.1
Ovarian	50	22.2
Primary peritoneal	16	7.1
Appendiceal	58	25.8
Mesothelioma	7	3.1
Others ^a	15	6.7
Pre-operative tumor markers [median (range)]		
CEA (µg/L)	3.3 (0.2–1407)	
CA19-9 (U/mL)	17.6 (0.6–6863)	
CA125 (U/mL)	21.8 (0.7–6131)	
CRP (mg/L)	2.6 (0.2–245)	
CRS/HIPEC procedure duration, hours [median (range)]	6.9 (3.3–14.7)	
PCI score [median (range)]	10 (0–39)	
CC score		
CC0/1	222	99.6
CC2	1	0.4
Blood loss, mL [median (range)]	1000 (0–11,000)	
Intra-operative blood transfusion, pints [median (range)]	1 (0–21)	
Post-operative blood transfusion, pints [median (range)]	0 (0–25)	
Complications		
High grade	33	14.7
Low grade	87	38.7
None	105	46.7
SICU stay, days [median (range)]	0 (0–40)	
Time to full feed, days [median (range)]	5 (3–41)	
Total hospital stay, days [median (range)]	12 (6–94)	

Sums of numbers may not add up to total number of patients in cohort due to missing data

CRS/HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, ECOG Eastern Cooperative Oncology Group, CEA carcinoembryonic antigen, CA19-9 carbohydrate antigen 19–9, CA125 cancer antigen 125, CRP C-reactive protein, PCI peritoneal carcinomatosis index, CC completeness of cytoreductive, SICU surgical intensive care unit

^aOther primary tumor types: 3 small intestine, 2 sarcomas, 5 gastric, 3 endometrial, 1 endocervical and 1 malignant neoplasm of the female genital organ

Table 2 Morbidity after CRS/HIPEC

Complications	Low-grade complications		High-grade complications		All	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Pulmonary	19	17.0	14	24.1	33	19.4
Renal	17	15.2	8	13.8	25	14.7
Gastrointestinal	18	16.1	2	3.4	20	11.8
Wound infection	16	14.3	4	6.9	20	11.8
Intra-abdominal collections	0	0	15	25.9	15	8.8
Hematological	14	12.5	0	0	14	8.2
Cardiac	7	6.3	2	3.4	9	5.3
Fever	6	5.4	0	0	6	3.5
Vomiting and nausea	4	3.6	1	1.7	5	2.9
Increased stoma output	3	2.7	1	1.7	4	2.4
Bleeding	1	0.9	2	3.4	3	1.8
Anastomotic leak	2	1.8	1	1.7	3	1.8
Urinary tract infection	3	2.7	0	0	3	1.8
Perforation	0	0	3	5.2	3	1.8
Infectious	1	0.9	1	1.7	2	1.2
Urological	1	0.9	1	1.7	2	1.2
Ureteric leak	0	0	1	1.7	1	0.6
Scrotal ulcer	0	0	1	1.7	1	0.6
Guillain-Barré syndrome	0	0	1	1.7	1	0.6

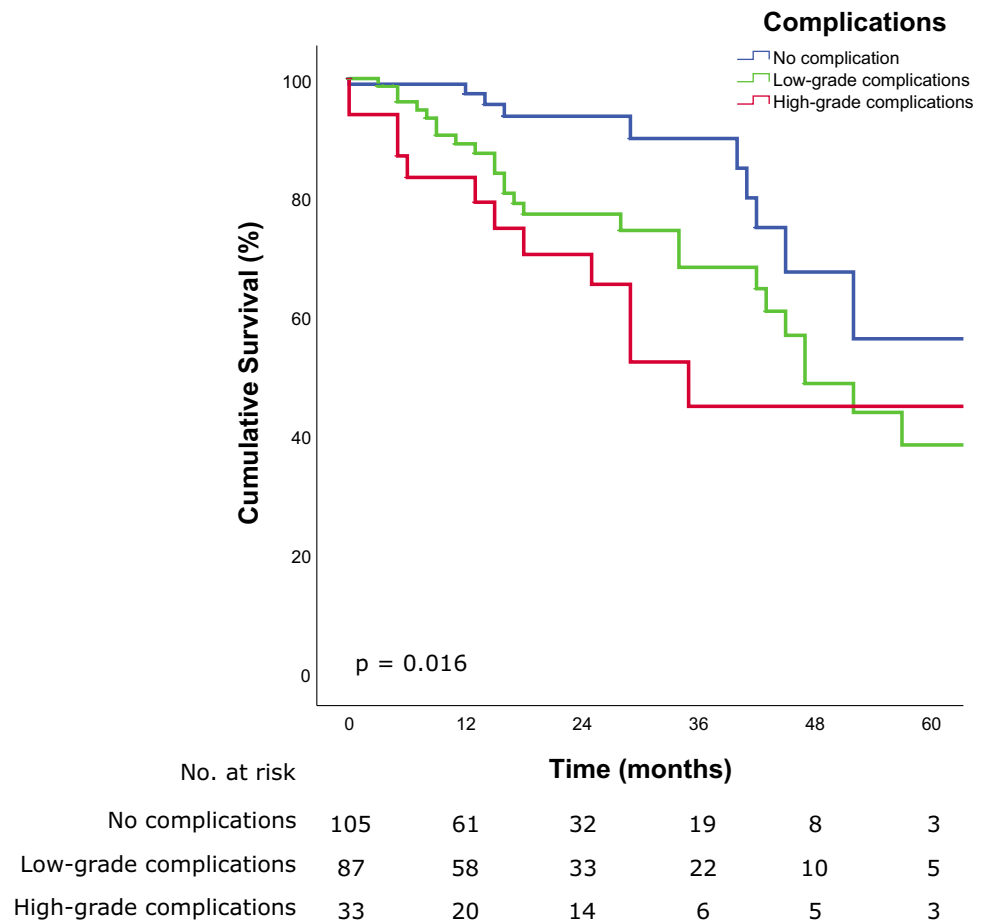
Fig. 1 Kaplan–Meier survival curve according to the type of complications. The difference amongst no complications, low- and high-grade complications is statistically significant ($p=0.016$)

Table 3 Univariate and multivariate Cox regression on overall survival

	Univariate			Multivariate		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age at CRS/HIPEC	0.99	0.97–1.02	0.481	–	–	–
Male	1.97	1.08–3.60	0.027	–	–	–
Race						
Chinese	Ref		0.746	–	–	–
Malay	1.36	0.42–4.43	0.604	–	–	–
Indian	1.69	0.40–7.07	0.474	–	–	–
Others	0.71	0.25–2.0	0.525	–	–	–
ECOG status						
0	Ref			–	–	–
1	1.12	0.49–2.53	0.791	–	–	–
Comorbidities						
None	Ref			–	–	–
Yes	1.15	0.63–2.11	0.650	–	–	–
Primary tumor						
Colorectal	Ref		0.005	Ref		<0.001
Ovarian and primary peritoneal	0.53	0.26–1.10	0.089	0.36	0.17–0.76	0.008
Appendiceal	0.49	0.21–1.13	0.092	0.22	0.17–0.76	0.002
Mesothelioma and others	2.01	0.92–4.38	0.078	1.50	0.67–3.37	0.322
Pre-operative tumor markers						
CEA (µg/L)	0.999	1.00–1.00	0.985	–	–	–
CA19–9 (U/mL)	1.00	1.00–1.00	0.985	–	–	–
CA125 (U/mL)	0.999	0.99–1.00	0.818	–	–	–
CRP (mg/L)	0.97	0.90–1.04	0.335	–	–	–
CRS/HIPEC procedure duration (h)	1.05	0.93–1.18	0.439	–	–	–
PCI score	1.02	0.99–1.05	0.269	–	–	–
Estimated blood loss (ml)	1.00	0.99–1.00	0.962	–	–	–
Intra-operative blood transfusion (pint)	1.03	0.95–1.11	0.457	–	–	–
Post-operative blood transfusion (pint)	1.03	0.96–1.10	0.485	–	–	–
Insertion of chest tube(s)	0.85	0.35–2.08	0.722	–	–	–
Stoma creation	1.70	0.96–3.03	0.070	–	–	–
Complications						
High grade	Ref		0.027	Ref		0.001
Low grade	0.84	0.43–1.67	0.629	0.84	0.43–1.67	0.086
None	0.35	0.15–0.81	0.014	0.35	0.15–0.81	<0.001
SICU stay (days)	0.92	0.81–1.06	0.242	–	–	–
Time to full feed (days)	0.995	0.949–1.044	0.841	–	–	–
Total hospital stay (days)	0.995	0.977–1.014	0.629	–	–	–
Recurrence	1.81	0.94–3.48	0.077	–	–	–

CRS/HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, ECOG Eastern Cooperative Oncology Group, CEA carcinoembryonic antigen, CA19–9 carbohydrate antigen 19–9, CA125 cancer antigen 125, CRP C-reactive protein, PCI peritoneal carcinomatosis index, SICU intensive care unit

morbidity and mortality should not be a pretext for the reluctance to consider this procedure in selected patients. Notwithstanding, there is a crucial need to carefully select patients for this procedure to enable better outcomes.

The most frequent complications observed in our patient cohort was pulmonary (19.4%) followed by renal complications (14.7%). This does not come across as surprising as

pulmonary complications are fairly common after abdominal surgery [30, 31]. Moreover, it is expected that diaphragmatic stripping would result in pleural effusions. Notably, our institution routinely inserts chest tubes following diaphragmatic peritonectomies, hence we report only six cases of pleural effusion in our cohort. Similarly, renal complications have been identified as a key complication post-HIPEC

Table 4 Univariate and multivariate multinomial logistic regression

	Univariate				Multivariate				
	Low-grade complications <i>n</i> = 87				Low-grade complications <i>n</i> = 87				
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
No complications <i>n</i> = 105 (reference category)									
Age at CRS/HIPEC	0.99	0.97–1.02	0.540	1.01	0.97–1.04	0.620	–	–	–
Male	1.95	1.05–3.62	0.034	1.74	0.75–4.01	0.196	3.30	1.31–8.30	0.011
Race									
Chinese	Ref			Ref			–	–	–
Malay	0.50	0.09–2.69	0.423	0.75	0.08–6.71	0.793	–	–	–
Indian	0.50	0.09–2.69	0.423	2.24	0.50–10.09	0.295	–	–	–
Others	1.75	0.80–3.83	0.163	2.01	0.71–5.63	0.186	–	–	–
ECOG status									
0	Ref			Ref			–	–	–
1	0.53	0.18–1.60	0.263	2.30	0.81–6.52	0.117	–	–	–
Comorbidities									
None	Ref			Ref			–	–	–
Yes	0.68	0.38–1.22	0.191	0.88	0.39–1.98	0.749	–	–	–
Primary tumor									
Colorectal	Ref			Ref			–	–	–
Ovarian and primary peritoneal	1.77	0.87–3.59	0.115	1.33	0.44–4.03	0.618	–	–	–
Appendiceal	2.47	1.14–5.38	0.022	4.64	1.69–12.74	0.003	–	–	–
Mesothelioma and others	2.69	0.96–7.58	0.061	2.20	0.48–10.11	0.310	–	–	–
Pre-operative tumor markers									
CEA (μg/L)	1.01	0.99–1.01	0.216	1.01	1.00–1.02	0.068	–	–	–
CA19–9 (U/mL)	1.00	1.00–1.00	0.780	1.00	1.00–1.00	0.783	–	–	–
CA125 (U/mL)	1.00	1.00–1.00	0.438	1.00	1.00–1.00	0.664	–	–	–
CRP (mg/L)	1.01	1.00–1.03	0.061	1.02	1.00–1.03	0.040	–	–	–
CRS/HIPEC procedure duration (h)	1.33	1.15–1.53	<0.001	1.68	1.38–2.04	<0.001	–	–	–
PCI score	1.07	1.03–1.11	<0.001	1.11	1.06–1.16	<0.001	–	–	–
Estimated blood loss (ml)	1.00	1.00–1.00	0.001	1.00	1.00–1.00	<0.001	1.001	1.0003–1.002	0.007
Intra-operative blood transfusion (pints)	1.30	1.13–1.51	<0.001	1.46	1.24–1.71	<0.001	–	–	–
Insertion of chest tube(s)	2.60	1.44–4.69	0.002	4.74	2.03–11.06	<0.001	–	–	–
Stoma creation	3.00	1.57–5.73	0.001	3.54	1.53–8.21	0.003	–	–	–
							</		

CRS/HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, ECOG Eastern Cooperative Oncology Group, CEA carcinoembryonic antigen, CA19–9 carbohydrate antigen 19–9, CA125 cancer antigen 125, CRP C-reactive protein, PCI peritoneal carcinomatosis index

[32]. We observed 16 cases of acute kidney injury (AKI) out of 25 renal complication cases in our patient cohort (64%). We note that majority of our patients (65%) who suffered from renal complications were treated with cisplatin during HIPEC, while the remainder had mitomycin-C. This observed association of cisplatin with renal complications has been reported previously [32–34]. Apart from the effects of platinum-based chemotherapeutic drugs, other mechanisms have also been proposed for the renal complications, such as fluid redistribution and intra-operative hemodynamic instability [32, 35].

The primary tumor type was significantly associated with our patient's OS. Patients with ovarian PC and primary peritoneal cancer, as well as appendiceal PC, had better survival outcomes than that of those with colorectal cancer. This is likely due to differences in tumor biology. The presence of high-grade complications was also independently associated with poorer OS outcomes in our patient cohort, which has been reported in the literature [36, 37]. A potential factor which may influence the prognosis of patients is the administration of adjuvant chemotherapy, which could be affected by the grade of complications. In our cohort, 37/105 (35.2%) of patients with no complications, 27/87 (31.0%) of those with low-grade complications, and 7/33 (21.2%) of those with high-grade complications went on to be treated with adjuvant chemotherapy. However, the difference was not statistically different ($p=0.316$).

To determine independent risk factors for the development of complications in patients undergoing CRS/HIPEC, we assessed risk factors associated with morbidity in our patient cohort. Males were more likely to develop low-grade complications. Although intriguing, we do not see an obvious explanation for this finding. Differences in gender have been suggested to correlate with the occurrences of complications in surgical procedures. For instance, Lambert et al. [38] identified female gender as an independent risk factor for the development of neutropenia in patients undergoing HIPEC with mitomycin C. Likewise, intra-operative blood loss reflects a multitude of factors including patient comorbidities, the extent of surgery, and type of surgical procedures performed. After adjusting for these factors, we note that intra-operative blood loss remained associated with the development of complications. Similar to our results, Tabrizian et al. [39] identified intra-operative blood loss as the sole prognostic factor associated with major complications in patients who underwent CRS/HIPEC in their tertiary institution. These predictive variables are potentially useful in the patient selection process. Patients deemed to be at high risk for the CRS/HIPEC procedure could be offered treatment with neoadjuvant therapies in an attempt to reduce their morbidity for the procedure. Additionally, strict intra-operative fluid management is essential throughout the procedure.

We achieved zero mortality and acceptable morbidity rates possibly due to increased knowledge and experience in our institution. As with any complex surgery, high-volume centers and skilled surgical teams are associated with improved patient outcomes [5, 40, 41]. Moreover, the learning curve has been established as a crucial feature to reduce the incidence of post-operative complications and improve overall survival of patients [5, 6, 20, 41–43]. In our previous publications, we reported a mortality rate of 1%, which was attributed to, by two patients who demised beyond 30 days, due to post-operative complications and prolonged hospitalization [24, 44]. These patients underwent CRS/HIPEC in our initial experience with this procedure, during which we were possibly within our learning curve. In the current study, we only analyzed patients operated on after we felt that we had overcome the inherent learning curve for this complex procedure, which possibly resulted in improved patient outcomes. This decision was supported by the observed change in complication rate during these periods. An analysis of our patients' data revealed that those treated before July 2011 experienced significantly higher complication rates (66.7%) as compared to those who underwent the CRS/HIPEC procedure after this period (53.3%) ($p=0.041$). Additionally, those operated on before July 2011 exhibited significantly higher grade 3 (36.5% vs 19.2%, $p=0.015$) and grade 5 (3.85% vs 0%, $p=0.031$) complication rates, with no differences between the groups for grades 1, 2 and 4 morbidity. Apart from improved technical expertise with time, a critical component of the learning curve is the development of better patient selection [42, 43]. To ensure our patients reap the benefits of this multimodal procedure, our institution is stringent with the inclusion and exclusion criteria of CRS/HIPEC. Additionally, all patients listed are assessed for suitability to undergo the procedure at the MDTM. Our team recently reported on the demographics of patients in our institution who were being considered for CRS/HIPEC [45]. Between 2011 and 2015, 407 patients were considered for the procedure of which 210 (51.6%) patients were not recommended for CRS/HIPEC during the MDTM. Reasons for exclusion included presence of distant metastatic disease, extensive disease or small bowel involvement observed on radiological images, poor tumor biology such as short disease-free interval, presence of signet ring cells, or progressive disease on chemotherapy, patients who were determined to be medically unfit for surgery, as well as indeterminate presence of extraperitoneal lesions. Only patients who were deemed likely to achieve complete cytoreduction would be recommended for CRS/HIPEC. Other strategies adopted by our team include the administration of “pseudo-neoadjuvant” chemotherapy to identify patients who may not benefit from CRS/HIPEC, and the increasing use of other imaging modalities such as positron emission tomography (PET)-CT and magnetic resonance imaging (MRI) [24] to

identify the presence of extra-abdominal disease, and better determine tumor resectability pre-operatively. These strategies have proven effective, as evidenced by 99.6% of our patients achieving complete cytoreduction (CC0/1).

This study has several limitations. This is a retrospective study from a single institution, possessing potential of patient selection bias. Nevertheless, our results reveal that having strict patient selection criteria facilitates the identification of the patient cohort who would achieve maximal benefits from CRS/HIPEC. Additionally, recent literature has urged for the use of 90-day morbidity and mortality assessment for complex procedures such as CRS/HIPEC [46–48]. In this study, we assessed the 30-day morbidity and mortality for our patients. Moreover, this study included all types of epithelial cancer which led to peritoneal disease in our patient cohort. The various malignancies are distinct in their behavior and prognosis, providing heterogeneity in our data. However, this study focuses on the morbidity and mortality of CRS/HIPEC, reducing its implications on our analysis. In conclusion, the presence of high-grade complication was associated with poorer overall survival in patients after CRS/HIPEC. Intra-operative blood loss was associated with developing any post-operative complications. Pre-operative careful assessment of patients for CRS/HIPEC suitability is thus pivotal to ensure favorable patient outcome following this complex procedure.

Acknowledgements Ms. Thakshayeni Skanthakumar, database manager; Ms. Li-Lian Kwok, biostatistician.

Author contributions GHCT and MCCT contributed to the study conception and design. Material preparation, data collection and analysis were performed by JWST and WYN. The first draft of the manuscript was written by JWST and GHCT. CAJO, CSC, KCS and MCCT provided essential clinical and intellectual inputs to the study and reviewed the manuscript critically for publication. All authors commented on previous versions of the manuscript, read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Koumpa FS, Xylas D, Konopka M et al (2019) Colorectal peritoneal metastases: a systematic review of current and emerging trends in clinical and translational research. *Gastroenterol Res Pract* 2019:30. <https://doi.org/10.1155/2019/5180895>
- Coccolini F, Gheza F, Lotti M et al (2013) Peritoneal carcinomatosis. *World J Gastroenterol* 19(41):6979–6994. <https://doi.org/10.3748/wjg.v19.i41.6979>
- Bristow RE, Puri I, Chi DS (2009) Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecol Oncol* 112(1):265–274. <https://doi.org/10.1016/j.ygyno.2008.08.033>
- Glehen O, Osinsky D, Cotte E et al (2003) Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. *Ann Surg Oncol* 10(8):863–869
- Glehen O, Gilly FN, Boutitie F et al (2010) Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1290 patients. *Cancer* 116(24):5608–5618. <https://doi.org/10.1002/cncr.25356>
- Passot G, Vaudoyer D, Villeneuve L et al (2016) What made hyperthermic intraperitoneal chemotherapy an effective curative treatment for peritoneal surface malignancy: a 25-year experience with 1,125 procedures. *J Surg Oncol* 113(7):796–803. <https://doi.org/10.1002/jso.24248>
- Elias D, Gilly F, Boutitie F et al (2010) Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol* 28(1):63–68. <https://doi.org/10.1200/JCO.2009.23.9285>
- Elias D, Gilly F, Quenet F et al (2010) Pseudomyxoma peritonei: a French multicentric study of 301 patients treated with cytoreductive surgery and intraperitoneal chemotherapy. *Eur J Surg Oncol* 36(5):456–462. <https://doi.org/10.1016/j.ejso.2010.01.006>
- Mirnezami R, Mehta AM, Chandrakumaran K et al (2014) Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. *Br J Cancer* 111(8):1500–1508. <https://doi.org/10.1038/bjc.2014.419>
- Huo YR, Richards A, Liauw W et al (2015) Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) in ovarian cancer: a systematic review and meta-analysis. *Eur J Surg Oncol* 41(12):1578–1589. <https://doi.org/10.1016/j.ejso.2015.08.172>
- Chia CS, Tan GH, Lim C et al (2016) Prospective quality of life study for colorectal cancer patients with peritoneal carcinomatosis undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 23(9):2905–2913. <https://doi.org/10.1245/s10434-016-5203-6>
- McQuellon RP, Danhauer SC, Russell GB et al (2007) Monitoring health outcomes following cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. *Ann Surg Oncol* 14(3):1105–1113. <https://doi.org/10.1245/s10434-006-9304-5>
- Seretis C, Youssef H (2014) Quality of life after cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies: a systematic review. *Eur J Surg Oncol* 40(12):1605–1613. <https://doi.org/10.1016/j.ejso.2014.08.477>
- Stearns AT, Malcomson L, Punnett G et al (2018) Long-term quality of life after cytoreductive surgery and heated intraperitoneal chemotherapy for pseudomyxoma peritonei: a prospective longitudinal study. *Ann Surg Oncol* 25(4):965–973. <https://doi.org/10.1245/s10434-017-6326-0>
- Verwaal VJ, Bruin S, Boot H et al (2008) 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 15(9):2426–2432. <https://doi.org/10.1245/s10434-008-9966-2>
- Yang XJ, Huang CQ, Suo T et al (2011) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol* 18(6):1575–1581. <https://doi.org/10.1245/s10434-011-1631-5>
- Spiliotis J, Halkia E, Lianos E et al (2015) Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a

- prospective randomized phase III study. *Ann Surg Oncol* 22(5):1570–1575. <https://doi.org/10.1245/s10434-014-4157-9>
18. van Driel WJ, Koole SN, Sikorska K et al (2018) Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med* 378(3):230–240. <https://doi.org/10.1056/NEJMoa1708618>
 19. Chua TC, Yan TD, Saxena A et al (2009) Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. *Ann Surg* 249(6):900–907. <https://doi.org/10.1097/SLA.0b013e3181a45d86>
 20. Levine EA, Stewart JH, Shen P et al (2014) Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1000 patients. *J Am Coll Surg* 218(4):573–585. <https://doi.org/10.1016/j.jamcollsurg.2013.12.013>
 21. Bartlett EK, Meise C, Roses RE et al (2014) Morbidity and mortality of cytoreduction with intraperitoneal chemotherapy: outcomes from the ACS NSQIP database. *Ann Surg Oncol* 21(5):1494–1500. <https://doi.org/10.1245/s10434-013-3223-z>
 22. Desantis M, Bernard JL, Casanova V et al (2015) Morbidity, mortality, and oncological outcomes of 401 consecutive cytoreductive procedures with hyperthermic intraperitoneal chemotherapy (HIPEC). *Langenbecks Arch Surg* 400(1):37–48. <https://doi.org/10.1007/s00423-014-1253-z>
 23. Jafari MD, Halabi WJ, Stamos MJ et al (2014) Surgical outcomes of hyperthermic intraperitoneal chemotherapy: analysis of the American college of surgeons national surgical quality improvement program. *JAMA Surg* 149(2):170–175. <https://doi.org/10.1001/jamasurg.2013.3640>
 24. Tan G, Chia C, Kumar M et al (2016) 201 consecutive cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) procedures in a single Asian tertiary centre. *Int J Hyperthermia*. <https://doi.org/10.1080/02656736.2016.1262064>
 25. Oken MM, Creech RH, Tormey DC et al (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5(6):649–656
 26. Sugarbaker PH (1995) Peritonectomy procedures. *Ann Surg* 221(1):29–42
 27. Sugarbaker PH, Ronnett BM, Archer A et al (2016) Pseudomyxoma peritonei syndrome. *Adv Surg* 30:233–280
 28. Sugarbaker PH, Jablonski KA (1995) Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. *Ann Surg* 221(2):124–132
 29. Sugarbaker PH (1999) Successful management of microscopic residual disease in large bowel cancer. *Cancer Chemother Pharmacol* 43(Suppl):S15–S25
 30. Patel K, Hadian F, Ali A et al (2016) Postoperative pulmonary complications following major elective abdominal surgery: a cohort study. *Perioper Med (London, England)* 5:10. <https://doi.org/10.1186/s13741-016-0037-0>
 31. Fernandez-Bustamante A, Frendl G, Sprung J et al (2017) Postoperative pulmonary complications, early mortality, and hospital stay following noncardiothoracic surgery: a multicenter study by the perioperative research network investigators assessing postoperative pulmonary complications after noncardiothoracic surgery assessing postoperative pulmonary complications after noncardiothoracic surgery. *JAMA Surg* 152(2):157–166. <https://doi.org/10.1001/jamasurg.2016.4065>
 32. Cata JP, Zavala AM, Van Meter A et al (2018) Identification of risk factors associated with postoperative acute kidney injury after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: a retrospective study. *Int J Hyperther* 34(5):538–544. <https://doi.org/10.1080/02656736.2017.1368096>
 33. Tan GHC, Shannon NB, Chia CS et al (2018) Platinum agents and mitomycin C-specific complications in cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). *Int J Hyperther* 34(5):595–600. <https://doi.org/10.1080/02656736.2017.1345014>
 34. Bouhadjari N, Gabato W, Calabrese D et al (2016) Hyperthermic intraperitoneal chemotherapy with cisplatin: amifostine prevents acute severe renal impairment. *Eur J Surg Oncol* 42(2):219–223. <https://doi.org/10.1016/j.ejso.2015.07.016>
 35. Ceresoli M, Cocolini F, Ansaloni L (2016) HIPEC and nephrotoxicity: a cisplatin induced effect? *Eur J Surg Oncol* 42(6):909–910
 36. Schneider MA, Eshmuminov D, Lehmann K (2017) Major post-operative complications are a risk factor for impaired survival after CRS/HIPEC. *Ann Surg Oncol* 24(8):2224–2232. <https://doi.org/10.1245/s10434-017-5821-7>
 37. Simkens GA, van Oudheusden TR, Luyer MD et al (2015) Serious postoperative complications affect early recurrence after cytoreductive surgery and HIPEC for colorectal peritoneal carcinomatosis. *Ann Surg Oncol* 22(8):2656–2662. <https://doi.org/10.1245/s10434-014-4297-y>
 38. Lambert LA, Armstrong TS, Lee JJ et al (2009) Incidence, risk factors, and impact of severe neutropenia after hyperthermic intraperitoneal mitomycin C. *Ann Surg Oncol* 16(8):2181–2187. <https://doi.org/10.1245/s10434-009-0523-4>
 39. Tabrizian P, Shrager B, Jibara G et al (2014) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: outcomes from a single tertiary institution. *J Gastrointest Surg* 18(5):1024–1031. <https://doi.org/10.1007/s11605-014-2477-5>
 40. Rajeev R, Klooster B, Turaga KK (2016) Impact of surgical volume of centers on post-operative outcomes from cytoreductive surgery and hyperthermic intra-peritoneal chemoperfusion. *J Gastrointest Oncol* 7(1):122–128. <https://doi.org/10.3978/j.issn.2078-6891.2015.099>
 41. Yan TD, Links M, Fransi S et al (2007) Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancy—a journey to becoming a Nationally Funded Peritonectomy Center. *Ann Surg Oncol* 14(8):2270–2280. <https://doi.org/10.1245/s10434-007-9406-8>
 42. Smeenk RM, Verwaal VJ, Zoetmulder FA (2007) Learning curve of combined modality treatment in peritoneal surface disease. *Br J Surg* 94(11):1408–1414. <https://doi.org/10.1002/bjs.5863>
 43. Kuijpers AM, Hauptmann M, Aalbers AG et al (2016) Cytoreduction and hyperthermic intraperitoneal chemotherapy: the learning curve reassessed. *Eur J Surg Oncol* 42(2):244–250. <https://doi.org/10.1016/j.ejso.2015.08.162>
 44. Teo MCC, Tan GHC, Tham CK et al (2013) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in Asian patients: 100 consecutive patients in a single institution. *Ann Surg Oncol* 20(9):2968–2974. <https://doi.org/10.1245/s10434-013-2947-0>
 45. Wang W, Tan GHC, Skanthakumar T et al (2018) Exploring the trend in referrals for consideration of CRS and HIPEC to understand the attitudes of clinicians in the development of a national cancer centre programme in peritoneal disease. *Int J Hyperthermia* 34(5):551–558. <https://doi.org/10.1080/02656736.2017.1387939>
 46. Mise Y, Vauthey JN, Zimmiti G et al (2015) Ninety-day post-operative mortality is a legitimate measure of hepatopancreatobiliary surgical quality. *Ann Surg* 262(6):1071–1078. <https://doi.org/10.1097/sla.0000000000001048>
 47. Schwarz L, Bruno M, Parker NH et al (2015) Active surveillance for adverse events within 90 days: the standard for reporting

- surgical outcomes after pancreatectomy. *Ann Surg Oncol* 22(11):3522–3529. <https://doi.org/10.1245/s10434-015-4437-z>
48. Alyami M, Kim BJ, Villeneuve L et al (2018) Ninety-day post-operative morbidity and mortality using the National Cancer Institute's common terminology criteria for adverse events better describe post-operative outcome after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Int J Hyperthermia* 34(5):532–537. <https://doi.org/10.1080/02656736.2017.1367846>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.