Treatment-related post-operative mortality after cytoreductive surgery and perioperative intraperitoneal chemotherapy

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Abstract

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has an established role in selected patients for the treatment of peritoneal surface malignancy. However, CRS/HIPEC is associated with increased risk of morbidity and mortality. The aim of this review was to identify risk factors for post-operative mortality in an attempt to improve patient outcomes post CRS/HIPEC.

This is a retrospective study of prospectively collected data on 1019 patients who underwent CRS/HIPEC by the same surgical team at St George Hospital, Kogarah, Australia, between January 1996 and July 2016.

During the 20-year time-period seventeen patients (1.67%) died postoperatively. A higher peritoneal cancer index (PCI), completeness of cytoreduction (CC) score, longer operative time and a volume of intra-operative transfusion were evident in the hospital mortality group and were significantly associated with postoperative mortality on univariate analysis. Postoperative complications including infection, bleeding, pneumonia, fistula, collection and pancreatic leak were also associated with post-operative mortality. The most common cause of death was sepsis (n=15, 88.2%).

It is difficult to determine pre-operative factors that can be utilized as predictors of post-operative mortality, as the overall incidence of in-hospital mortality post CRS/HIPEC was very low on our unit. Nevertheless, a cascade of events and learning curve was displayed.

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Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has an established role in the treatment of selected patients with peritoneal surface malignancy as it results in a significant survival benefit especially compared to palliative and best supportive therapy.[1-4] Mortality after major CRS/HIPEC is clearly an important concern for patients and the treating team.[1-4] It has been reported that there is a learning curve associated with CRS/HIPEC, where mortality rates of up to 18% were experienced in the 1990's when this treatment modality was still being explored and established.[5-7] Commonly, patients present with a higher burden of disease, which has been extensively reported as a predictor for post-operative morbidity, mortality, as well as reduced survival outcomes in certain tumours.[8] However, as a result of increasing experience, particularly mortality rates have progressively fallen, now ranging from 0.9% to 5.8% at high-volume, tertiary referral centres.[9]

As such, the aim of this study was to analyse the post-operative mortality rates of our high-volume center and if these have changed with increase institutional experience. Furthermore, we attempted to determine factors, which may help predict which patients are at increased risk of mortality to improve outcomes of our patients undergoing CRS/HIPEC.

Materials and Methods

Treatment setting

The Department of Surgery Peritonectomy Unit at St George Hospital, located in Kogarah (Sydney), Australia, is a major surgi-

cal oncology referral unit. Cytoreductive surgery with perioperative intra-peritoneal chemotherapy was introduced for patients with peritoneal surface malignancy in 1996. All patient demographics, postoperative morbidity, mortality and other relevant outcome data have been collected in a prospectively maintained database at the centre. As such, the present study is a retrospective analysis of 1019 patients who underwent CRS/HIPEC by the same surgical team at our unit between January 1996 and July 2016. Following an assessment by a multidisciplinary team meeting (see below), all patients provided informed consent. Institutional ethics board approval for this study was obtained.

Patient and selection criteria for CRS/HIPEC

Suitability to undergo CRS/HIPEC was assessed by the multidisciplinary team (MDT) during a weekly meeting. Patients who were regarded as candidates for this treatment had to demonstrate a good performance status, no untreatable for cure extra-abdominal disease, limited small bowel involvement, and no significant comorbidity. There was no restriction on Peritoneal Cancer Index (PCI) except for colorectal peritoneal carcinomatosis (CRPC), in which selection was amended from a PCI ≤20 to a PCI ≤15 from 2012 onwards.[10] In CRPC with liver metastases, a PCI ≤10 with a maximum of three liver lesions was accepted. For those who were considered for a repeat CRS/HIPEC for CRPC, a PCI≤10 was also required with at least one-year recurrence free survival time from the date of the primary CRS. All patients were selected based on the ability to achieve complete cytoreduction with maintenance of quality of life and/or substantial survival benefit from the procedure.

All the patients received standard preoperative assessments, including radiological evaluation, and managements, as previously described.[11] As part of the management, patients received 5000 units of heparin twice daily for five days from the day of surgery and continued prophylactic subcutaneous low-molecular-weight heparin 1 mg/kg twice daily to cover a total of six weeks from the day of surgery.

Variables prospectively collected

Age at the time of operation was recorded. Obesity was defined as body mass index (BMI) ≥30 kg/m^2. The Prior Surgical score (PSS-0 to PSS-3) was used to measure the extent of surgery prior to CRS, as described previously.[12] The American Society of Anesthesiologists (ASA) score was calculated before CRS/HIPEC to assess the physical status of the patients.[13] The Eastern Cooperative Oncology Group (ECOG) score was used to quantify the functional status of the patients.[14] Preoperative serum albumin levels were recorded and hypoalbuminemia was defined as an albumin level <35 g/L.

All CRS procedures were performed and documented as previously described by Sugarbaker.[15] The PCI, ranging from 0 to 39, was used to assess the extent of peritoneal disease. The completeness of cytoreduction (CC0 to CC3) score was recorded to report residual tumour volume, as previously described.[16]

Perioperative intraperitoneal chemotherapy (PIC), either HIPEC or early post-operative intraperitoneal chemotherapy (EPIC), was delivered to patients under the standard protocol, as previously described.[10] For pseudomyxoma peritonei (PMP), mitomycin C (MMC) (12.5 mg/m^2 over 90 min) was given. For diffuse malignant peritoneal mesothelioma (DMPM), cisplatin (100 mg/m^2) and MMC (12.5 mg/m^2) in 1000 mL of normal saline were used over 90 min. For appendix adenocarcinoma and CRPC, oxaliplatin (350 mg/m^2) in 500 mL of 5% dextrose was used over 30 min from 2012 onwards.[17] For ovarian carcinoma, cisplatin (100 mg/m^2) in 1000 mL of saline was given for 60 min. Massive transfusion was defined as ≥6 units of packed red blood cells transfused intraoperatively.[18] The length of hospital stay and postoperative complications were recorded. Morbidity was measured based on the Clavien-Dindo Classification (CDC) of surgical complications.[19] Hospital mortality was defined as death that occurred during the same hospital admission. Major causes of death were retrospectively investigated using an on-site database.

Statistical analysis

All statistical analyses were performed using IBM SPSS (Mac Version 23). Categorical or dichotomous variables were described with frequencies and percentages and compared with Chi-square test or Fisher's exact test when the expected numbers were small. Non-normally distributed continuous data were described with median/range and were analysed with Mann-Whitney U test. A P-value less than 0.05 was considered statistically significant.

Results

Over the last 20 years, the number of total CRS performed in our institution has increased (Figure 1). Thus far, the same surgical team has performed 1,019 CRS. The procedure-related hospital mortality rate has fallen from 4% in the initial 100 cases to 1% in the last 100 cases (Figure 2). The compounded hospital mortality over the total treatment period is 1.67% (n=17 of 1019).

Characteristics of patients suffering an in-hospital mortality post CRS/HIPEC

A summary of patient characteristics stratified by postoperative mortality is shown in Table 1. Seventeen patients (1.67%) were identified who died in hospital after CRS/HIPEC. Twelve of these patients (70.6%) were females. Their median age was 56 years (range: 31-74). The two most common primary tumour histology was appendix adenocarcinoma (n=5 of 249, tumour-specific mortality 2.01%) and PMP (n=4 of 264, tumour-specific mortality 1.52%). Three patients had DMPM (n=3 of 87, tumour specific mortality 3.45%), two patients had CRPC (n=2 of 298, tumour-specific mortality 0.67%), and 1 patient had ovarian carcinoma (n=1 of 47, tumour-specific mortality 2.13%). Other indications for CRS included primary adrenal carcinoma and signet ring cell carcinoma of unknown origin (n=2 of 74, 2.70%).

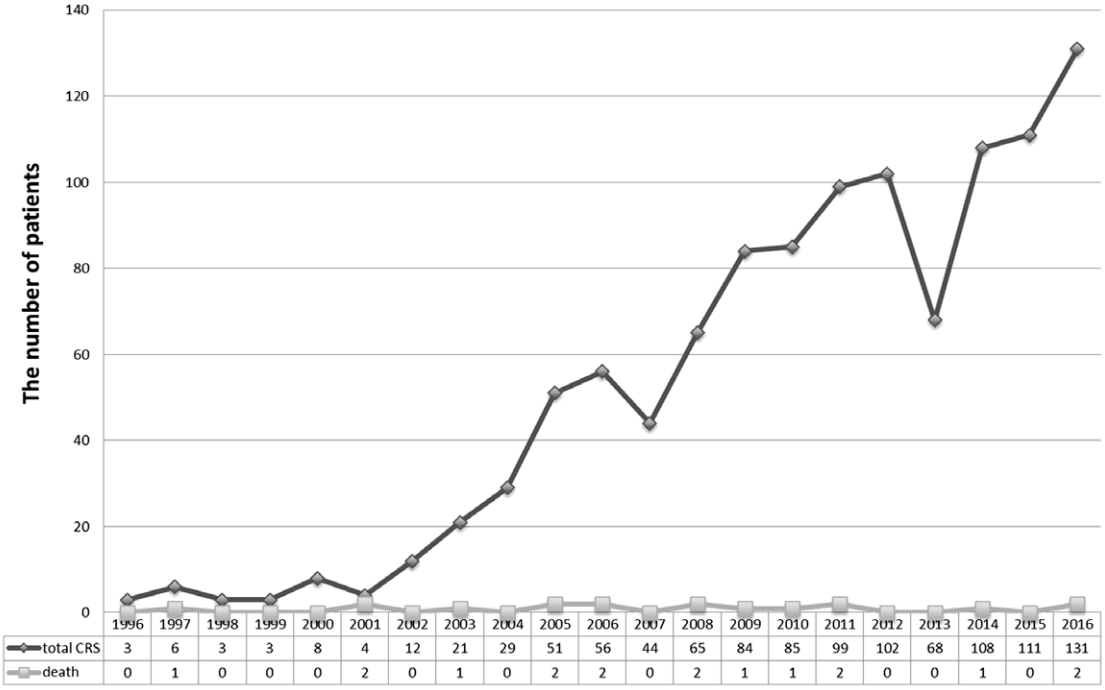
Comorbidities recorded in the postoperative mortality group included hypertension (n=5, 29.4%), obesity (n=5, 29.4%), respiratory diseases (n=2, 11.8%) and chronic kidney disease (n=2, 11.8%), ischaemic heart disease (n=1, 5.9%). Other background history included breast cancer, Meniere's disease, gout, hemochromatosis, hypothyroidism, and Cushing's syndrome.

ASA scores and the percentage of patients with ECOG ≥2 were higher in the post-operative mortality group compared to the other patients (P=0.012 and 41.2% *vs* 12.5%, P=0.003, respectively). The median preoperative serum albumin level was significantly lower in the post-operative mortality group [30 g/L (range: 16-46) *vs* 38 g/L (range: 13-51), P=0.014].

Surgical and HIPEC data

A summary of the operative data is presented in Table 2. The median PCI was higher (23 (range: 8-39) *vs* 14 (range (0-39), P=0.005) and fewer patients had a CC0 cytoreduction in the post-operative mortality group compared with the non-mortality patients (35.3% *vs* 68.5%, P=0.018). The median operative time of the post-operative mortality group was significantly longer (11 h (range: 7.5-23) *vs* 8.2 h (2-24), P=0.002) and they received greater volume of red blood cell transfusion during the operation [12 units

(range: 1-38) *vs* 3 units (range: 0-49), P<0.001]. The percentage of patients who received massive transfusion of 6 or more units of packed red blood cells was considerably higher in the post-operative mortality group (88.2% *vs* 30.6%, P<0.001). In regards to the different procedures done as part of CRS, the percentage of gastrectomy in the post-operative mortality group was significantly greater than in the non-mortality group (29.4% *vs* 8.73%, P=0.014). Procedures such as splenectomy and liver resection were more commonly performed in the post-operative mortality group, however this did not reach statistical significance. In addition, the percentage of patients treated with HIPEC was lower, although this was not statistically significant (76.5% *vs* 88.5%, P=0.127). The most commonly used agent was MMC (38.5% *vs* 54.2%, P=0.128) and the proportion of cisplatin HIPEC was higher



	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
total CRS	3	6	3	3	8	4	12	21	29	51	56	44	65	84	85	99	102	68	108	111	131
death	0	1	0	0	0	2	0	1	0	2	2	0	2	1	1	2	0	0	1	0	2

Figure 1. Yearly changes in the number of hospital death and total CRS from January 1996 to December 2016.

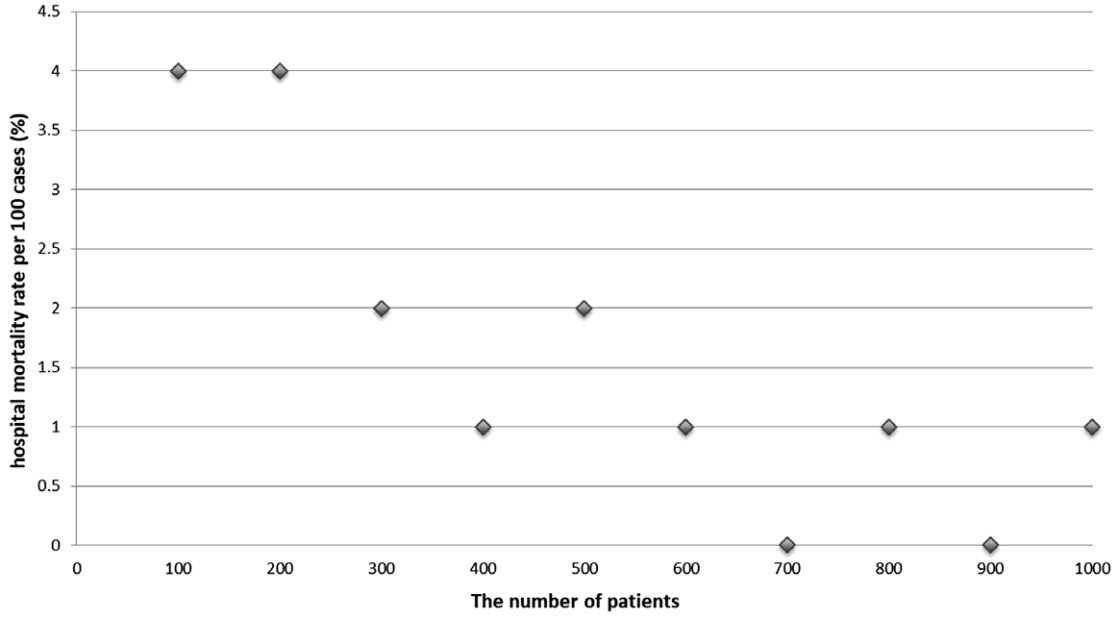


Figure 2. Changes in the hospital mortality from the initial 100 cases to the last 100 cases.

in the mortality group though it was not significantly different (30.8% *vs* 13.0%, P=0.127).

Postoperative outcomes and complications

A summary of postoperative complications is listed in Table 3. The median length of ICU stay (10 *vs* 2 days, P<0.001) and total hospital stay (41 *vs* 21 days, P=0.048) were significantly longer in the post-operative mortality group. The median time to death after CRS/HIPEC was 41 days (range 3-201). The patient who had the longest length of survival (201 days) suffered from fistula, bowel leak, and fungal sepsis after a redo CRS. Only three patients died within a week after CRS/HIPEC and nine patients died within a month.

These patients also suffered from a greater number of postoperative complications, such as infection (88.2% *vs* 35.2%, P<0.001), bleeding (35.3% *vs* 6.1%, P<0.001), pneumonia (29.4% *vs* 7.0%, P=0.006), fistula (41.2% *vs* 11.1%, P=0.002), collection/abscess (70.6% *vs* 36.3%, P=0.004), pancreatic leak (29.4% *vs* 6.2%, P=0.004), and return to theatre (82.4% *vs* 13.9%, P<0.001). Most patients had multiple complications (n=16 of 17, 94.1%). Sepsis was identified as the most common cause of death (n=15, 88.2%) and was significantly more common in the mortality group compared to the rest of the patients (88.2% *vs* 16.1%, P<0.001). The causative organisms for sepsis identified in some of the patients, such as bacterial (pseudomonas aeruginosa, serratia marcescens, enterococcus fecaelis, and methicillin-resistant *Staphylococcus aureus*) or fungal (candida albicans). Other major causes of death were pneumonia/respiratory failure (n=8, 47.1%), bone marrow depression (n=2, 11.8%), renal failure (n=2, 11.8%), and stroke (n=1, 5.9%). Supportive care was withdrawn in some patients, mainly due to respiratory failure or poor prognosis related to early recurrence. All 17 patients had grade IV morbidity (100% *vs* 16.8%, P<0.001). No patients died in theatre. The detailed data set of 17 patients in the mortality group is listed in Figure 3.

Discussion

Over the last two decades, mortality and the morbidity associated with CRS/HIPEC for peritoneal carcinomatosis (PC) has fallen considerably, which has been attributed to a surgical and institutional learning curve.[20-22] The morbidity and mortality of CRS/HIPEC is now little different from major gastrointestinal surgery.[9] We can report that the overall hospital mortality is 1.67% at our centre (17 of 1019). The median time to death was longer than a month (41 days, range: 3-201), which supports the previous suggestion that 90 days is a better metric than 30 days for evaluating surgical quality.[23] This is further reflected, by a recent study conducted by Simkens *et al.* (2016), who reported that the 30-day mortality (1.6%) was lower than hospital mortality (2.4%) after CRS/HIPEC in patients with CRPC.[24] Reflection on practice and analysis of our experience with the 17 post-operative mortality patients is essential in an attempt to recognise associated factors to reduce the hospital mortality associated with CRS/HIPEC in the future.

Numerous studies have already identified a number of factors that are linked to morbidity and mortality in CRS/HIPEC. Consistent with the previous findings, our results show that PCI, CC score, massive blood transfusion (≥6 units), and long operating time are associated with post-operative mortality.[18,25,26] It is particularly important to note that the weight of PCI and CC score slightly varies depending on the histology of primary tumour. In terms of CRPC, a previous study at our centre showed the improvement of the 5-year survival rate from 16% to 31%, with the adjusted PCI limit from 20 to 15 in CRPC in 2012 as a contributing factor for improved clinical results.[21] The mortality for CRPC (0.67%, 2 of 298) is commensurate with a less extensive procedure, especially considering that CRPC is the most common indication for CRS/HIPEC at our centre (29.2%, 298 of 1019). In contrast, the hospital mortality among patients with DMPM was relatively high

Table 1. Patient characteristics.

	Hospital mortality (n=17)	Non-mortality (n=1002)	P-value
Gender			
Male	5 (29.4%)	443 (44.2%)	
Female	12 (70.6%)	559 (55.8%)	
Age (median and range)	56 (31-74)	54 (14-85)	0.203
Primary tumour			
Appendix adenocarcinoma	5 (29.4%)	244 (24.4%)	0.579
PMP	4 (23.5%)	260 (25.9%)	1.000
DMPM	3 (17.6%)	84 (8.4%)	0.171
CRPC	2 (11.8%)	296 (29.6%)	0.176
Ovarian carcinoma	1 (5.9%)	46 (4.6%)	0.555
Others	2 (11.8%)	72 (7.2%)	0.353
PSS			0.599
0-1	8 (47.1%)	532 (53.5%)	
2-3	9 (52.9%)	463 (46.5%)	
ECOG			0.003**
0-1	10 (58.8%)	870 (87.5%)	
2-3	7 (41.2%)	124 (12.5%)	
ASA			0.012**
1	0 (0%)	34 (3.87%)	
2	3 (17.6%)	278 (31.7%)	
3	8 (47.1%)	492 (56.0%)	
4	6 (35.3%)	74 (8.43%)	
Preoperative serum albumin (median and range)	30 (16-46) g/L	38 (13-51) g/L	0.014**

#	age	gender	PCI	CCS	Type of cancer	HIPEC	EPIC	PSS	ASA	op time	Blood trans fusion	Primary or redo	ICU stay	HDU stay	total stay	time of death	back to OT	blee ding	sepsis
1	55	F	23	0	Appendix adenocarcinoma	MMC	Y	2	3	15.5	14	Primary	15	11	41	41	N	N	Y
2	58	F	20	0		MMC	Y	3	3	9	1	Redo	3	9	201	201	Y	N	Y
3	66	F	12	1		No	Y	0	2	7.5	2	Primary	10	5	23	19	Y	Y	Y
4	67	F	27	1		Oxaliplatin	N	1	4	9.4	10	Primary	29	21	50	50	Y	Y	Y
5	73	F	25	0		Oxaliplatin	N	2	3	7.8	12	Primary	60	0	60	60	Y	N	Y
6	55	F	16	0	PMP	No	Y	2	2	9	6	Primary	3	0	20	19	Y	N	Y
7	55	M	39	2		MMC	N	3	4	23	21	Primary	10	15	164	134	Y	Y	Y
8	73	M	39	1		MMC	N	2	4	11	12	Redo	7	11	55	42	Y	Y	Y
9	74	F	14	1		MMC	N	3	3	8	21	Primary	5	5	10	10	N	N	Y
10	33	M	39	1	DMPM	Cisplatin	N	0	3	14	38	Primary	45	14	111	111	Y	Y	Y
11	52	F	39	1		Cisplatin	N	1	3	11.5	16	Primary	17	1	70	63	Y	N	Y
12	68	M	39	2		No	Y	0	4	7.5	14	Primary	14	0	15	14	Y	N	Y
13	56	M	11	1	CRPC	Oxaliplatin	N	1	4	12	17	Primary	3	0	3	3	Y	N	Y
14	58	F	8	0		Oxaliplatin	N	1	3	11	10	Primary	16	3	20	19	Y	N	N
15	31	F	20	0	Others	Cisplatin	N	2	2	11.5	10	Primary	2	3	7	5	N	N	N
16	43	F	16	1		No	Y	2	4	11.5	7	Primary	18	0	19	18	Y	N	Y
17	55	F	24	1	Ovarian adenocarcinoma	Cisplatin	N	1	3	10	8	Primary	10	6	81	81	Y	Y	Y

Figure 3. The detailed data set of 17 patients in the mortality group.

Table 2. Operative and HIPEC data.

	Hospital mortality (n = 17)	Non-mortality (n=1002)	P-value
PCI (median and range)	23 (8-39)	14 (0-39)	0.005**
0-10	1 (5.9%)	384 (38.3%)	
11-20	7 (41.2%)	276 (27.5%)	
21-30	4 (23.5%)	166 (16.6%)	
>30	5 (29.4%)	176 (17.6%)	
CCS			0.018**
CC0	6 (35.3%)	683 (68.5%)	
CC1	9 (52.9%)	268 (26.9%)	
CC2	2 (11.8%)	42 (4.2%)	
CC3	0 (0%)	4 (0.4%)	
CRS			
Primary	15 (88.2%)	821 (81.9%)	0.751
Redo	2 (11.8%)	181 (18.1%)	
Operative time (median and range)	11 (7.5-23) h	8.2 (2-24) h	0.002**
Surgical Procedures			
Omentectomy	9 (52.9%)	631 (63.4%)	0.377
Oophrectomy	4 (23.5%)	197 (19.8%)	0.758
Hysterectomy	4 (23.5%)	126 (12.7%)	0.259
Splenectomy	10 (58.8%)	384 (38.6%)	0.089
Cholecystectomy	9 (52.9%)	549 (55.1%)	0.858
Liver resection	4 (23.5%)	86 (8.63%)	0.056
Gastrectomy	5 (29.4%)	87 (8.73%)	0.014**
Small bowel resection	10 (58.8%)	495 (49.7%)	0.456
Large bowel resection	12 (70.6%)	645 (64.8%)	0.618
Pancreas			
Pancreatectomy	1 (5.9%)	40 (4.02%)	0.507
Strip	2 (11.8%)	75 (7.53%)	0.348
Ureter reimplant	3 (17.6%)	86 (8.63%)	0.182
Nephrectomy	1 (5.9%)	20 (2.01%)	0.302
Appendix	1 (5.9%)	142 (14.3%)	0.492
Diaphragm strip	11 (64.7%)	527 (52.9%)	0.334
HIPEC agent	13 (76.5%)	887 (88.5%)	0.127
Cisplatin	4 (30.8%)	115 (13.0%)	0.127
MMC	5 (38.5%)	481 (54.2%)	0.128
Oxaliplatin	4 (30.8%)	290 (32.7%)	0.790
Blood transfusion (median and range)	12 (1-38)	3 (0-49)	<0.001**
≥6 units	15 (88.2%)	307 (30.6%)	<0.001**
EPIC	6 (35.3%)	385 (38.5%)	0.786

(3.45%, 3 of 87), which can be attributed to a more extensive procedure as patients present with a higher PCI and are often malnourished due to repeated ascitic paracentesis.[27] In our mortality group, all three patients with DMPM had a PCI of 39 and incomplete cytoreduction (CC1 or CC2). Additionally, one had incurable aggressive recurrence of sarcomatoid type and supportive care was withdrawn 64 days after CRS/HIPEC. Our data support the importance of the learning curve associated with CRS/HIPEC in order to improve clinical outcomes and reduce the mortality of patients with DMPM.[7]

Our results also show that massive transfusion (≥6 units) is associated with hospital mortality. Its effects on the immune system and recurrence have been described.[28] Saxena *et al.* (2009) identified risk factors for requiring massive transfusion during CRS/HIPEC, which include preoperative anemia (hemoglobin <125 g/L), impaired coagulation profile (INR ≥1.2) and high tumour burden (PCI ≥16).[18] In an attempt to avoid this adverse event, our centre routinely performs intraoperative point-of-care (POC) coagulation testing and rotational thromboelastometry (ROTEM) in theatre every 2 h to aggressively detect and correct any abnormal results.

Our study also demonstrates that a low preoperative serum albumin level is associated with post-operative mortality. This is consistent with the previous study conducted by Huang *et al.* (2016), which reported that preoperative hypoalbuminaemia (<35 g/L) is an important prognostic factor for poor perioperative outcome and overall survival following CRS/HIPEC.[29] In addition, our study confirms that poor preoperative physical status, measured with ECOG and ASA, is associated with post-operative mortality. Whilst these measurements are clearly prognostic, there is a lack of clear strategies to improve them or the associated outcomes.

In terms of specific CRS procedures, our data shows that only gastrectomy was significantly associated with increased post-operative mortality. Of all five patients who underwent gastrectomy in our post-operative mortality group, three patients had appendix adenocarcinoma. To date there is limited data on the risks and safety of gastrectomy in CRS/HIPEC. Two small case series concluded that gastrectomy is safe in experienced centers.[30,31] As Di Fabio *et al.* (2016) discussed that the need for gastrectomy usually reflects the extent of the disease, recent studies on gastrectomy in patients with advanced PMP showed that gastrectomy as part of complete cytoreduction results in relatively good long-term outcomes if performed in experienced institutions.[32,33] Our mortality rate of 5.43% (5 of 92) among patients with gastrectomy is comparable with their results.

Although our data does not show any association between PIC (HIPEC or EPIC) and post-operative mortality, it is important to point out that bone marrow depression was the major cause of death in two patients. Previous studies have reported on the toxicities associated with PIC agents, such as MMC, cisplatin, and oxaliplatin. MMC is commonly associated with neutropenia and myelosuppression.[34] Sugarbaker has proposed that the total dose of MMC and the volume of chemotherapy solution be based on the patients' body surface area to minimise MMC-related toxicities.[35] Furthermore, a recent study showed that HIPEC with cisplatin can be complicated by nephrotoxicity,[36] however in our study, those who developed renal failure in the mortality group did not receive cisplatin for PIC. Post-operative bleeding has also been a major problem after HIPEC with oxaliplatin, but we have seen little of this probably because of the lower dose used.[37]

Our results also show that many of the postoperative complications are associated with post-operative mortality such as infection, bleeding, pneumonia, fistula, collection, and pancreatic leak. As most of the patients in the mortality group suffered from multiple postoperative complications, it is important to note that these complications are intertwined, prolonging the length of hospital stay and increasing the likelihood of patients returning to theatre. In our study, infection and subsequent sepsis remains the most significant cause of hospital death even with the standardized use of

Table 3. Postoperative complications and major causes of death.

	Hospital mortality (n=17)	Non-mortality (n=1002)	P-value
ICU (median and range)	10 (2-60)	2 (0-101)	<0.001**
HDU (median and range)	5 (0-21)	2 (0-39)	0.125
Total hospital stay (median and range)	41 (3-201)	21 (4-306)	0.048**
Time to death after CRS (median and range)	41 days (3-201)	-	-
Infection	15 (88.2%)	352 (35.2%)	<0.001**
Bleeding	6 (35.3%)	61 (6.1%)	<0.001**
Cardiovascular issues	2 (11.8%)	87 (8.7%)	0.654
Pneumonia	5 (29.4%)	70 (7.0%)	0.006**
Pleural effusion	5 (29.4%)	246 (24.6%)	0.582
Fistula	7 (41.2%)	111 (11.1%)	0.002**
Enterocutaneous	3 (17.6%)	58 (5.79%)	0.076
Pancreatic	1 (5.9%)	50 (4.94%)	0.585
Perforated viscous	2 (11.8%)	26 (2.6%)	0.077
Collection/abscess	12 (70.6%)	363 (36.3%)	0.004**
Renal impairment	2 (11.8%)	27 (2.7%)	0.082
Pancreatic leak	5 (29.4%)	62 (6.2%)	0.004**
Pulmonary embolism	1 (5.9%)	65 (6.5%)	1
Return to OT	14 (82.4%)	139 (13.9%)	<0.001**
Sepsis	15 (88.2%)	161 (16.1%)	<0.001**
Morbidity grade IV	18 (100%)	168 (16.8%)	<0.001**

perioperative prophylactic antibiotics. Patients undergoing CRS/HIPEC are vulnerable to infections due to a number of factors, such as multiple bowel resections and anastomoses, prolonged operating time, HIPEC-related immunosuppression, lengthy hospital stay, presence of urinary and central venous catheters, as well as multiple drains.[38] A previous study done by Valle *et al.* (2014) reported that the establishment of a prevention, surveillance and treatment protocol led to the early detection of asymptomatic patients with an infection.[38] Early identification of a causative organism and the sensitivity is always a crucial part of effective management of infections. One of our patients was identified to have died from overwhelming sepsis due to an organism (Serratia) that was not sensitive to the antimicrobial agents used. Some other opportunistic organisms were identified among the hospital mortality group. Pneumonia is one of the commonly acquired infections, often leading to respiratory failure and sepsis. One of the patients died of HSV1 pneumonitis.

A fistula, enterocutaneous (ECF) or pancreatic (PF), is one of the major complications of CRS. Previous studies on ECF and PF reported that both ECF and PF were associated with longer hospital stay, but only ECF was linked to hospital mortality.[39,40] According to Berry *et al.* (1996), 75-85% of gastrointestinal fistulas are due to bowel injury, inadvertent enterotomy and/or anastomotic leakage.[41] Valle *et al.* (2016) reported that longer operating time and PCI were associated with an increased chance of ECF formation, with a greater number of bowel resections and enterotomies.[39] In addition, patients with ECF suffered from a greater number of complications, such as bleeding, pleural effusion, collection, and sepsis.[39] Our centre aims to manage ECF conservatively with total parenteral nutrition (TPN) and somatostatin analogues. This therapy results in spontaneous closure of ECFs in up to 50%, however failure of spontaneous closure increases the length of hospital stay, which may put patients at greater risks of other complications.[39] Therefore, it may be helpful to identify those who are unlikely to achieve spontaneous closure and to consider treating them more aggressively with early surgical intervention. Current indications for surgical management at our institution include distal obstruction and failure of spontaneous closure after two months of conservative management.

It is promising that myocardial infarction or pulmonary embolism (PE) were not the cause of any mortality. We had only one patient who suffered from PE among the 17 patients, however this was not the causative factor for death. It was reported that PEs following CRS/HIPEC rarely require escalation of care or lead to significant cardio-respiratory dysfunction.[42] As discussed above, we administer prophylactic anticoagulants to all patients undergoing CRS/HIPEC, including post-discharge prophylaxis using low molecular weight heparin (LMWH), and have an aggressive protocol if PE is suspected with CTPA. Yet, the risk for PE is known to be higher in CRS/HIPEC, compared to other isolated major surgeries.[42] Our results show that the incidence of PE in patients post-CRS/HIPEC was 6.48% at our center (66 of 1019), which was slightly increased since the last study on PE in 2013 (4.4%).[42] This may be due to an active clinical trial at our centre in patients undergoing major surgery, including CRS/HIPEC, where the intervention protocol includes a routine CTPA. This may result in higher detection of PE, especially in patients that are clinically asymptomatic, and as a result increase the incidence at our centre.

Strategies to rescue patients with severe complications deserve more attention. Ferraris *et al.* (2014) discussed the importance of identifying the minority of patients who were likely to die so that more intensive postoperative care can be provided for them to reduce the failure-to-rescue rate.[43] In addition, they showed that cardiac events, pulmonary failure, renal failure, and stroke tended to have much higher failure-to-rescue rates, most of which occurred one week before post-operative mortality.[43] These findings are consistent with our data, suggesting that a frequent observation and timely intervention can potentially reduce failure to rescue during the limited period for rescue. A variety of factors are known to decrease the failure-to-rescue rate, such as aggressive and extreme interventions, and high-quality structural components, including better ICU care, nurse to patient ratios, involvement of residents and subspecialty surgeons, and effective teamwork.[43] In clinical settings, one of the major decisions evolves around when to intervene more aggressively. Based on our clinical experience, we believe that earlier reoperative management may have resulted in better clinical outcomes than the later ones, reducing the failure-to-rescue rate. The quality of structural components of our team has improved over the last two decades with increasing experience in our institution. In addition, it was shown that standardized clinical pathway considerably decreases the failure-to-rescue rate.[44] Therefore, cytoreductive surgery and HIPEC is best to be performed at a high-volume centre with a highly experienced multidisciplinary team, where preventable failure to rescue can be avoided.

Although baseline characteristics were comparable, selection bias between subgroups cannot be excluded due to the retrospective interpretation of our prospective database. Due to the relatively small number of post-operative mortality patients, a reliable multivariable analysis is difficult to perform. A multicentric review in high-volume centres that have overcome their learning curve on hospital mortality should be considered to determine factors associated with post-operative mortality in a larger cohort and potentially obtain pre-operative factors to allow for more optimal selection of patients that would benefit from this procedure.

Conclusions

It is difficult to determine risk factors for post-operative in-hospital mortality, as the overall incidence of in-hospital mortality post CRS/HIPEC was low. We can report, however, that a reduction over time in hospital mortality rate was seen, which can be attributed to a surgical and institutional learning curve. This study does provide important information describing the typical post-operative cascade of events leading to in-hospital mortality post CRS/HIPEC. A review of all mortality experienced in high-volume centres may be beneficial to obtain further information on risk factors for post-operative mortality.

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